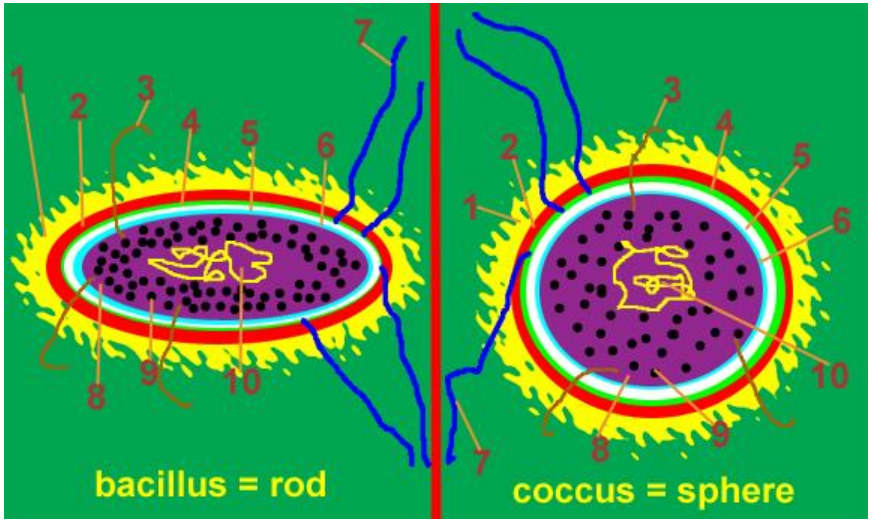
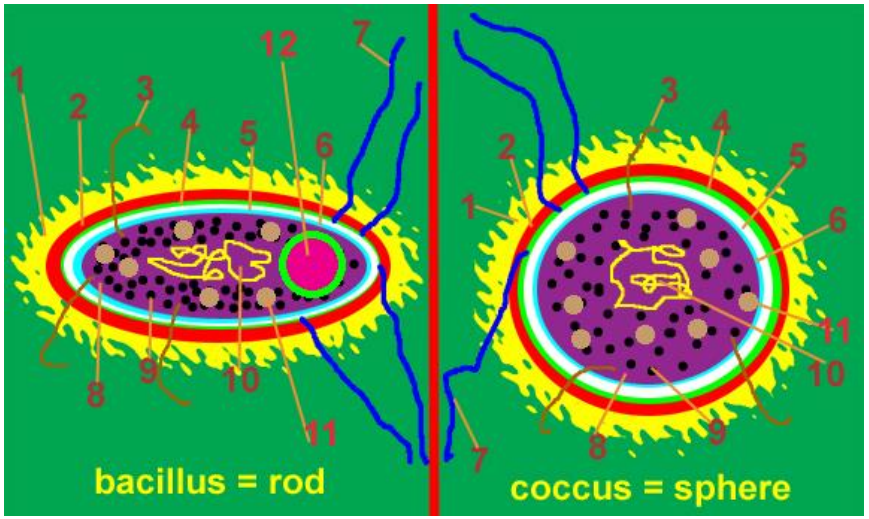
Typical Cells Encountered in Anatomy, Biology and Biochemistry

The Prokaryotic Cell -- Anatomy

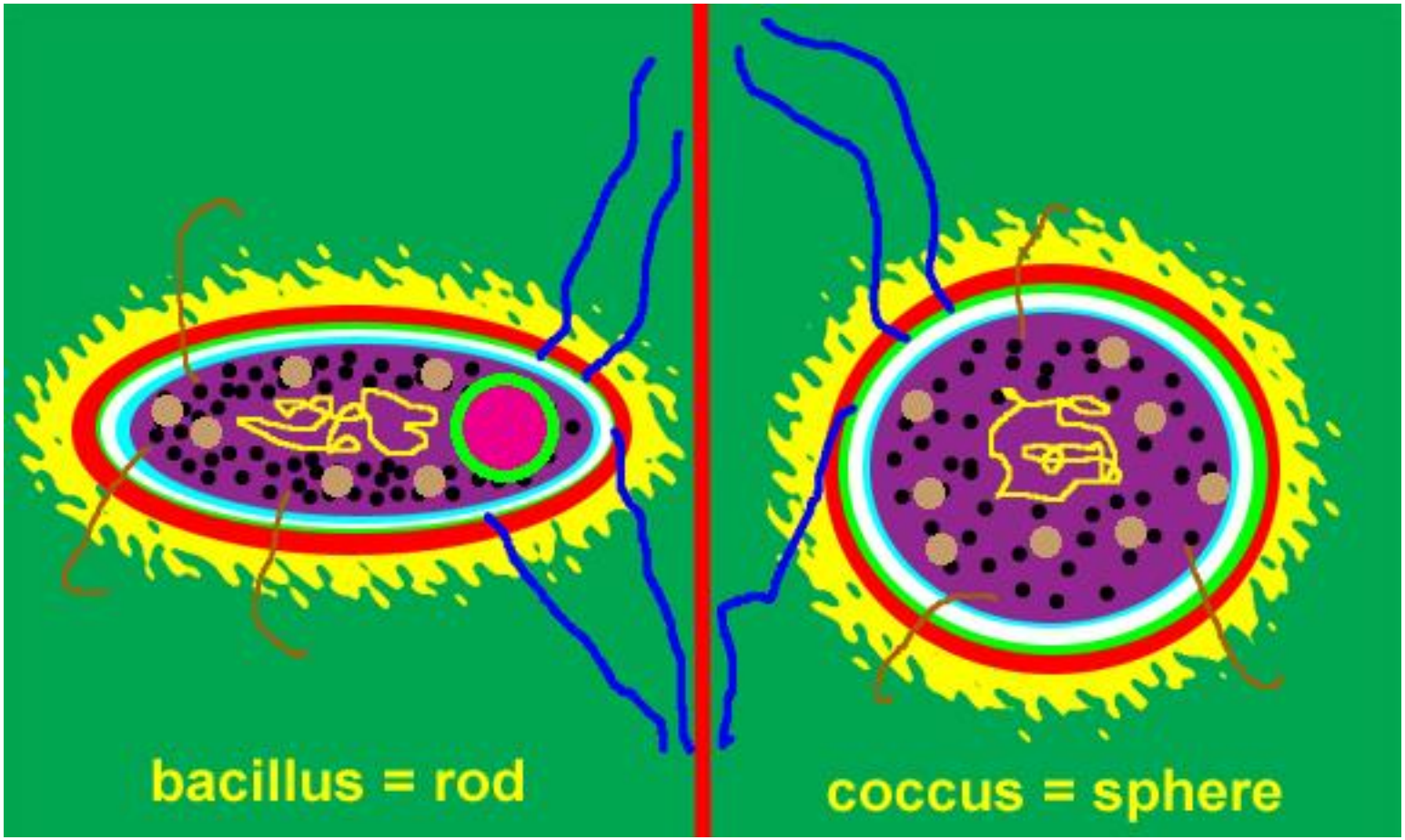




1. Capsule (Slime Layer)
2. Outer Membrane
3. Pilus (Pili = plural)
4. Cell Wall
5. Periplasmic Space
6. Plasma Membrane
7. Flagellum (flagella = plural)
8. Cytosol
9. Ribosomes
10. Nucleoid (Circular DNA)
11. Inclusions
12. Endospore (when present; remainder of cell called sporangium)

The Prokaryotic Cell

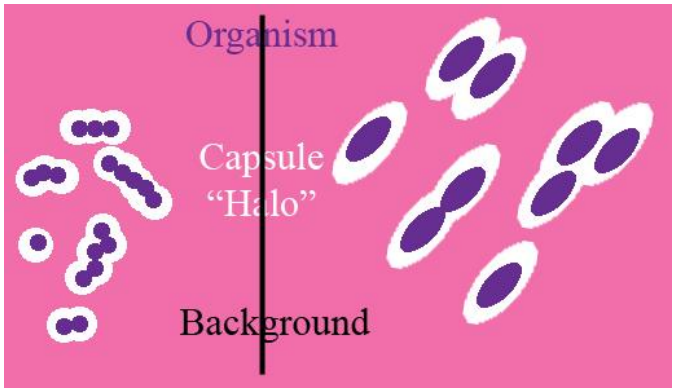
Physiology



Source for a portion of this section = http://www.cellsalive.com/cells/bactcell.htm

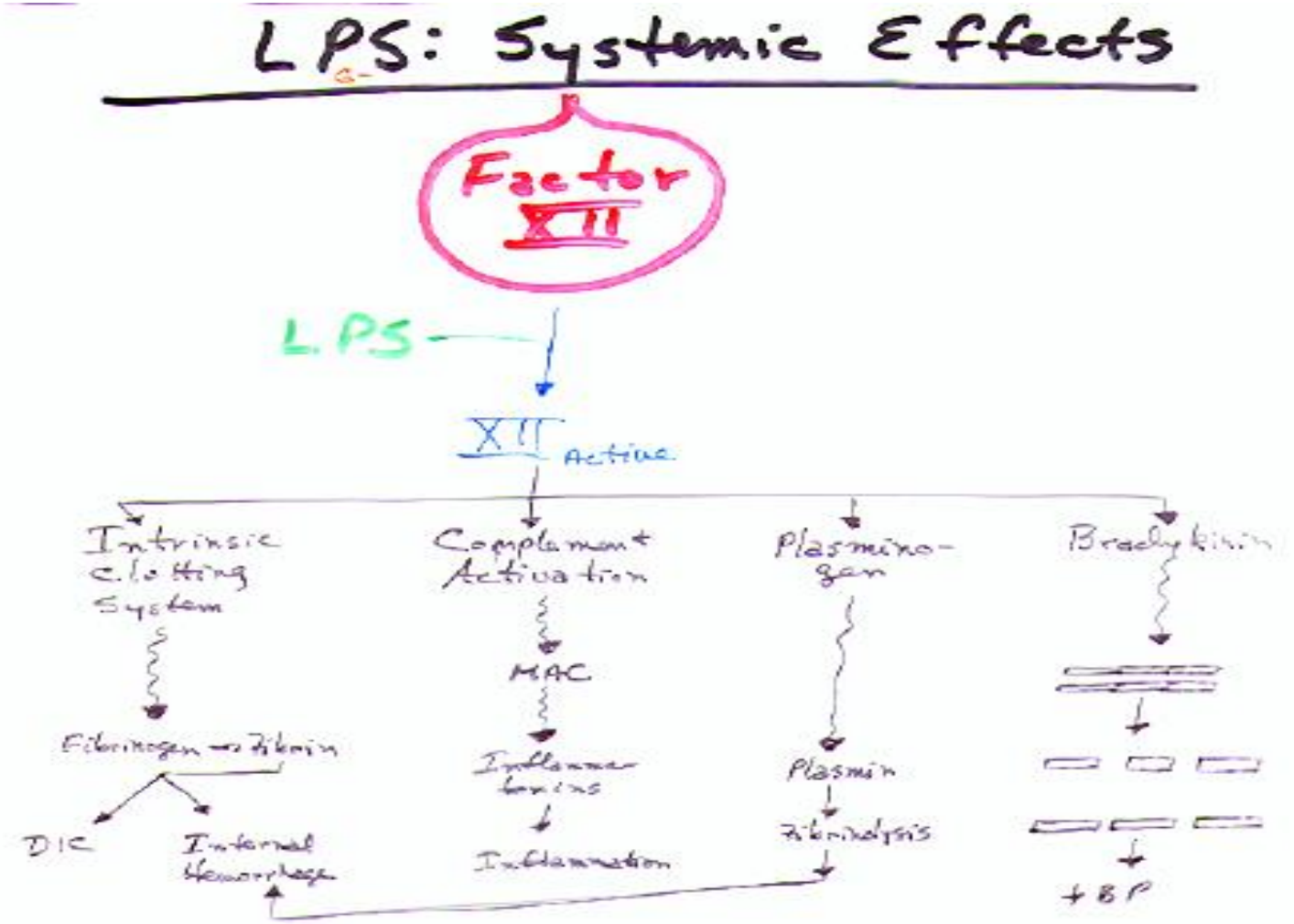
Surface Structures

- Capsule: polysaccharide (or proteins); protects the cell and is often associated with pathogenic bacteria (it serves as a barrier against phagocytosis by white blood cells).
- The capsule, slime layer or glycocalyx is either polysaccharide or small protein that serves as an environmental buffer to the bacteria. It is a thick gelatinous layer outside the cell wall. It requires a special stain to visualize it. This layer increases the virulence of the organism and protects the cell from phagocytosis, much like how hamburger hides tablets from your pets when they have to take medicines. The capsule is present in plaque bacteria (S. mutans), pneumococci and is the source of ropy milk.



- Figure, above, shows how capsules would appear on a background stain. The bacteria are stained violet/purple, the background black and the capsules are the colorless spaces between the 2 colors.
- Bacteria, which form capsules in tissues and in culture, include S. pneumoniae and K. pneumoniae. Those that produce capsules in tissues only include B. anthracis, C. perfringens and Y. pestis. Microorganisms that produce thin capsules include N. meningitidis, S. pyogenes, B. pertussis and H. influenzae.

- **Outer Membrane: found in Gram negative bacteria and is the source of lipopolysaccharide (LPS). LPS is toxic and turns on the immune system.**



- **Cell Wall: Composed of peptidoglycan (polysaccharides + protein);**
- The cell wall is for cell protection and shape determination of the microbes.
  - Gram positive cells contain peptidoglycan and teichoic acid.
  - Gram negative cells contain LPS.
- The cell wall is the site of penicillin (PCN) activity.
- The cell wall is absent in Mycoplasma which is why PCN doesn't work for walking pneumonia.
- **The three primary shapes in bacteria are**
  - **coccus (spherical),**
  - **bacillus (rod-shaped) and**
  - **spirillum (spiral).**
  - **Mycoplasma are bacteria without a cell wall and have no definite shape.**

- **Periplasmic space: found only in bacteria that have both an outer membrane and plasma membrane (e.g. Gram negative bacteria). Contains enzymes and other proteins that help digest and move nutrients into the cell.**
- **Plasma Membrane: a lipid bilayer much like the cytoplasmic (plasma) membrane of other cells. Proteins moving within or upon this layer are responsible for ions, nutrients and waste transport across the membrane.**

Appendages

- Pili: These are hollow, hairlike structures composed of protein; allow bacteria to attach to other cells. A specialized pilus, the sex pilus, allows the transfer from one bacterial cell to another of genetic information. Also called fimbriae (*sing*., fimbria). These tend to be present on Gram negative bacteria and serve to stimulate our immune system when we're infected with these bacteria.
- Flagella: The purpose of flagella (*sing*., flagellum) is motility. Are long appendages which rotate by means of a "motor" located just under the cytoplasmic membrane. Bacteria may have one, a few, or many flagella in different positions on the cell and vary in the number per bacteria genus/species. Many rods and only a few cocci contain flagella. They are protein, used for movement. The flagella turn either clockwise or counter-clockwise.

Internal Structures

- Nucleoid: DNA in the bacterial cell is generally confined to this central region; isn't bounded by a membrane, it is visibly distinct (by transmission microscopy) from the rest of the cell interior.
- Ribosomes: give the cytoplasm of bacteria a granular, grainy or rough appearance in electron micrographs. Though smaller than the ribosomes in eukaryotic cells, they have the same protein synthesis function. Ribosomes may be inhibited by various antibiotics that will be discussed at a later date.

- The cytosol is the functioning substance of the cell.
- It contains "everything" in the cell.
- It is the metabolic and growth center of the cell and has the consistency of apple-jelly.
- One bacterium contains metachromatic granules. The organism is C. diphtheriae. These granules are phosphate and are storage forms for the microbe.
- Magnetosomes contain magnetite. The organisms that contain magnetosomes use them for cellular orientation, i.e., a compass.
- **Storage granules (or inclusions): Nutrients and reserves stored in the cytoplasm; in the form of glycogen, lipids, polyphosphate, or in some cases, sulfur or nitrogen.**

Additional Comments

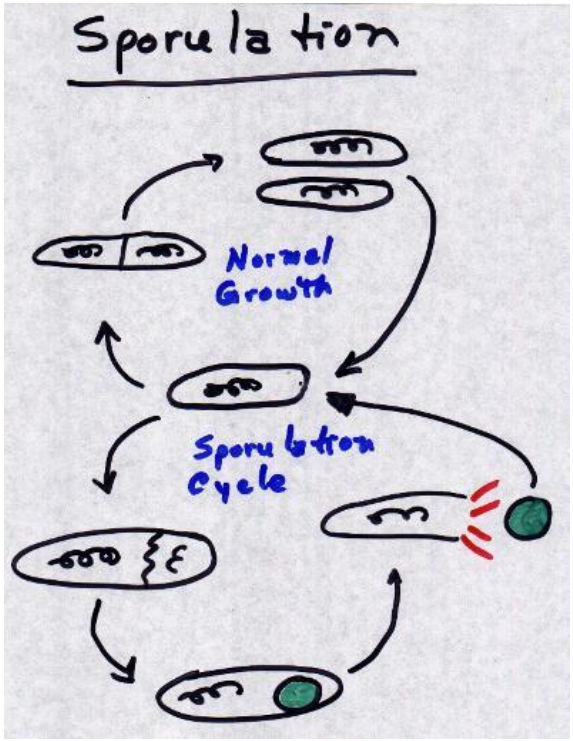
- Nucleoid: DNA structure: single closed loop – associated with histones; Chromosomes are, of course, DNA. This is the genetic code of the cell and is all the information inherited by the cell during fission.
- Ribosomes: free
- **Nucleus**: absent
- Cell wall: generally present – complex composition
- Subcellular organelles: absent
- Reproduction occurs by binary fission
- Chlorophyll inclusions: dissolved in cytosol when (if) present
- Examples of prokaryotes: bacteria, rickettsia, chlamydiae

Endospores

- Some bacteria, like C. botulinum, C. tetani, C. perfringens, C. difficile form produce thick walled spores that are highly resistant to drought, high temperature and other environmental hazards. Once the hazard is removed, the spore germinates to create a new bacillus. **Spores in bacteria are NOT for reproductive purposes – ONLY for survival.**

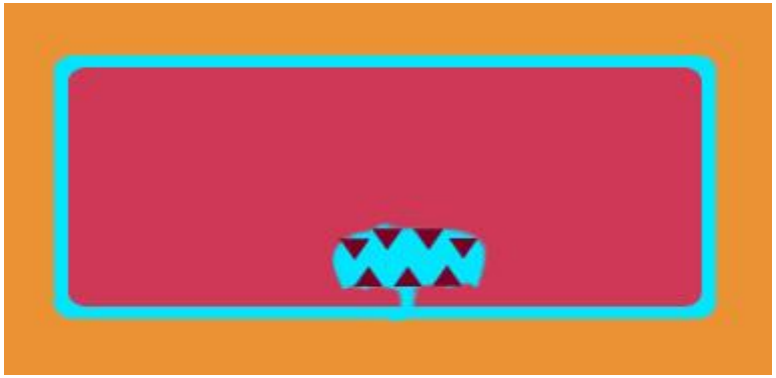
- Spores are complex. They are resistant to environmental changes such as drying, heat. Indeed, some spores recovered from amber from some of the ancient pyramids of Egypt have been successfully cultured and have "come back to life" after 1000's of years. The sporeformers are the anaerobic genus Clostridium and the aerobic sporeforming genus Bacillus. Clostridium is involved in causing tetanus, gas gangrene, botulism and colitis. Bacillus is involved in causing anthrax and food poisoning.

- Spores are the most resistant living thing known. Sporulation depends upon the depletion of some particular nutrient at a time when conditions for growth are otherwise favorable. It usually occurs in the later stages of an artificial culture. It DOES NOT occur in tissues!
- Under normal growth conditions, the sporeformers go through normal fission.
- Once, though, one nutrient is withdrawn, the organism develops a thick wall that isolate its genetic material from the rest of the cell.
- The wall encapsulates the nuclear material and an endospore is now formed.
- The rest of the cell is called the sporangium.
- The sporangium then bursts, releasing the spore. It will remain dormant until a suitably warm, moist environment that contains trigger nutrients is available, then it will form a vegetative cell and continue it's life cycle.
- Sporulation in bacteria, **unlike that of in fungi**, is NOT for reproductive purposes, **rather it is for survival**! Each spore germinates into a single bacillus, so the process, as a whole, is NOT reproductive!



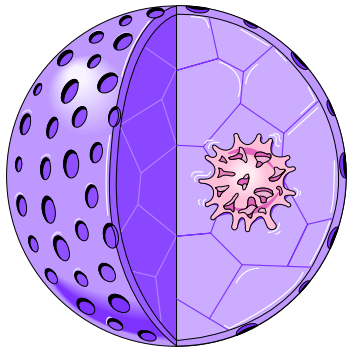
- The most important property of spores is their extreme resistance to desiccation, heat and disinfectants and the fact that they can remain viable in a dormant stage and are a potential source of danger for long periods of time.
- The resistance of spores dictates the use of stringent methods of sterilization in medical practice and in the food industry.

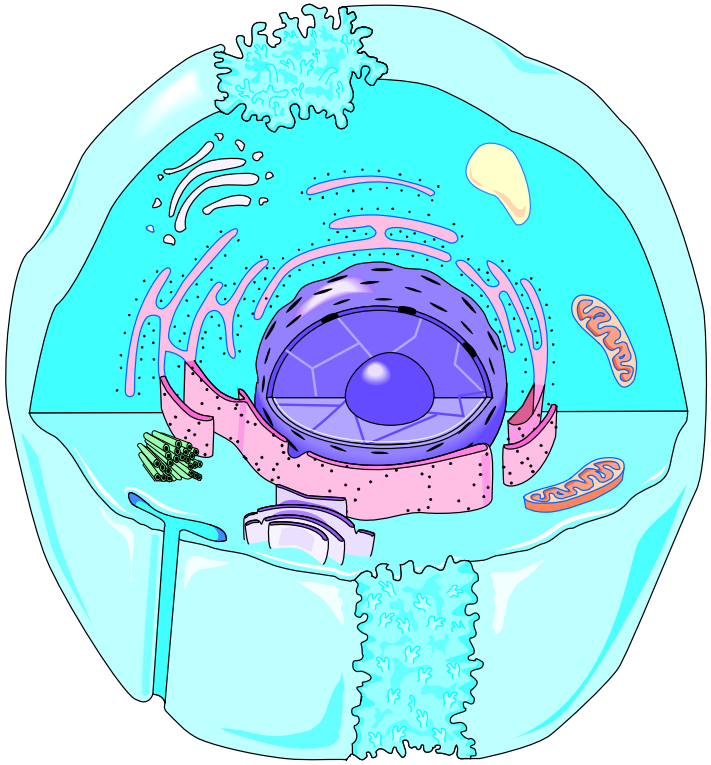
A Word on Mesosomes -- Controversial

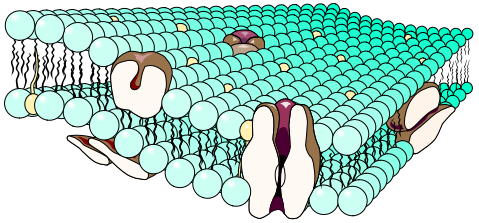


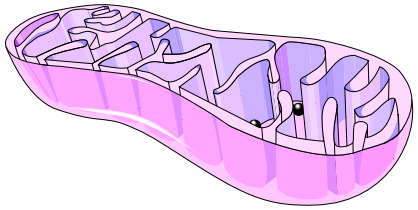
- The plasma membrane of bacteria may invaginate into the cytoplasm or form stacks or vesicles attached to the inner membrane surface. These structures are sometimes referred to as **mesosomes.**
- Such internal membrane systems **may be analogous to the cristae of mitochondria** or the thylakoids of chloroplasts which increase the surface area of membranes to which enzymes are bound for specific enzymatic functions. The photosynthetic apparatus (light harvesting pigments and ATPase) of photosynthetic bacteria is contained in these types of membranous structures.
- Mesosomes may also represent specialized membrane regions involved in DNA replication and segregation, cell wall synthesis, or increased enzymatic activity.
- Membrane foldings and vesicles **sometimes** appear in electron micrographs of bacterial cells as artifacts of preparative techniques.
- These membranous structures, of course, are not mesosomes, but their existence does not prove that mesosomes are not present in bacteria, and there are several examples of bacterial membrane topology and appearance that are suggestive of mesosomes.
- Source: http://www.bact.wisc.edu/bact330/thebacteria -- Dr. Kenneth Todar, University of Wisconsin-Madison Department of Bacteriology

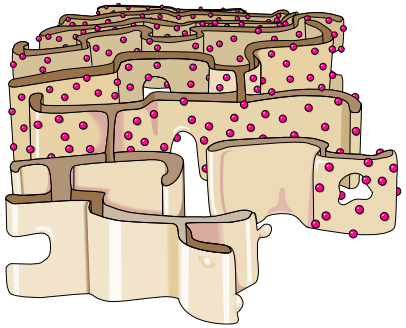
The Eukaryotic Animal Cell











- The size of a cell varies from as small as 200 nanometers (one billionth of a meter) up to the size of an ostrich egg.
- The minimal size of any cell is dependent on the content of the cells.
- The primary contributors to the size of a cell are macromolecules like DNA (the "brains" of the cell) and protein (the ultimate signal coded for in the DNA).
- Both macromolecules (large molecules) are required for control of cellular activity and to sustain cellular activity.

- The size of the average cell in the human body is between 0.5 micrometers and 20 micrometers (one millionth of a meter;
  - the old unit was micron).
- The diameter of the average red blood cell is between 8 and 10 micrometers.

The Potential Size of The Cell is Dependent upon Two Characteristics

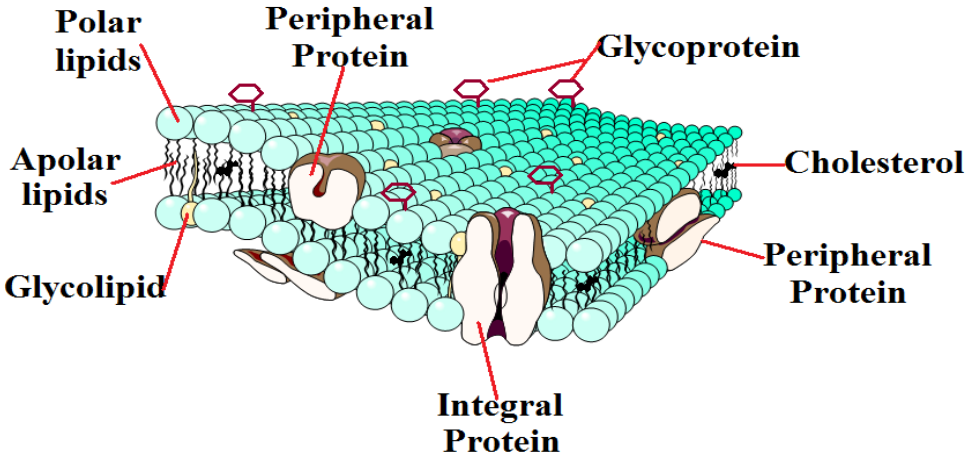
- 1) the relationship between the nucleus (NOOK lee uss) and the cytoplasm (SIGH toe plazum),
  - e.g., a lymphocyte (LIMM foe sight) has a large nucleus and little cytosol (SICH toe soll).
- This cell synthesizes many useful proteins,
  - e.g., antibodies, but does not have the cytosol to retain them for very long, hence, the synthesized compounds are released into the general circulation.
- On the other hand, monocytes have a large nucleus and a large volume of cytosol.
  - These cells function, among many, as macrophages (MACK row fa juz).
- These cells synthesize lytic substances that work intracellularly on phagocytized (fa GOE si tized) micro-organisms, cellular debris, excretions or anything else the body does not want or need.

- 2) The amount of surface for nutrient and/or waste transport.
- The more surface area on a cell, the more nutrients the cell may take up and the more waste that may be efficiently excreted.
- The more a cell takes up and utilizes, the larger the cell.

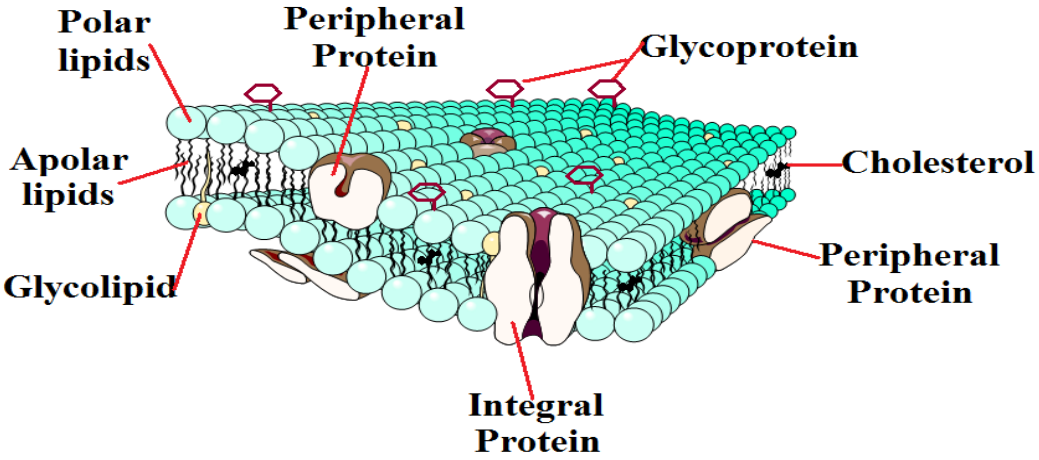
Any Eukaryotic Cell Has Three Parts

1. Membrane Systems
2. Cytoplasm (Cytosol)
3. Nucleus

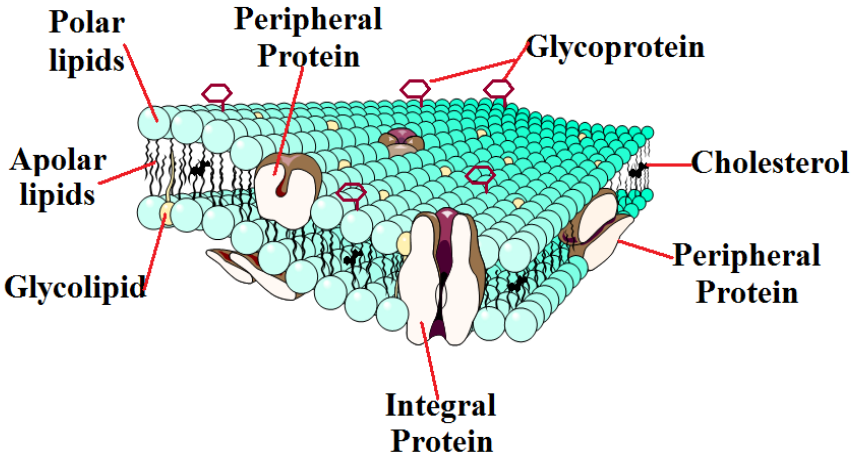
Part I - Membrane Systems



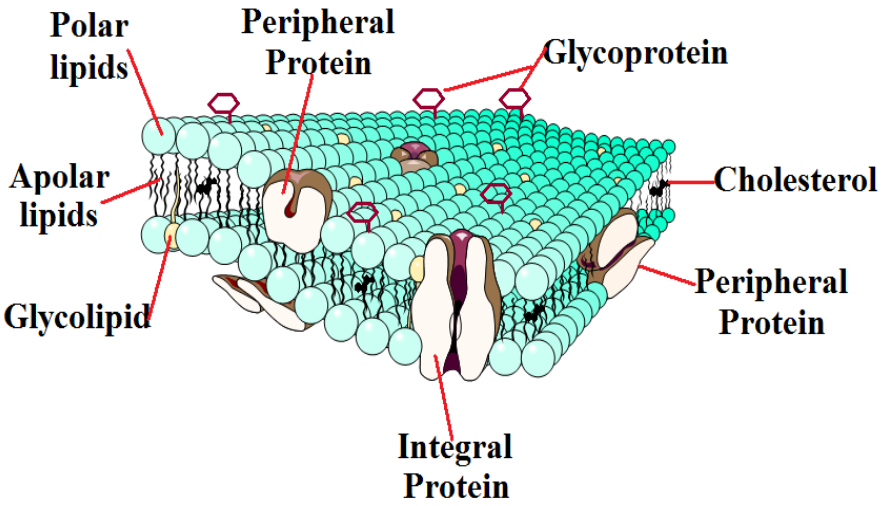
- This membrane has three-dimensional structure, although we'll examine it from only 2 dimensions.
- Note that it is a lipid (fat) bilayer (two layers) membrane, i.e., there are two layers of lipid that surround the cell.
- The outer-most and inner-most of the two layers are polar (hydrophilic [high droe FILL ick] - water loving - or lipophobic [lye poe FOE bick] - fat fearing) lipids.
- This is important for they must interact with the aqueous solvent of which bodies and cells consist: water.
  - Water is a polar molecule.
- The two middle-most regions of this lipid bilayer are apolar (hydrophobic - water fearing -- or lipophilic - fat loving).
- It is this middle region that gives the membranes a powerful way of separating the cell "innards" from the outside and from other cells, allowing different cells to "bunch together" to form different kinds of tissues and, hence, organs and organ systems and organisms.



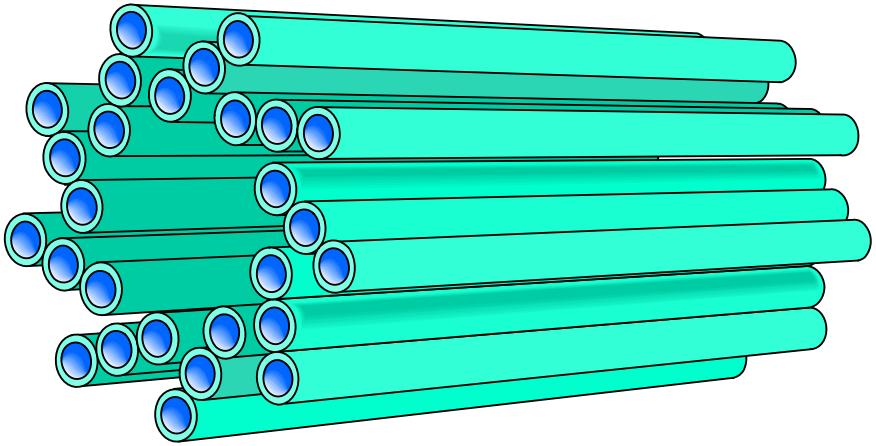
- The outer layer of a typical cell is primarily phosphatidylcholine (PC or lecithin) and sphingomyelin; the inner layer is primarily phosphatidylethanolamine and phosphatidylserine.
- The value of this is that the outer layer is a bit more rigid and the inner layer is more flexible, much like taking two sheets of corrugated aluminum roofing and layering them, then bending them.
- With the aluminum roofing, the inner layer seems to extend beyond the edges of the outer layer when it's bent.
- By making the inner layer of a membrane more flexible, it bends, as it were, to retain its alignment with the outer layer without extending beyond the outer layer.
- Cholesterol (ko LESS turr all) works with the rigidity of the membrane.



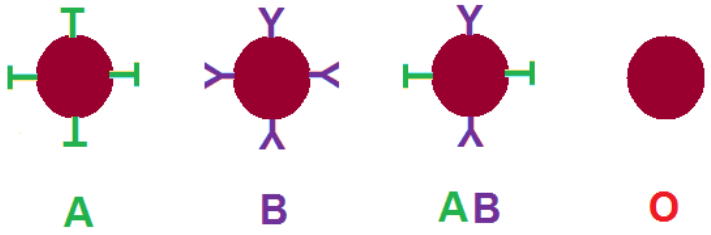
- There is also protein associated with the cell membrane:
  - peripheral proteins that are attached to either the inner layer or the outer layer of the membrane that act as receptors for molecules that are unable to get through the membrane and
  - integral proteins that are completely inserted through the membrane.
- The latter proteins are often-times ion channels, as their outer layer is hydrophobic and more interactive with the cell membrane, while the center portion is hydrophilic.
- This hydrophilic region allows ions to traverse the cell membrane to regulate ion balance inside and outside the cell.



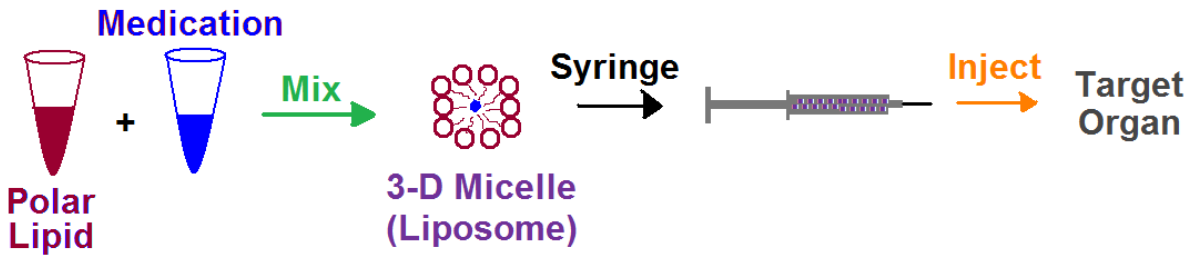
- Glycoproteins (GLY koe PRO teens; a combination of carbohydrate and protein) are also found on the surface of the membrane.
- As a general rule, these compounds are the compounds used for cell recognition or cell identification.
- Glycolipids are also found in the membrane.
- They tend to stabilize the structure of the membrane.
- Cholesterol is found in cell membranes, as well.
  - As a general rule, the more cholesterol in the membrane, the more rigid the membrane; the converse is equally true.



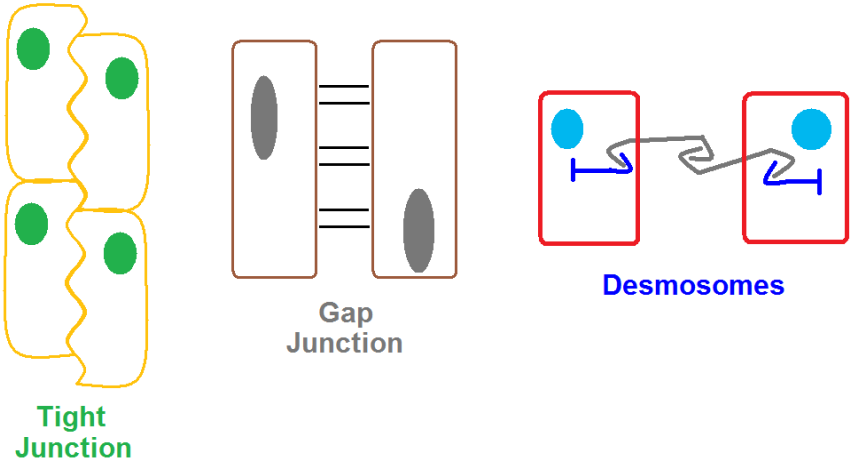
- Inside the cell, underneath the cell membrane is a system of microtubules that acts as the cytoskeleton.
- These microtubules provide a framework to give a shape to the cell.
- They also act as the cell's irrigation system - more on this, later.



- One use of glycoproteins by the body is as the antigens on the surfaces of red blood cells -- RBC.
- The illustration, above, shows that different glycoproteins provide RBC's with unique identifying markers.
  - RBC that are of the Group A persuasion have only that glycoprotein on their surfaces;
  - those with Group B have only the Group B glycoprotein;
  - those that are Group AB, have both glycoproteins;
  - those with Group O lack both glycoproteins.
- It is estimated that at least 85% of the population secretes soluble blood group substances in saliva, gastric juice, milk, seminal fluid, urine, ovarian cyst fluid and amniotic fluid.
- Indeed, before the invention of DNA testing, it was by these substances that people were determined to be at the scene of a crime.



- Pharmacologists, biochemists and physiologists have been studying the chemical properties of the various cell membranes in the human body in hopes of understanding how to use the information to make a carrier (called a liposome - fat sac or fat pocket) that will take a specific drug from a syringe, through the blood without enzymatic modification to a specific target cell or tissue.
- The figure, above, shows graphically how this, theoretically, occurs.
- A polar lipid that has the same characteristics as the membrane to which it is to migrate and traverse is mixed with the drug it is to carry.
- The polar regions of the lipid rearrange around the drug in such a manner that the apolar regions bind with the drug so that a three-dimensional cage is formed around the drug.
- This cage is called a micelle (MYE cell; liposome).
- The liposomes are then injected into the blood, travel to the target organ and keep the drug safe from blood enzymes that might inactivate it prior to getting to the target organ, tissue or tumor.
- There has been some success with this in the lab.



- Cells are connected to each other by one of three Intercellular Connections: Tight Junctions, Gap Junctions or Desmosomes.
- The Figure, above, illustrates each type of connection.
- Tight junctions occur by fusing membranes.
  - These are commonly found in the intestine and blood-brain barrier.
  - It is this kind of connection in the central nervous system that makes it so difficult to get drugs to cross the blood-brain barrier and, hence, to treat disorders of the nervous system.
- Gap junctions occur between cells to connect them by narrow channels and are separated by small spaces (synapses).
  - These are common in the nervous system.
- Desmosomes consist of filaments that surround the cell and cement or suture cells together
  - to form solid, "crumbly" tissues like the liver and kidney.

Cell Membrane Functions

- Cell membranes control the passage of substances across themselves
  - Selectively (allow some materials to cross without difficulty, e.g., water) and
  - Semipermeably (SE mye PER mee abb lee; restricts the passage of other compounds, e.g., glucose and proteins).
- The permeability of the cell membrane depends on a number of conditions:
  - 1) Membrane thickness: the thicker it is, the longer it takes the compound to cross the membrane;
  - 2) The size of the materials: tiny molecules like urea easily pass through the membrane, while slightly larger molecules, like glucose will not and very large molecules like proteins simply won't cross the membrane;
  - 3) Lipid solubility: like dissolves like, i.e., if the compound is soluble in lipid, it will cross the membrane easily; conversely, if the molecule is polar, it will not cross;
  - 4) Electrical charge: the time of crossing increases or decreases based upon the charge of the material AND the membrane;
  - 5) Active transport systems: more on this coming up;
  - 6) Binding sites: more on this coming up.

Transmembrane Movement

Passive Movements

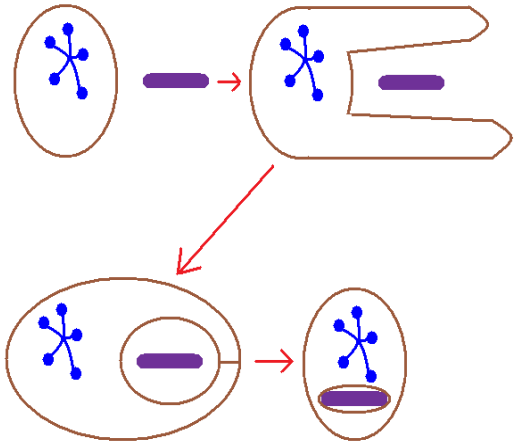
- Passive movements are caused by pressure or concentration changes WITHOUT the use of energy. Diffusion has already been discussed.
- Facilitated diffusion is defined as diffusion assisted by integral proteins in the membrane which act as carriers, e.g., glucose.
- Facilitated diffusion has a rate that is faster than diffusion, proper.
- The rate of facilitated diffusion is proportional to the concentration gradient,
  - i.e., if there is a lot more of a substance outside a cell than inside the cell, then the rate is rapid.
- It is proportional to the amount of carrier available,
  - i.e., if there are only 5 carriers and 500 molecules to be carried, then the rate of uptake will be very slow.
  - Conversely if there are 5000 carriers and 500 molecules, then the rate of uptake will be very rapid.
- The rate of facilitated diffusion depends on how quickly the carrier and substance combine,
  - e.g., insulin.
  - Insulin catalyzes the rapid binding of glucose to the glucose transporter to drive glucose inside the cell.
  - This is called enhancement and greatly increases the efficiency of glucose uptake into our cells.

Transmembrane Movement

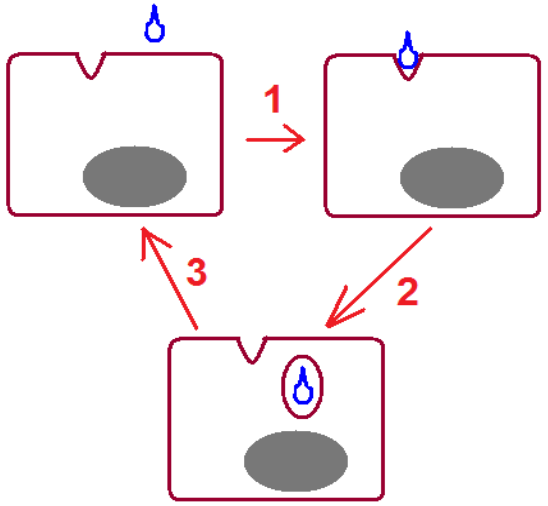
Active Movements

- Active movements are defined as those movements that are caused by the release of energy to move material across the membrane from low concentration to high concentration,
  - i.e., AGAINST or ACROSS a concentration gradient.
- These movements require energy in the form of ATP (Adenosine TriPhosphate; uh DENN o sin tri PHOS phate).
  - We use up to 40% of the ATP we synthesize daily for active transport.
  - Considering that we synthesize about 4 pounds of ATP per day, that comes to 1.6 pounds of ATP a day we use in these movements.
- Active movements require integral proteins, e.g., Glucose/Sodium (Na^+) transporter.

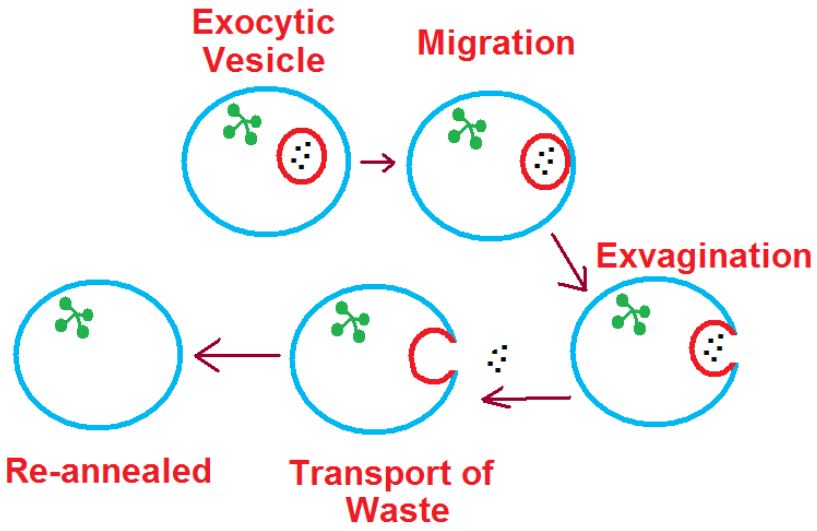
- The first active movement to be discussed is endocytosis.
- There are 2 sub-categories under this heading:
  - phagocytosis (FAGG oh sigh TOE siss; cell eating) and
  - pinocytosis (PEE noe sigh TOE siss; cell drinking).



- Phagocytosis is initiated by the recognition that something is where it's not supposed to be, e.g., a micro-organism.
- The cell responding (a white blood cell called a PMN) extends pseudopodia (sue doe POE dee uh; false feet) around the organisms or particle and then encloses the "object" with the pseudopodia to form a phagosome (FAGG oh some; an eating sac or eating pocket).
- The phagosome is internalized and it differentiates and fuses with a lysosome (LYE so some) and, presto!, the "object" is hydrolyzed.



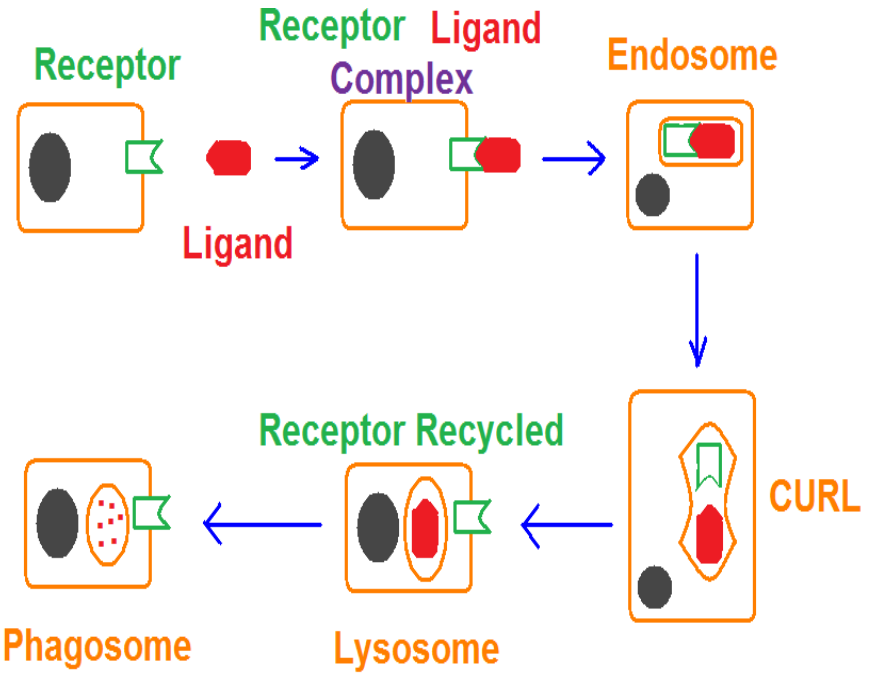
- Pinocytosis is similar to phagocytosis.
- Cell drinking begins with a water droplet "foraging" around on the surface of a cell.
- Once the water finds a small invagination (inn VAJ i NA shun), it falls into it and causes the membrane to change shape so that the pinosome (drinking sac or drinking pocket) is internalized and the water is sent to the appropriate compartment in the cell



- The next active transport mechanism to be discussed is exocytosis (getting something out of the cell).
- Exocytosis occurs when a cell has an excretion or a secretion it wishes to release.
- The exocytic vesicle containing the secretion or excretion migrates to the cell membrane where it fuses with the membrane, exvaginates and "dumps" out the particles, e.g. hormone, enzyme, waste.
- This is how pancreatic enzymes are dumped into the GI tract.
- Remember, this transport requires ATP, too.

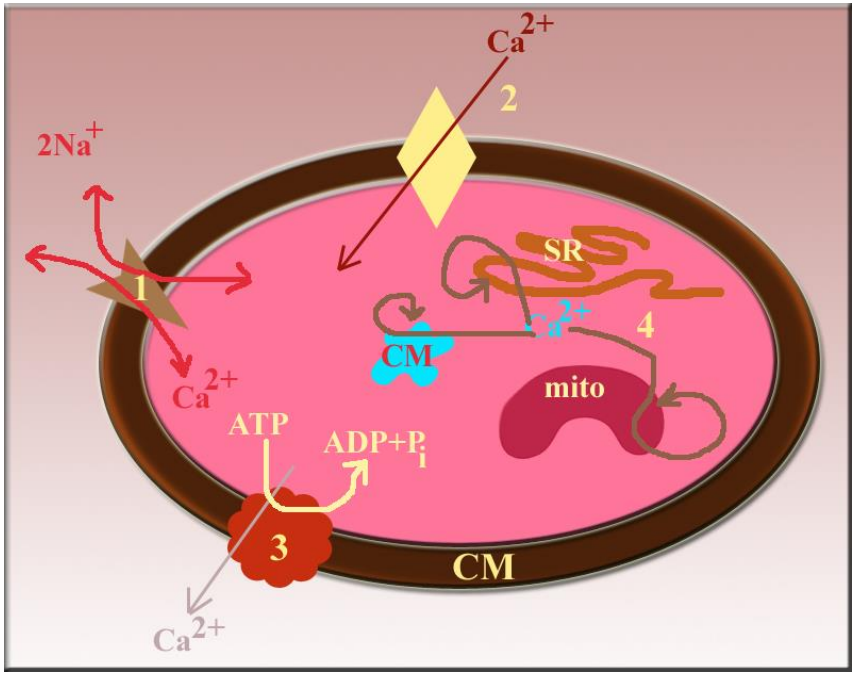
Receptor-Mediated Endocytosis

- Receptor-Mediated Endocytosis requires that the substance to be internalized have its own cell-bound receptor.
- The substance to be internalized is called a substrate (remember enzymes?).
- When the receptor (very specific - binds only one substance or one kind of substance based upon its R group – much like enzymes) binds the substrate, there is a change in the shape of this complex and it is called a receptor-ligand complex.
- The receptor-ligand complex is internalized into an endosome (an inside pocket or inside sac) which undergoes differentiation to a CURL (Compartment of Uncoupling of Receptor and Ligand).
- The receptor is recycled to the membrane for re-use while the ligand in its endosome fuses with a lysosome to cause the destruction of the particle.



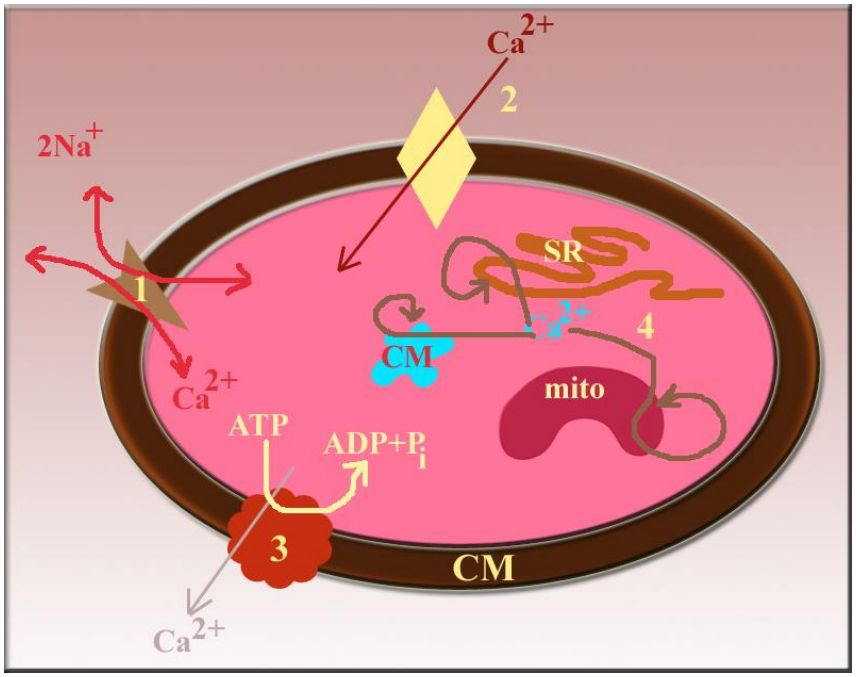
The Last Endocytic Movement for BIOL 190 – Ca^{2+} Transport Mechanisms

Sodium:Calcium Exchange: 1



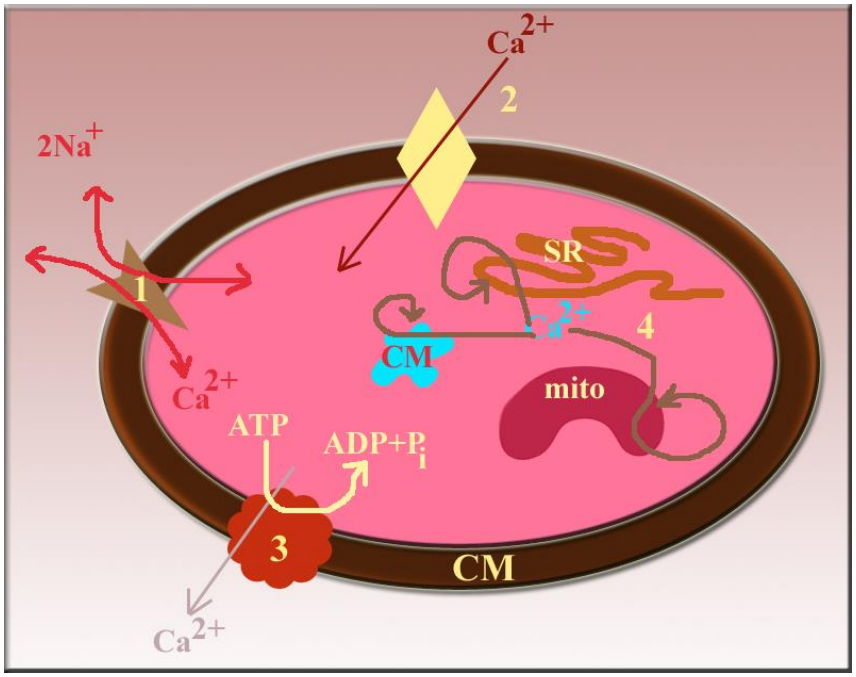
- Requires 2 sodium ions to go the opposite direction for every calcium ion that goes into or out of the cell, respectively.

Calcium:ATP'ase Efflux: 3



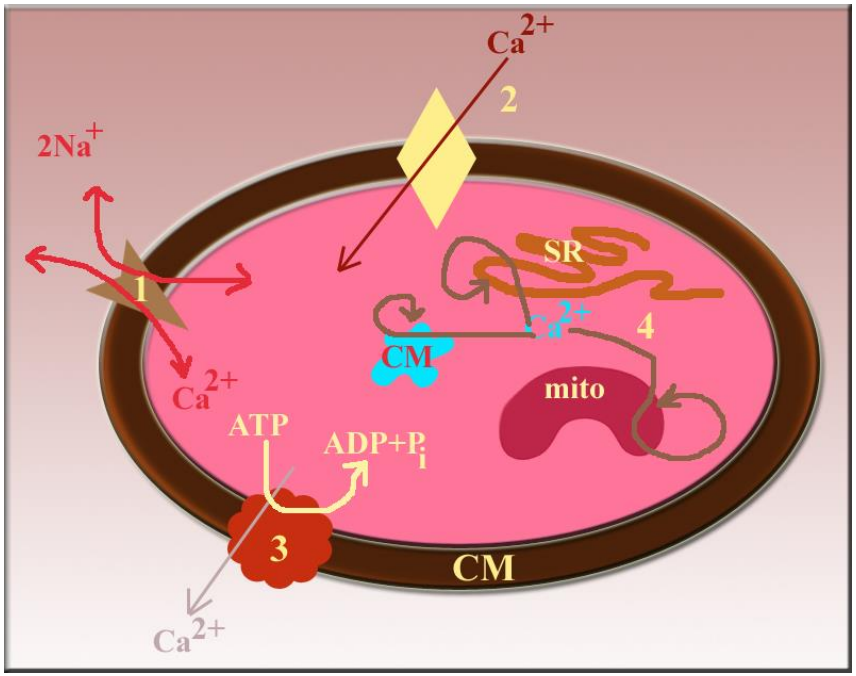
- an energy driven mechanism (at the expense of ATP) that removes calcium ions from our cells

Calcium Sequestration: 4



- an intracellular mechanism by which our cells sequester calcium ions by "tying" them up in the mitochondrion of the cell, the sarcoplasmic reticulum or by calmodulin

Receptor Mediated Calcium Ion Influx Mechanism: 2

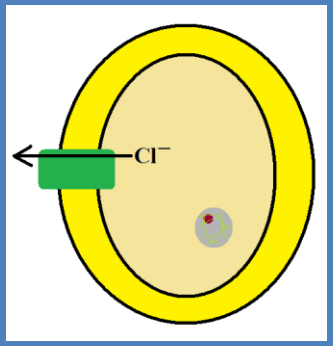


- The calcium ion channel we <u>can</u> control is the receptor-mediated calcium ion influx mechanism.
- We can turn them off using calcium ion channel blockers such as verapamil (Calan or Isoptin) which effects both smooth and cardiac muscle, diltiazem (Cardizem) which effects both smooth and cardiac muscle or nifedipine (Procardia) which effects smooth muscle.
- We can turn these channels on, as well, with drugs like nitrendipine (lowers blood pressure), nimodipine (causes cerebrovascular dilation) or amlodipine (lowers blood pressure).

Transporter Organization

Transporters to move ions, atoms or compounds back-n-forth through the cell are organized in one of three ways		
uniports (YOO nee ports)	symports (SIMM ports)	antiports (AUNT ee ports)

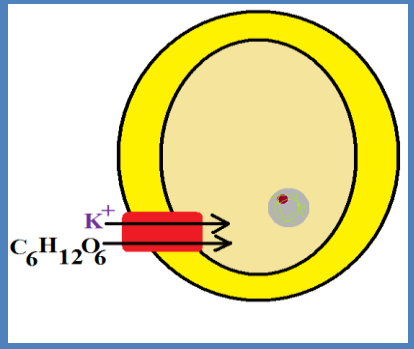
Transporters



Uniports are transporters that transport a single molecule across a membrane.

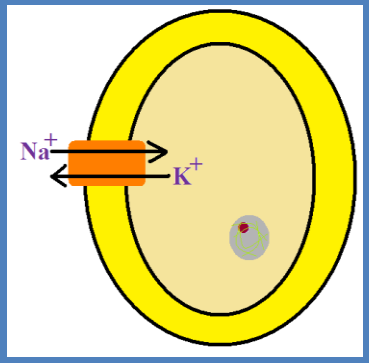
This is either facilitated diffusion or active transport.

One example of a uniport is a potassium ion uniport that moves potassium ions out of cells.



Symports are transporters that transport 2 different molecules that have to be bound to the symport in such a manner that the two particles are transported in the SAME direction.

One example of a symport is the sodium/glucose symport system in the small bowel that requires that both be bound for the adequate uptake of glucose from the lumen into the bowel endothelium.



Antiports do the opposite of symports, i.e., they transport two molecules in DIFFERENT directions.

A good example of an antiport is the ADP-ATP translocase that takes ATP from inside the mitochondrion and puts it in the cytosol and brings ADP from the cytosol into the mitochondrion so that it may be used to re-form ATP.

Grey thick bars are the intercalated disks;

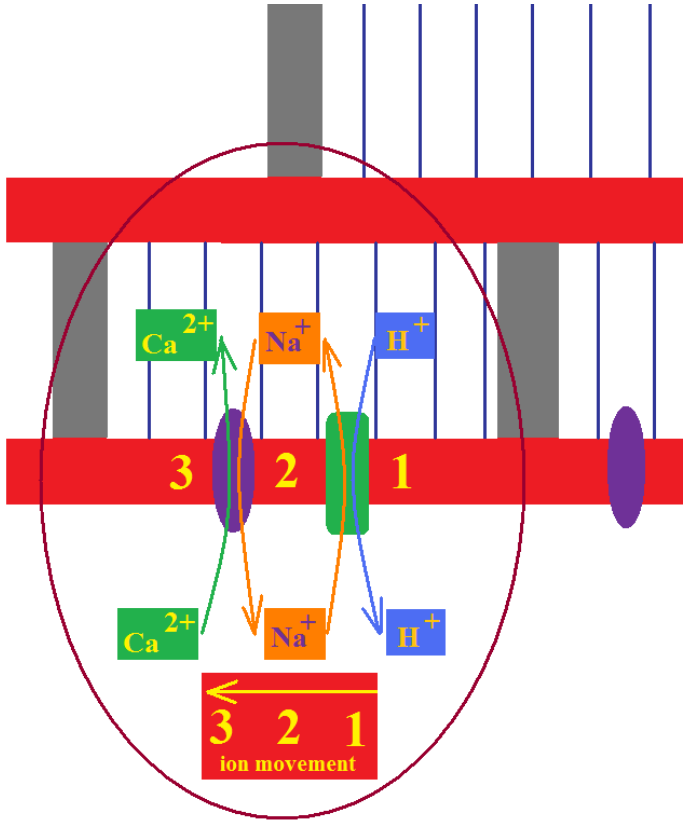
thin blue bars are the striations found in myocardiocytes;

red thick bars represent the cell membrane;

purple oval a Na^+ -- Ca^{2+} exchange transport protein;

green rectangle a H^+ -- Na^+ transport protein;

numbers in yellow indicate the direction of ionic transport



One of the biggest concerns clinicians have regarding heart health during a myocardial infarction (MI; heart attack) is that the $[H^+]$ may increase due to a build-up (and dissociation) of lactate and/or fatty acids, which may contribute to a metabolic acidosis in the heart muscle, which will thus kill more and more heart muscle.

This process is rendered even more critical in that as the H^+ are exchanged OUT of the cardiac cells to compensate for the intracellular metabolic acidosis, Na^+ and Ca^{2+} exchange occurs leading to excessively high levels of Ca^{2+} in the cells which may progress to further cell, and, hence, organ, death.

Local Anesthetics and Membranes

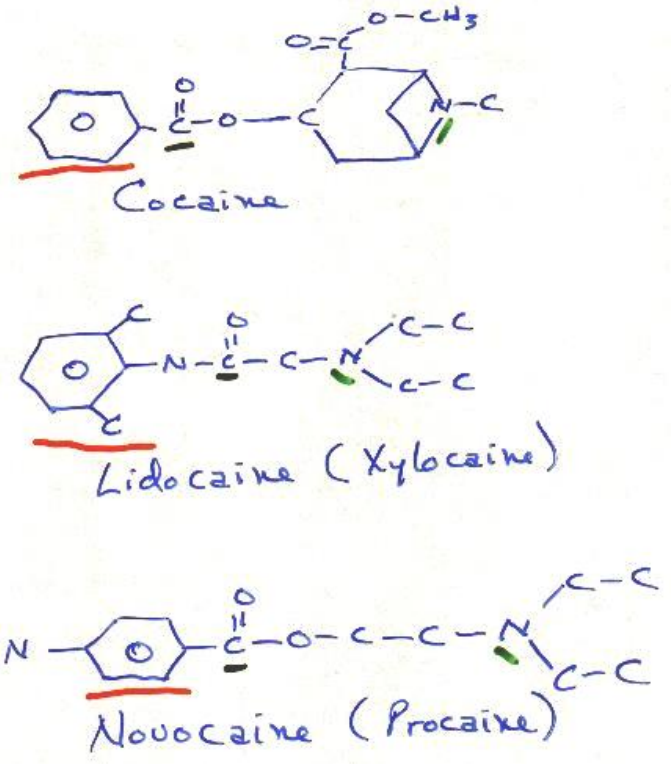
How local anesthetics work

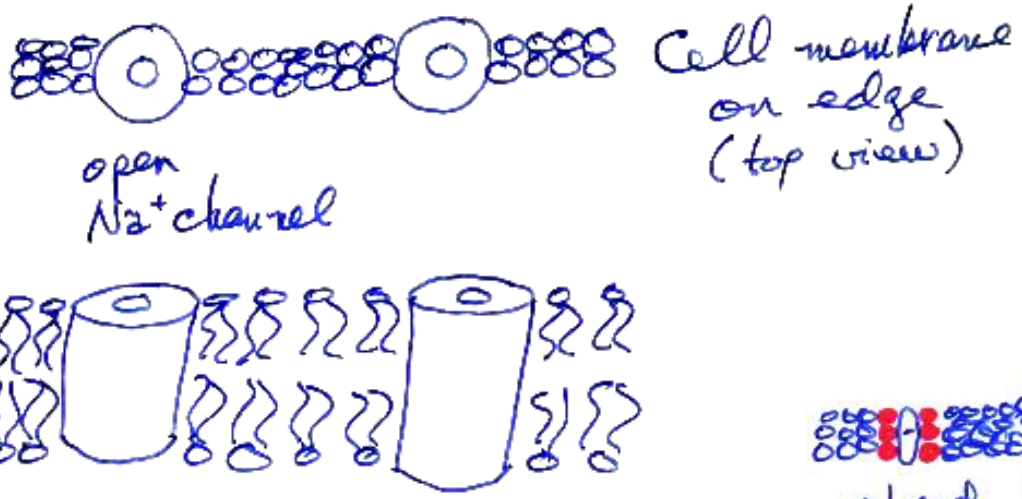
-- (members of the "caine" family in the graphic)

-- Note that the "caines" all have a benzene ring, a carbonyl carbon (C=O) and a tertiary nitrogen (N with 3 "things" bound to it).

-- With non-judicial use of these drugs, all are hyper-allergenic, including benzocaine, a common drug in over the counter (OTC) sunburn preparations.

-- Imagine a bad sunburn complicated by an allergic dermatitis caused by injudicious use of benzocaine.





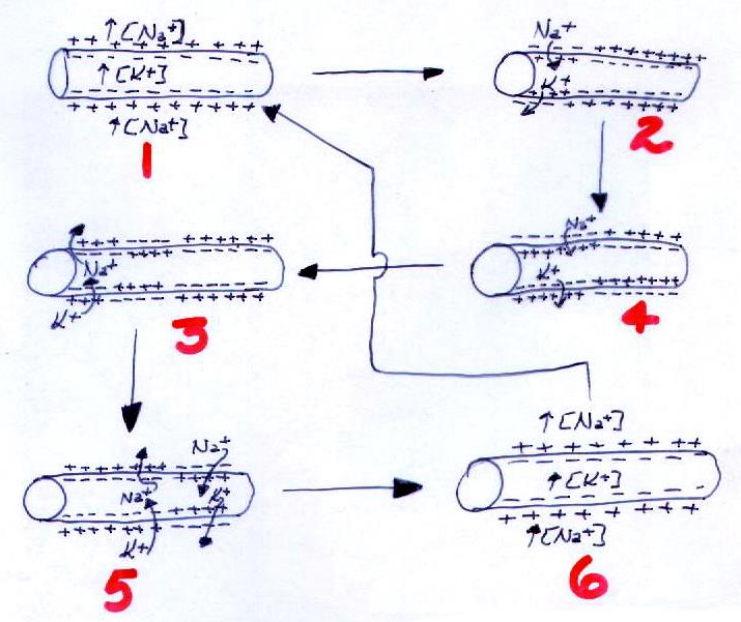
- All of the "caines" block sodium ion channels so that sodium ions can not get into the cell from the outside. This causes anesthesia, i.e., a lack of ionic movement cuts off the electrical activity we know as feeling pain.

- The "caines" also work by being lipid soluble. The "caines" pass into the membranes and then "swell". With this swelling, the sodium ion channels are compressed shut which blocks the sensation of pain, causing the sensation of numbness. Further information on how the "caines" block the sodium ion channel directly is covered in the neurological portion of A&P.

- Some cells, e.g., muscle cells, must be “hit with” a small electrical current – a way to think about this is to take a 9V battery and touch the terminals to your tongue.
- This current is called an “action potential”. The action potential – as long as you don’t get carried away with its intricacies – is pretty basic.
- It simply reflects the movement of sodium ions, potassium ions and the hydrolysis of ATP to form ADP and P_i.

- In general, for every 3 sodium ions that move across the membrane and for every 2 potassium ions that move across the membrane concurrently, 1 ATP molecule is hydrolyzed so that there is enough energy to drive the potential along the membrane.

The action potential is roughly illustrated and discussed below:



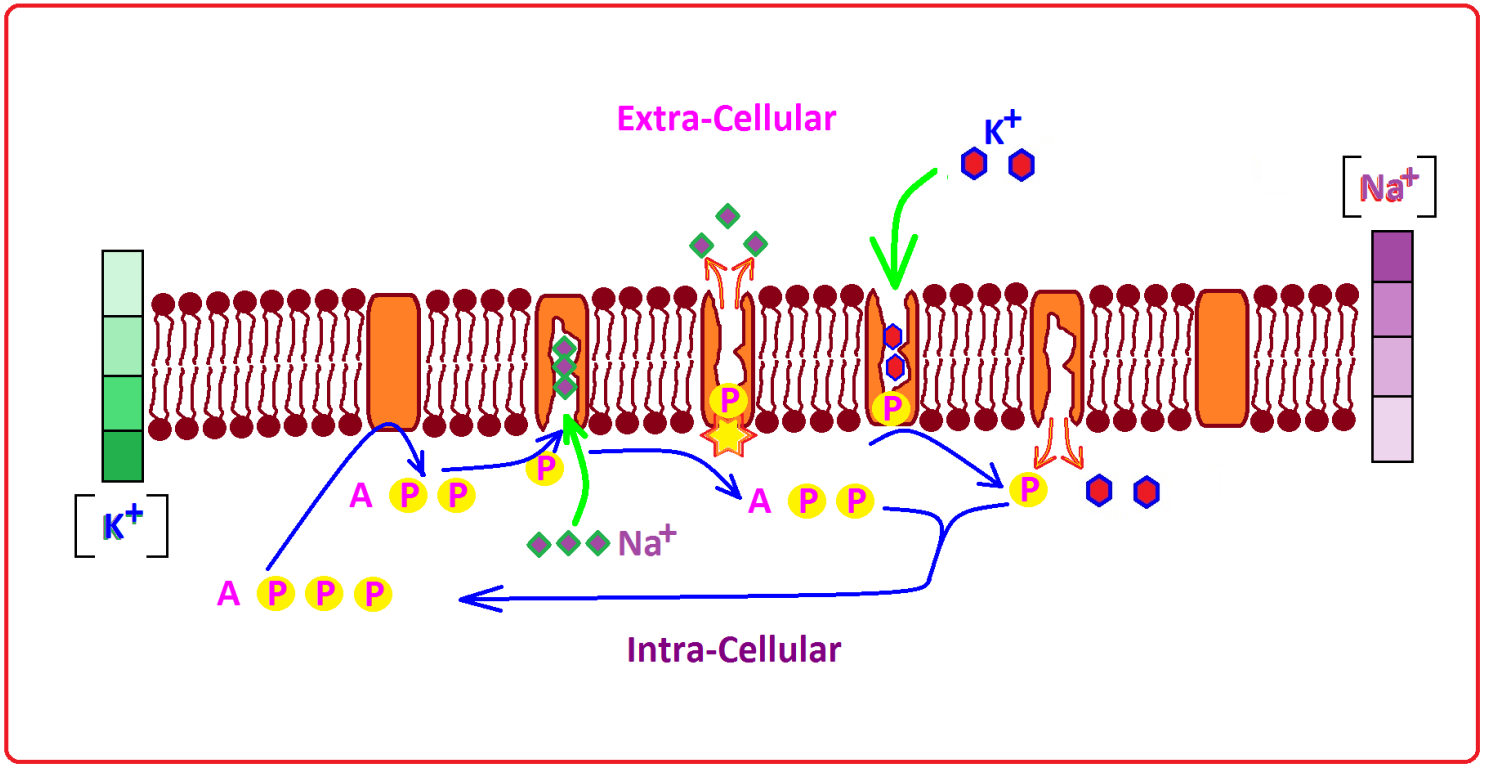
- Briefly, the action potential is sort of like the "wave" people do at sporting events – it just uses ions in this case.
- In cartoon #1, the membrane is resting – potassium ion concentrations are high inside the fiber and sodium ion concentrations are high outside the fiber.
- Once the fiber depolarizes (cartoon #2, above; this is equivalent to a muscle contracting), the sodium and potassium ions exchange places moving across the membrane.

- This movement causes part of the outside of the membrane to become negatively charged and the inside to become positively charged.
- The ion exchange (via the Na-K pump or Na-K ATP'ase) continues down the membrane (cartoon #4).
- Once depolarization has progressed far enough down the membrane, the ions are returned to their original spaces, i.e., Na^+ to the outside and K^+ to the inside of the membrane (cartoon #3).

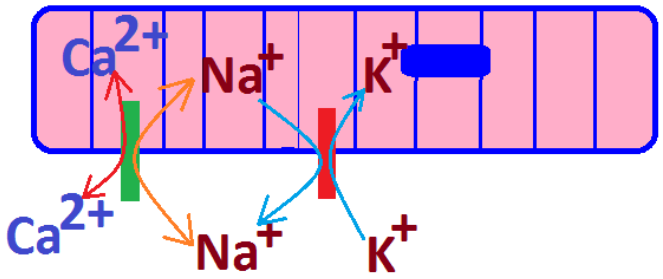
- This is called repolarization (this is equivalent to a muscle relaxing).
- The movement of ions continues along the membrane depolarizing and repolarizing the membrane (cartoons #5 and #6) until the full sequence has caused a neurotransmitter to be released and can rest (cartoon #1) until the next time it's needed to elicit a response.

Na-K ATP'ase

- Under resting conditions, Na^+ slowly leaks into the cells and K^+ leaks out of the cell.
- To maintain the concentration gradients for Na^+ and K^+ following an action potential, it is necessary to transport Na^+ out of the cell and K^+ back into the cell.
- The Na-K ATP'ase maintains the gradient AGAINST the gradient, i.e., the amount of Na^+ pumped out of the cell and the amount of K^+ pumped back into the cell are smaller than their final location concentrations.



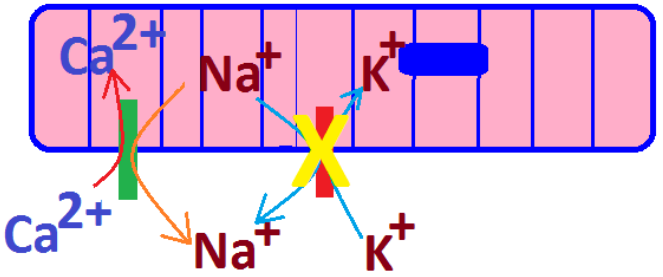
Na-K ATP’ase and Na-Ca Exchanger: Digitalis



Na-Ca Exchanger

Na-K ATP'ase

Plus Digitalis



K levels remain high outside the membrane.
Na levels elevate inside the cell.
Ca exchanges for the Na at a ratio of 1:2.

Ca binding to TnC increases contractility (inotropy).

Putative mechanism of Dig preps activity.

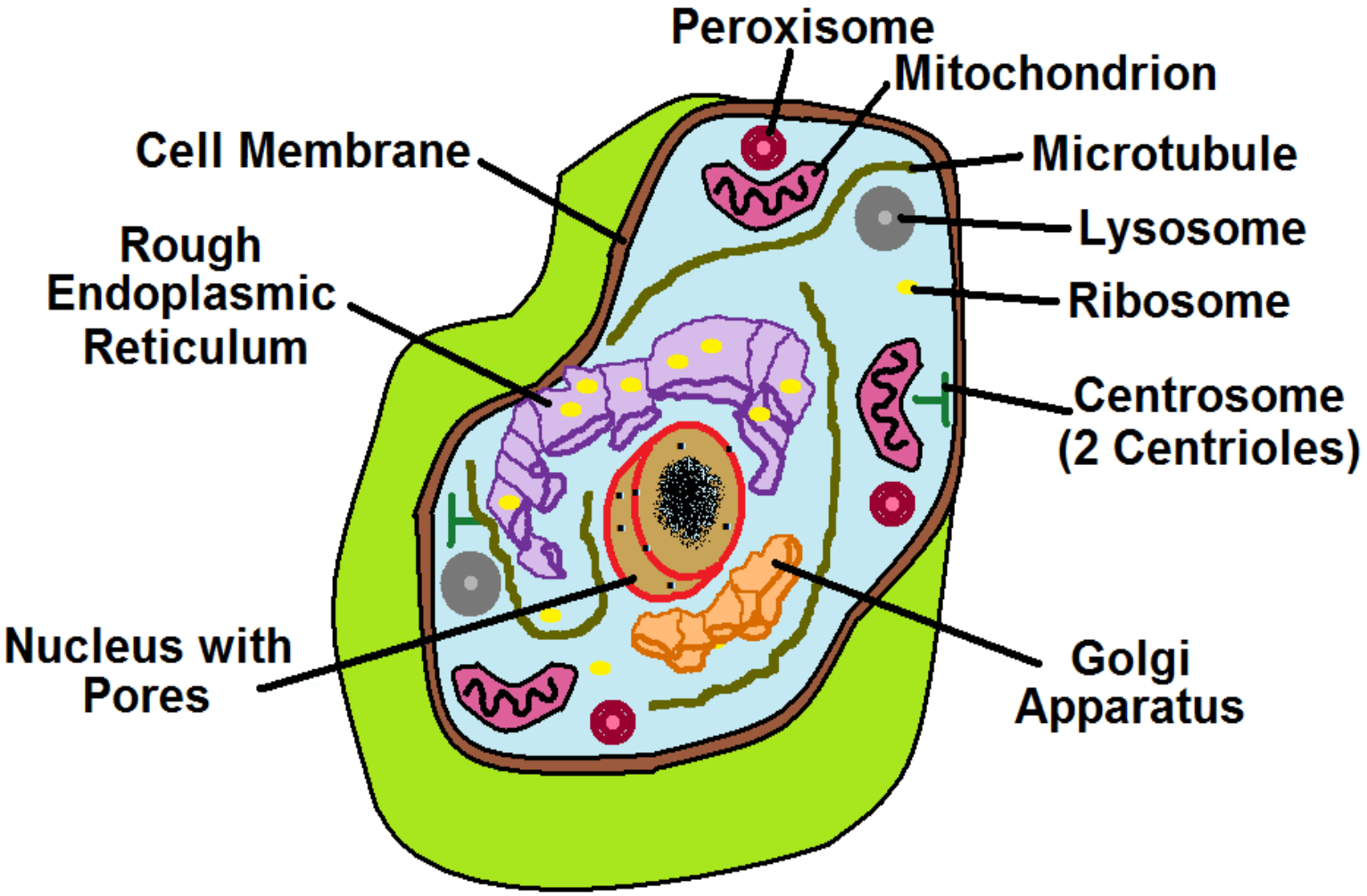
Part II -- The Cytosol

- The cytosol is also known as the cytoplasm.
- This is the primary region of the cell where reactions occur.
- There are three types of metabolic reactions that we're interested in:
  - catabolism (reactions that destroy nutrients for energy production),
  - anabolism (reactions that cause our bodies to store up nutrients for future use, i.e., "bulking up") and
  - amphibolic (reactions that can “run” either direction)

- The cytosol contains subcellular organelles (oar gan ELLS; little organs smaller than the cell).
- These organelles guarantee compartmentalization,
  - i.e., that there are specific areas in the cytosol where specific reactions will occur in such a manner that there will be no interference from any other [competing] reactions.
- These organelles are permanent and are metabolically active.
- The latter means that the reactions of the Embden-Myerhof-Parnas pathway (EMP or glycolysis), hexose monophosphate shunt, electron transport and protein synthesis occur in either the cytosol or in the specific subcellular organelle - more on this later in metabolism in A&P II.
- These organelles are also self-reproducing.
- This is of significance, for example, in muscle tissue or in heart muscle tissue:
  - as we exercise to improve our muscle tone or aerobic capacity, these tissues must be able to grow with us.
  - So must the subcellular organelles to provide us with the necessary biochemical pathways to support the new growth and activity of our bodies.

- The cytosol also contains inclusions:
  - for storage (e.g., glycogen),
  - for waste (e.g., urates) and/or
  - for raw materials for cellular activity (e.g., fat, pigment granules).
- In addition, the cytosol contains salts that help maintain the ionic environment of the cell and maintain the pH of the cell.
- Enzymes,
  - bound (which allows for enzyme orientation in the case of sequential reactions;
  - bound to internal membranes and/or to filaments) and
  - free (dissolved in the cytosol) are located here, as well.

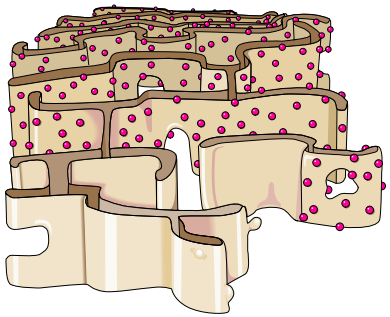
The Subcellular Organelles

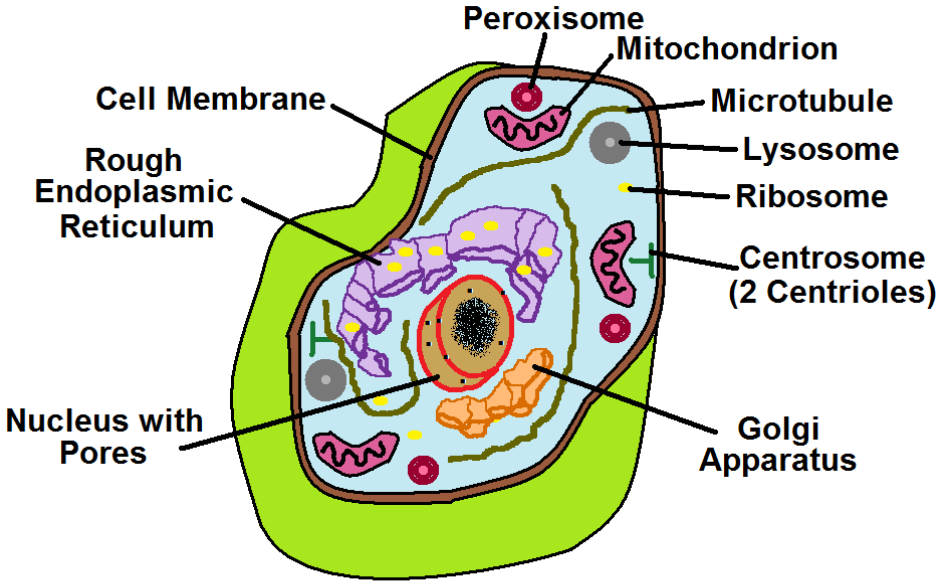


Smooth Endoplasmic Reticulum not Illustrated Here

Rough Endoplasmic Reticulum

- For protein synthesis;
- high numbers of these in
  - antibody-producing cells,
  - liver cells,
  - pancreatic cells





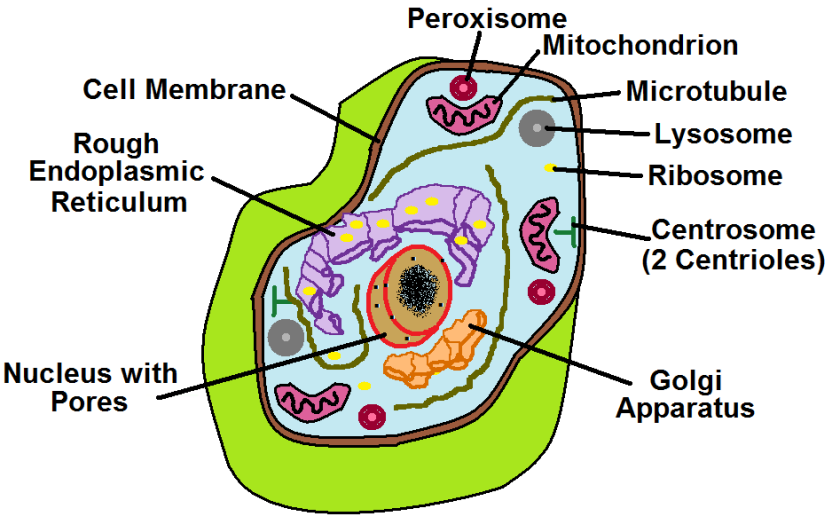
Smooth Endoplasmic Reticulum not Illustrated Here

- For steroid synthesis and complex carbohydrate synthesis; in liver (detoxification center)

Smooth Endoplasmic Reticulum

Ribosomes

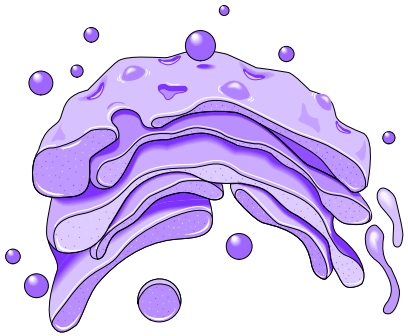
- protein synthesis; bound ribosomes to the endoplasmic reticulum; free in cytosol (remember, too, that the consistency of the cytosol is like jelly - NOT water); proteins are synthesized on ribosomes, then transported in the tubular endoplasmic reticulum to the Golgi apparatus

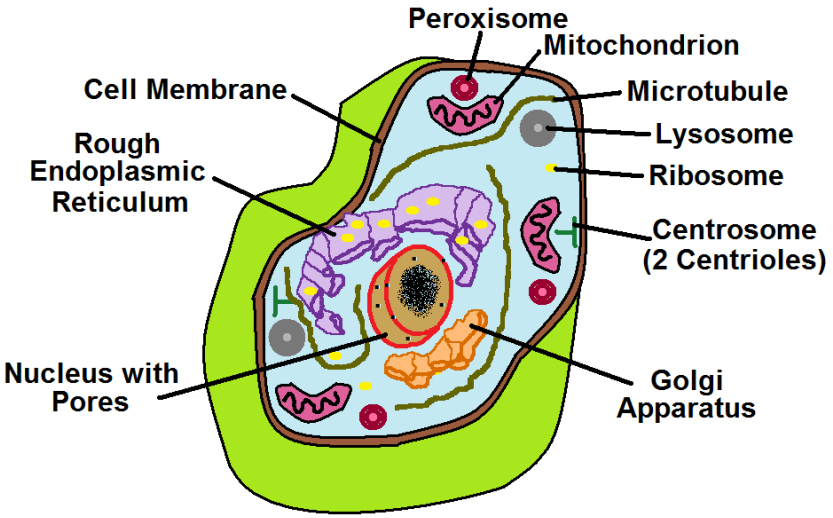


Smooth Endoplasmic Reticulum not Illustrated Here

Golgi Apparatus

- located near nucleus; used in protein packaging; synthesis of glycoproteins, glycolipids, mucus; proteins come in one side of Golgi and go out the other; high levels in liver and pancreas

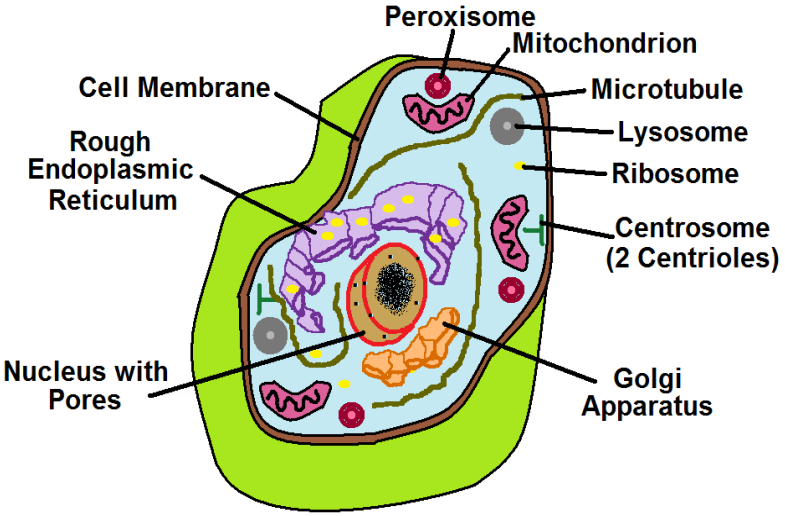




Smooth Endoplasmic Reticulum not Illustrated Here

Lysosomes

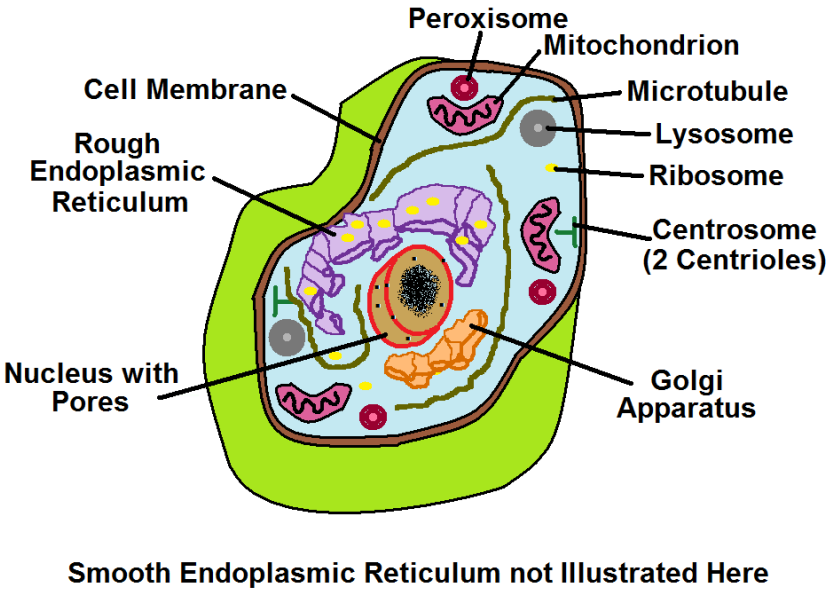
- Suicide sac of the cell; has powerful hydrolytic enzymes; implicated in cell death and digestion due to increased intracellular release; implicated in rheumatoid arthritis; very acidic contents.
- Gold therapy for rheumatoid arthritis
  - 1) inhibits lysosomal enzymes directly by stabilizing lysosomal membranes;
  - 2) lymphocyte responses to mitogens/antigens are inhibited by gold in culture;
  - 3) monocyte activity decreases after gold therapy
- all of which lead to reduced joint erosion



Smooth Endoplasmic Reticulum not Illustrated Here

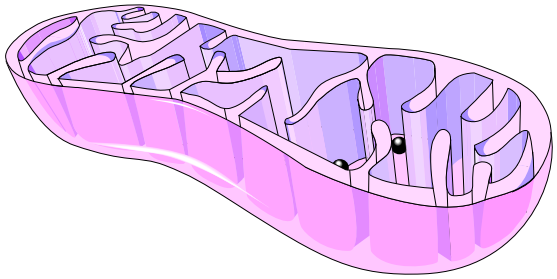
Peroxisomes

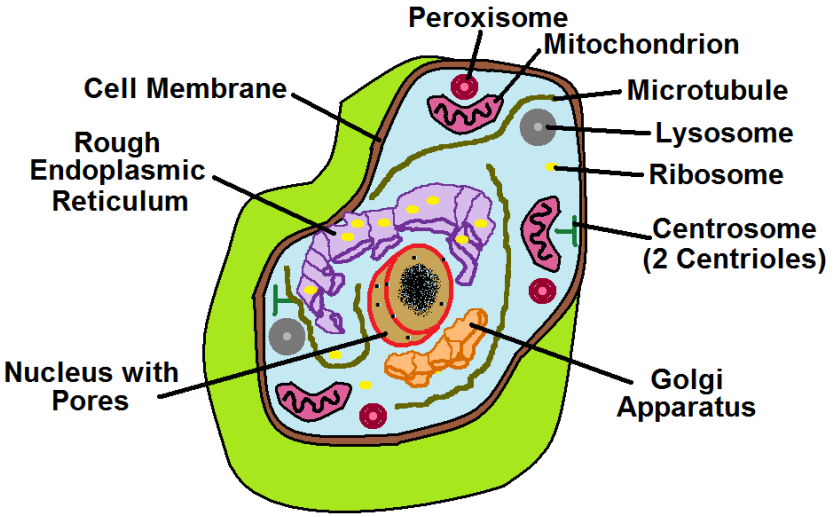
- produce hydrogen peroxide; catalase is also present which hydrolyzes hydrogen peroxide to oxygen and water; protects the rest of the cell from the toxicity of the hydrogen peroxide; found primarily in the liver and kidney



Mitochondrion

- "powerhouse of the cell";
- double membrane system; ATP synthesis, urea synthesis, lipid oxidation;
- it's the ONLY organelle to contain its own DNA,
- BUT still requires nuclear DNA to function;
- there is a theory that mito were originally bacteria that got trapped in the primordial goo from which cells arose.
- Contain 5 complexes necessary for ATP synthesis

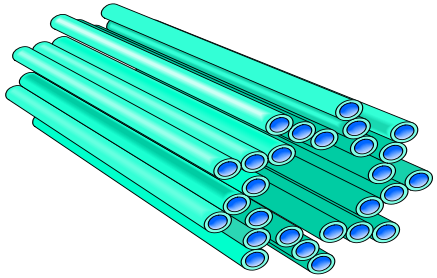




Smooth Endoplasmic Reticulum not Illustrated Here

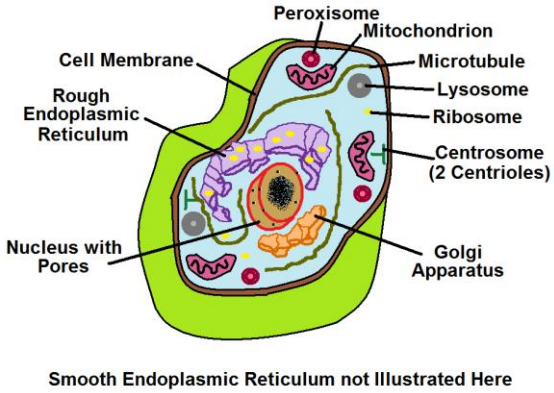
Microtubules

- used to make the cytoskeleton;
- aka microfilaments;
- used for irrigation system of cell;
- used in cell division

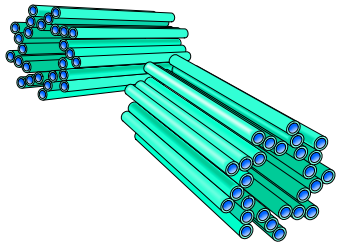


Centrioles

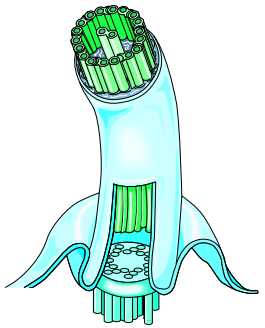
A **centriole** is a small set of microtubules arranged in a specific way.
There are nine groups of microtubules/centriole.
Two **centrioles** are generally perpendicular to each other.
The **centrioles** are found in pairs and move towards the poles of the nucleus during cell division.



- consists of 2 **centrioles**;
- used in cell division;
- used to form cilia and flagella which move materials across cell surfaces (lungs) or propel cells in fluid (sperm)



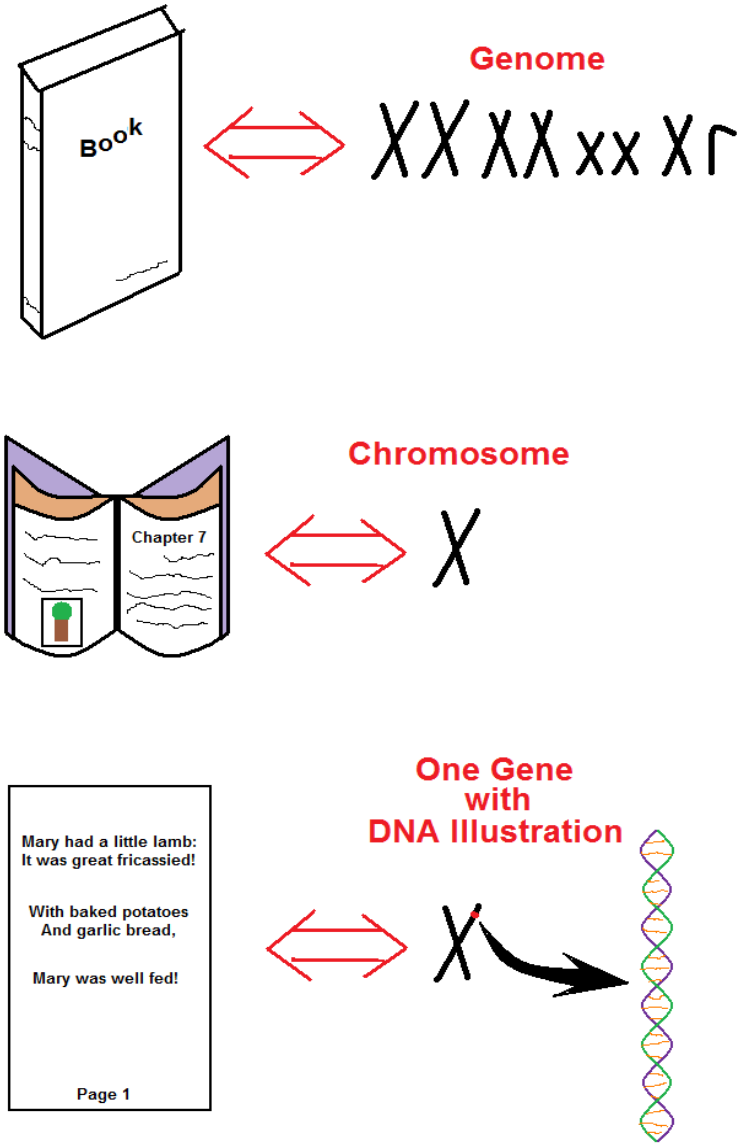
Cilium



Centrosome

The Nucleus

- The nucleus is the "brains" of the cell.
- It provides the direction of cellular activity.
- The nucleus is surrounded by an envelope with pores.
- The nuclear envelope contains the nucleolus (new KLEE oh luss) which consists of ribonucleoprotein) and karyolymph (CARE ee oh limph; the cytosol, if you will, of the nucleus).
- The nucleus also stores the DNA, isolating it from the rest of the cell in eukaryotes.
- The figure, right, illustrates a simplified way in which to view DNA, i.e., from a book analogy.
  - The book represents the entire genome (collection of chromosomes);
  - one chapter represents one chromosome;
  - one page represents one gene (DNA sequence of the gene).



TRANSCRIPTION

- DNA is the blueprint for the cell, coding for everything that that cell will do throughout its lifetime.
- There is one bit of a problem, however.
- That is the fact that DNA is
  - 1) isolated from the rest of the cell,
  - 2) it's too large to leave the nucleus and
  - 3) as the cell is designed, the DNA is incapable of directly running the show.
- To solve this problem, there are enzymes in the nucleus that "read" the DNA in such a manner that the DNA is used as a template for the synthesis of another macromolecule, RNA.
- When the DNA is used as a template for RNA synthesis, this is called transcription.

TRANSLATION

- The RNA is small enough that it is able to leave the nucleus through the nuclear pores and go out into the cytosol.
- This movement of the RNA is the "message" sent by the DNA to initiate many events in the cell, hence this form of RNA is called messenger RNA (mRNA).
- mRNA binds with ribosomes on the rough endoplasmic reticulum (rER).
- When it binds on the rER, it initiates a cascade of events called protein synthesis or translation.
- In short, the ribosome acts as a sort of zipper handle, sliding on the mRNA.
- As the ribosome reads a set of three (3) nucleotides in the mRNA sequence, it interprets this triplet to code for a single amino acid.
- As each triplet is read, another form of RNA transfers the specific amino acid to the mRNA-ribosome complex to perpetuate translation.
- This type of RNA is called transfer RNA (tRNA).
- This process of amino acid addition is called translation, or protein synthesis.

Listed below in the table is an incomplete list of codons for some of the amino acids:

Triplet Code (Codon with Amino Acid -- NOT Inclusive)		
AGA = Arg	CCC = Pro	CUA = Leu
AAG = Lys	CAC = His	CGA = Arg
AAC = Asn	UAC = Tyr	UGG = Trp
ACA = Thr	AGC = Ser	UGC = Cys
GAU = Asp	AUA = Ile	GUG = Val
GAA = Glu	GGG = Gly	UUU = Phe
CAA = Gln	AUG = Met (Start)	GCA = Ala
UAA = Stop "Ochre"	UAG = Stop "Amber"	UGA = Stop "Opal"

Note that, in some instances, the difference between amino acids is one (1) nucleotide in the triplet, e.g.,

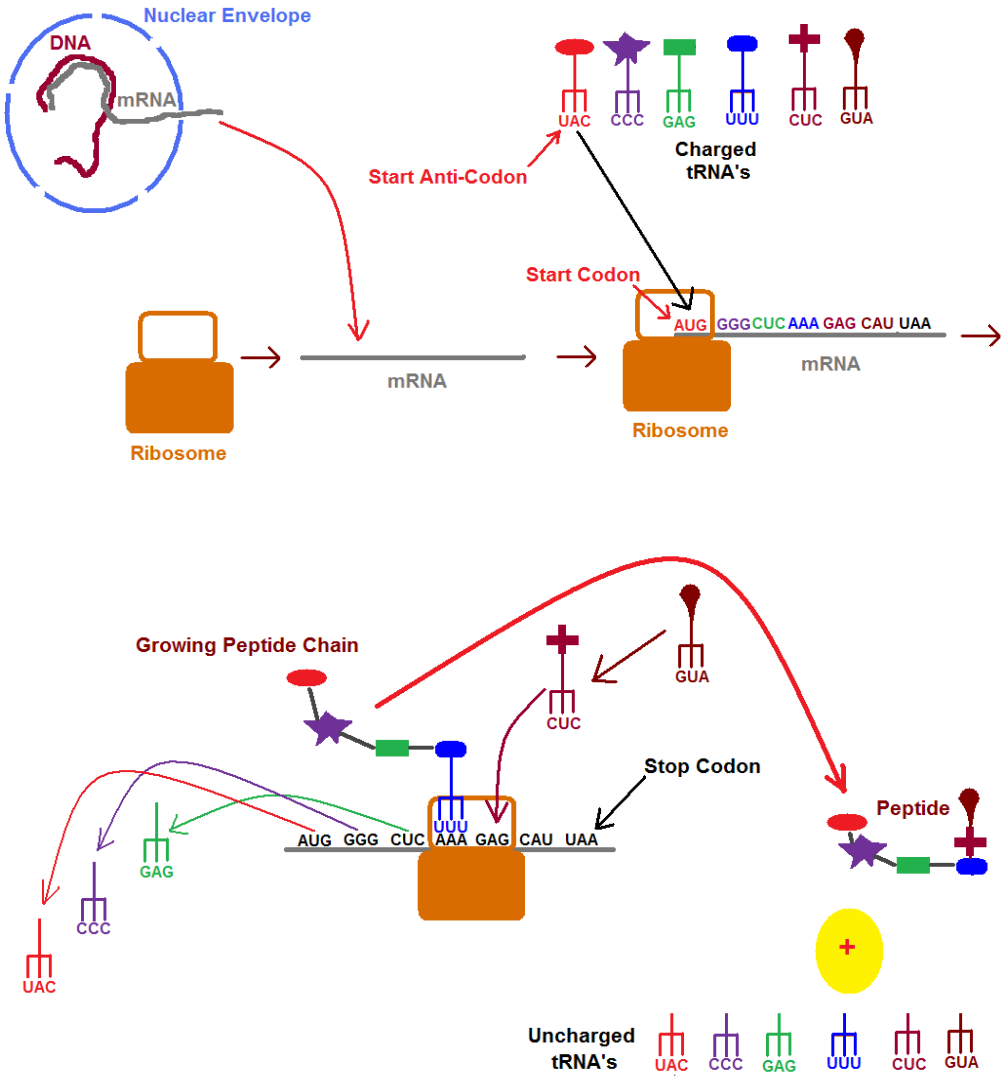
- mRNA sequence: AUG-CAC-AGA-CCC-UGC-UAA
-
- amino acid sequence:

(Start) Met-His-Arg-Pro-Cys-Stop

-
- If you alter this sequence by placing an "**A**" after 9 bases, the new sequence is:
- mRNA sequence: AUG-CAC-AGA-**A**CC-CUG-CUA-A__
- New amino acid sequence:

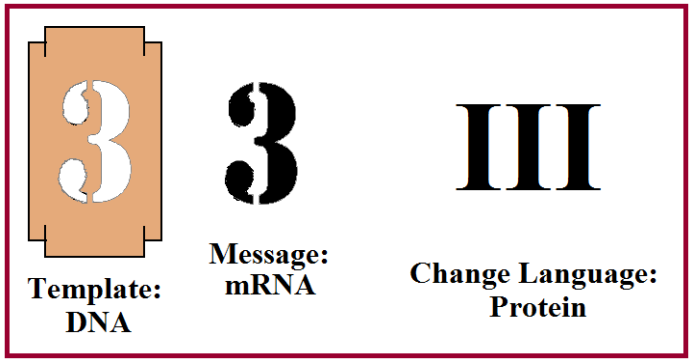
(Start) Met-His-Arg-Thr-Leu-Leu-----

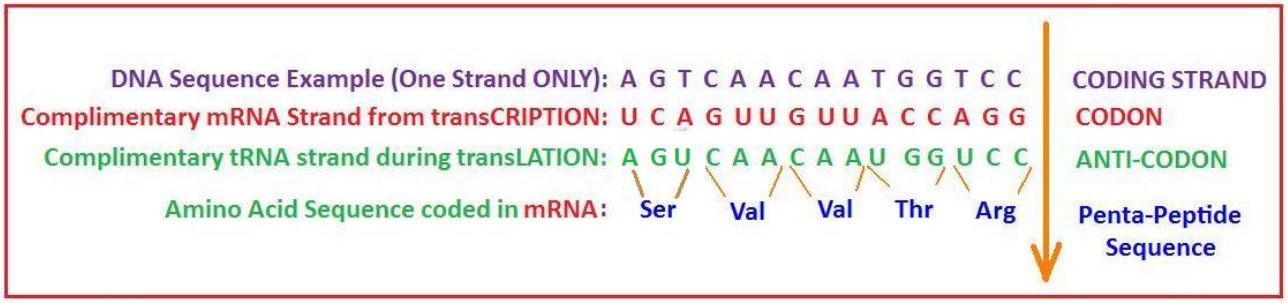
- One shift, one base change alters the whole protein after the insertion of the "**A".** We'll discuss this more in the near future. In the mean time, the process of using the mRNA to synthesize proteins is called translation and that's the next chapter.

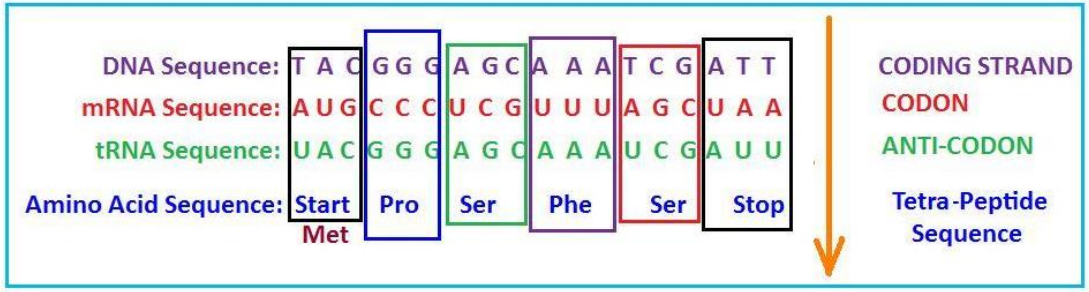


Graphically –

DNA → mRNA → Ribosomes → tRNA → Protein


3
3
III
Template:
DNA
Message:
mRNA
Change Language:
Protein

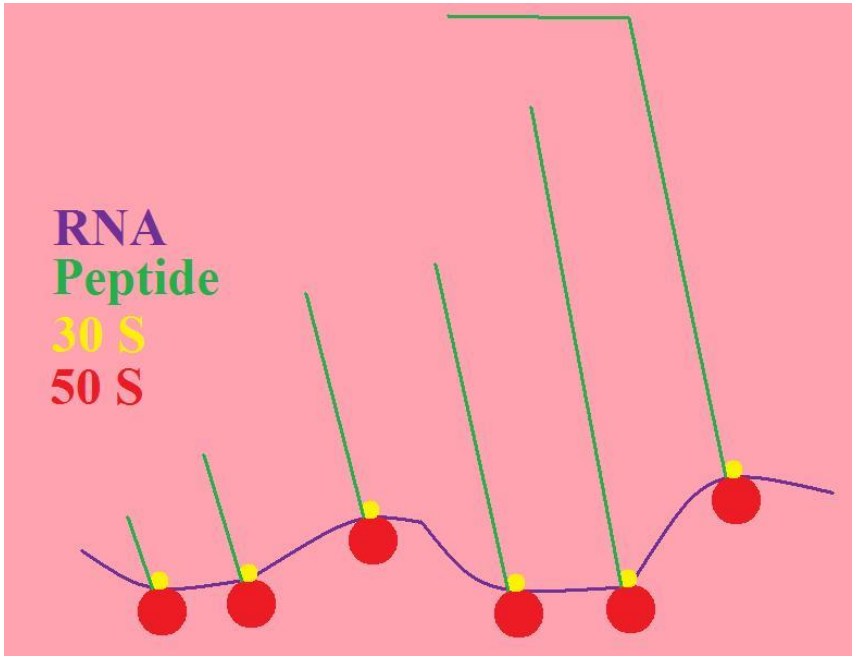

DNA Sequence Example (One Strand ONLY): A G T C A A C A A T G G T C C
CODING STRAND
Complimentary mRNA Strand from transCRIPTION: U C A G U U G U U A C C A G G
CODON
Complimentary tRNA strand during transLATION: A G U C A A C A A U G G U C C
ANTI-CODON
Amino Acid Sequence coded in mRNA:
Ser
Val
Val
Thr
Arg
Penta-Peptide
Sequence


DNA Sequence: T A C G G G A G C A A A T C G A T T
mRNA Sequence: A U G C C C U C G U U U A G C U A A
tRNA Sequence: U A C G G G A G C A A A U C G A U U
Amino Acid Sequence: Start
Met
Pro
Ser
Phe
Ser
Stop
CODING STRAND
CODON
ANTI-CODON
Tetra-Peptide
Sequence

Energy Requirements and Perspective of Translation:

-
- 2 ATP's are required to charge each amino acid
- 2 GTP's are required to elongate per elongation step
- 1 calorie = the energy necessary to raise 1 gram of water by 1° C
- 2 ATP's and 2 GTP's give approximately 28,000 calories of energy: this is equivalent to the energy necessary to raise 28 liters of water 1° C.
-
- In short, it takes LOTS of energy to synthesize proteins.
- A portion of that energy has to do with how the proteins are sequentially synthesized: once 25 amino acids (more or less) are linked by peptide bonds during translation, the AUG site is available/exposed for binding by ANOTHER 70S ribosome. This new ribosome initiates ANOTHER round of translation, *ad nauseum*.

- Eventually, the mRNA is literally smothered by ribosomes every 25 or so amino acids, i.e., about every 75-80 nucleotides on the mRNA.
- This smothered mRNA by ribosomes is called a polysome or polyribosome.

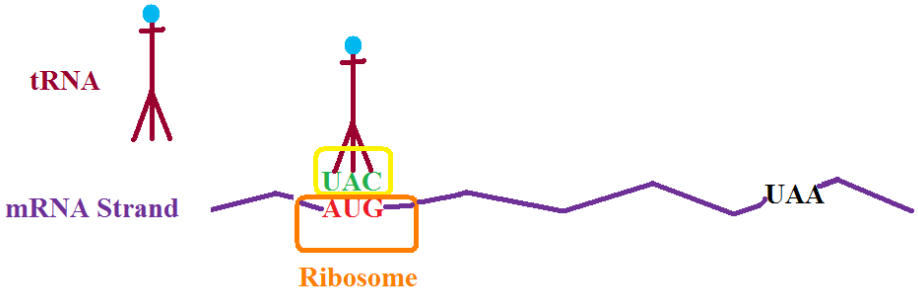


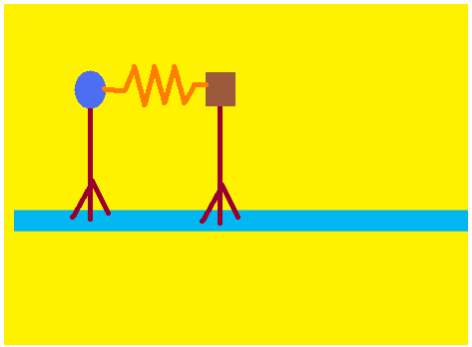
- This is the general form of the "translation unit in all cells".
- Polysomes increase the rate of translation per unit of time as compared to 1 ribosome on a mRNA strand – and translates 5’ to 3’ (left to right in graphic).

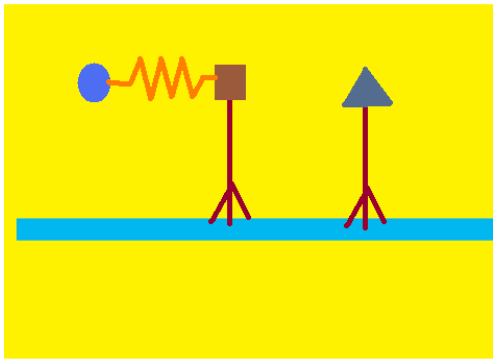
- Each amino acid has its own tRNA; tRNA's are constantly re-cycled for re-use during translation.
- As the ribosome continues to read more of the mRNA, more amino acids are brought in by the corresponding tRNA and the peptide chain grows.
- Eventually, the ribosome reaches a triplet sequence known as the stop sequence on the mRNA.
- When the ribosome reaches this sequence, the peptide is "snipped" from the mRNA-ribosome complex, packaged, processed and transported to the proper cellular locale.

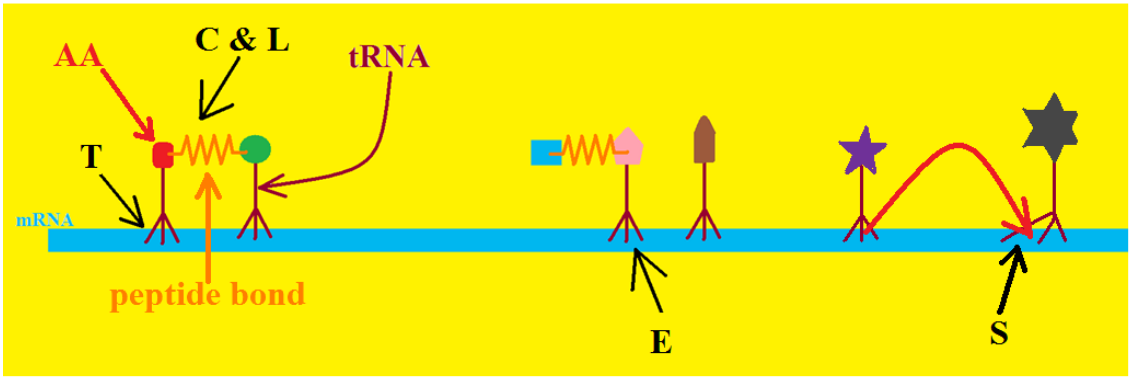
- Once translation is completed, one of at least 4 modifications will occur to the protein[s] (called post-translational modification):
  - 1) glycosylation -- addition of carbohydrate to the protein;
  - 2) phosphorylation -- add a phosphate;
  - 3) proteolytic cleavage -- proteins may be synthesized in an inactive form and require cleavage to become active, e.g., insulin and C-peptide. C-peptide is the portion from pre-insulin that is cleaved to leave active insulin;
  - 4) sub-unit binding -- quaternary structure formations, e.g., the 4 sub-units of hemoglobin binding together, myoglobin subunits binding together, the 3 subunits of arginase binding together.

- Translation is inhibitable (**normal translation = top and middle 2 graphics**).
- That very fact makes it of significance to any one going into health care as many micro-organisms are capable of being killed by translation inhibitors (**bottom graphic**) such as chloramphenicol (C), tetracycline (T), streptomycin (S), lincomycin (L) and erythromycin (E) to name five.
- C inhibits/blocks peptidyl transferase,
-
- T inhibits binding of charged tRNA to the A site of the ribosome,
- S blocks proper codon-anticodon binding to cause different peptides to be synthesized,
- E inhibits the translocase and
- L blocks peptidyl transferase and blocks tRNA from binding, although not at the same time.









Normal Cell Division

- The nucleus regulates cell growth and reproduction, as well.
- The cell cycle consists of 4 discrete periods – coming shortly.
- Cell division occurs when the cells reproduce themselves.
- Somatic cell division (body cell division) occurs when a parent cell produces 2 identical daughter cells.
  - The division of the nuclear material is called mitosis;
  - The cytoplasmic division is called cytokinesis.
- The daughter cells have the same number and the same kind of chromosomes (KROME uh somes) as does their parent cell.

- Somatic cells contain 46 chromosomes (2N), which are also equal to 23 pairs of chromosomes for ALL activities of the cell.
- In a sense, 23 chromosomes are duplicate.
- "N" or "n" describe the number of different chromosomes within the nucleus.
- Somatic cells contain 2 sets of each chromosome.
- These cells are called diploid (DYE ploid) cells and are identified, as well, by 2N or 2n.
- In diploid cells, 2 chromosomes in a pair are called homologous chromosomes.
- Cells that contain 2N chromosomes contain 22 pairs that are autosomal (regulate the body) and 1 pair of sex chromosomes (X and X or X and Y for female and male, respectively).
- The chromosome number does NOT double in meiosis, rather, it halves producing haploid cells: N, n or 23 chromosomes.

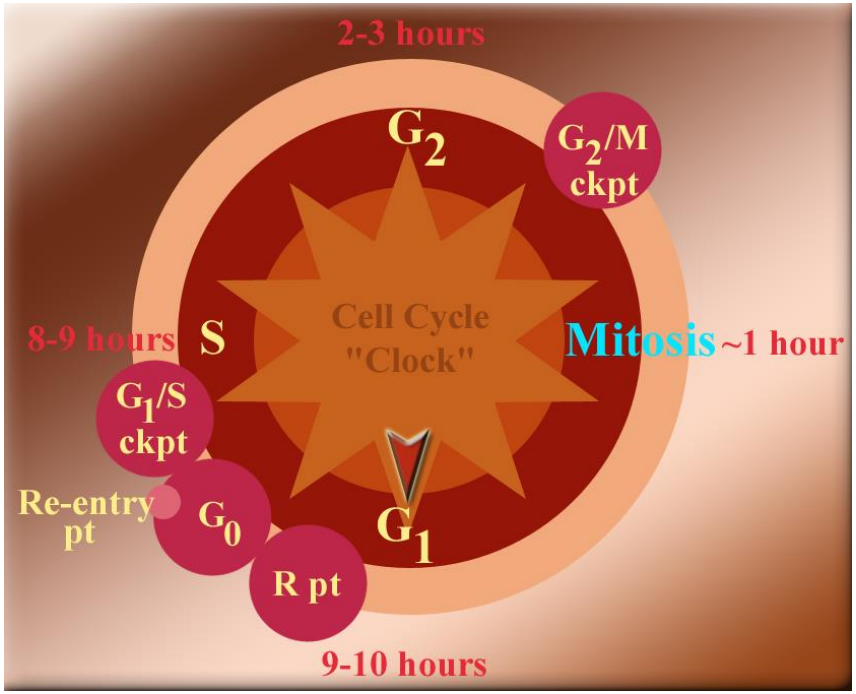
- Reproductive cell division also has division of its/their nuclear material.
- This is called meiosis (my OH siss); cytokinesis (sigh to kunn EE siss)also occurs.
- When a parent cell divides by meiosis, haploid cells are formed.
- It is by this mechanism that spermatogenesis (spur ma toe GEN uh siss) occurs in the testes and oogenesis (oh oh GENN uh siss) in the ovaries.
- There are two (2) successive nuclear divisions in meiosis:
  - reduction division (meiosis I) and
  - equatorial (or equational) division (meiosis II).
- In terms of the reproductive cell divisions, the sex cells are called gametes (GAMM eets).
- In the female they are also called ova; in the male, sperm.
- Union/fusion of gametes is called fertilization and forms a zygote.

Cell Reproduction

Cell Cycle

G_1 Phase

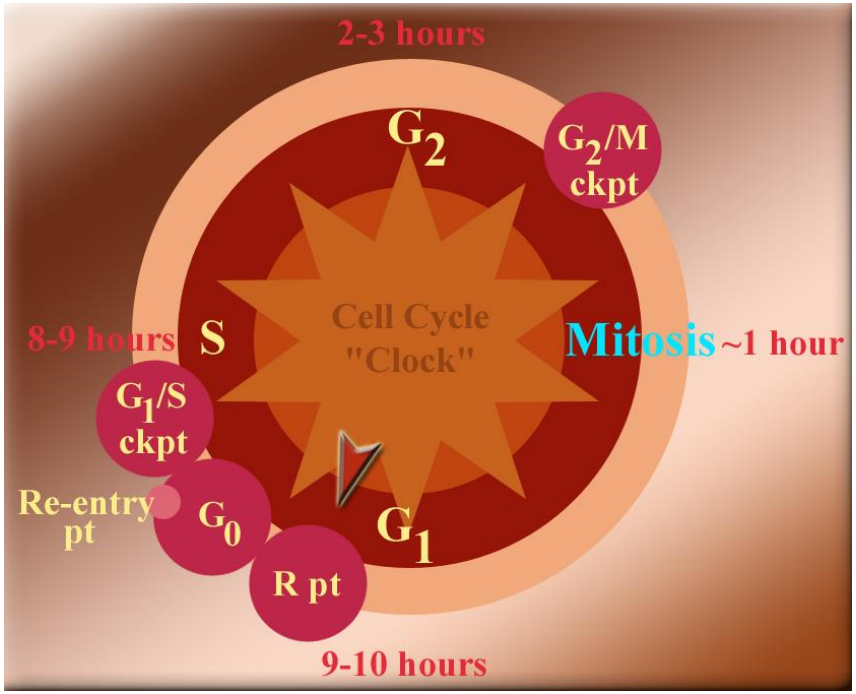
G_1 phase
~ 8-10 hours in length
Growth phase
Increased metabolism occurs; Gaps in DNA synthesis
Cells that will NOT divide, again, are stopped in this phase, e.g., nerve cells



G_1, S and G_2 phases are collectively known as Interphase. During these three phases, chromosomes replicate, centrosomes and centrioles replicate, RNA synthesis and protein synthesis increase.

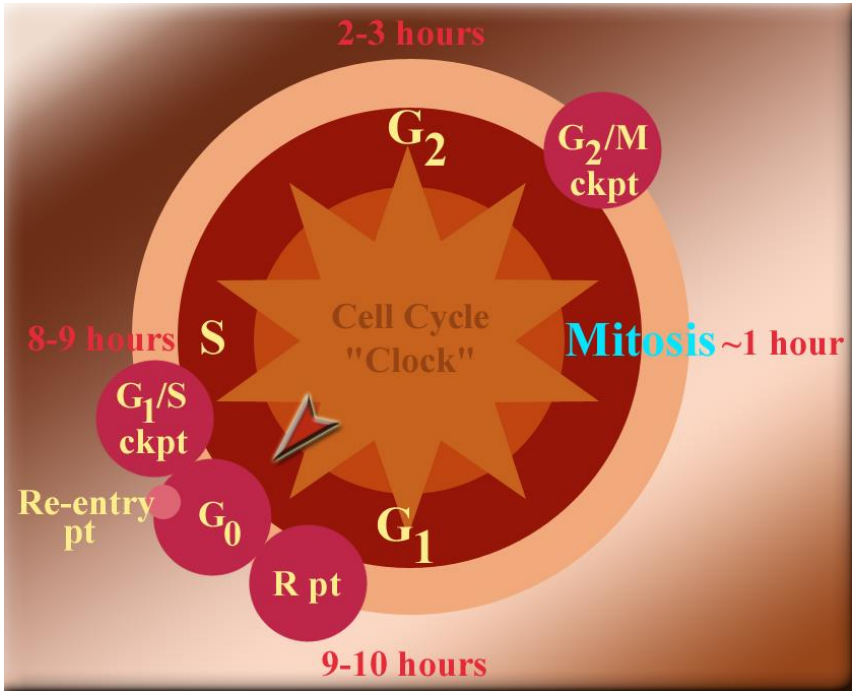
Restriction Point (R point)

R point
Restriction point: is a decision point; cell decides to grow or quiesce [for later stimulation to regain entry into the growth cycle]



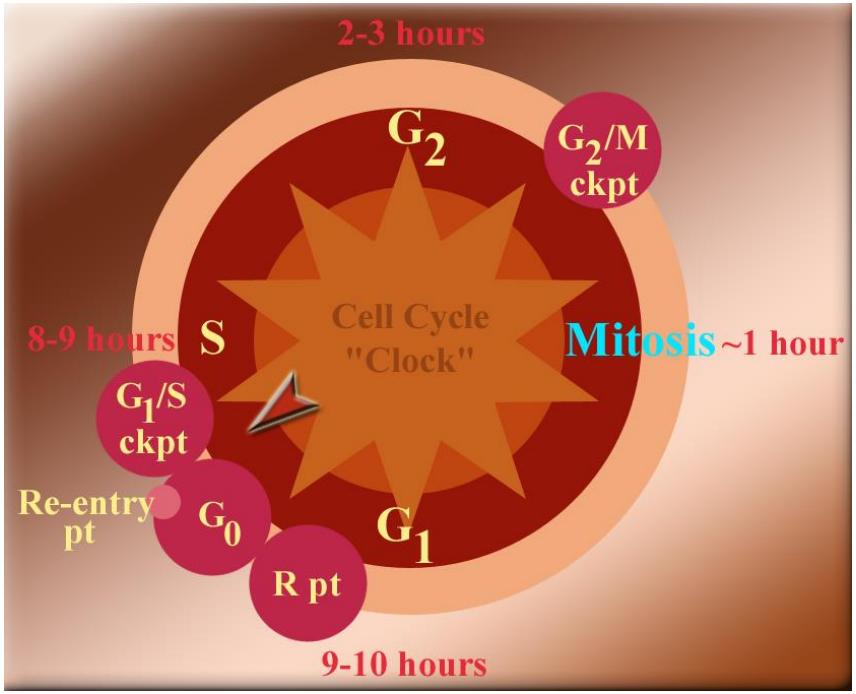
G_0 Phase

G_0 phase
Cells that come here are not proliferative; are viable; have metabolic activity; quiescent; cancer cells avoid this stage; Recently, research has shown that some nerve cells that enter here actually DO re-enter interphase



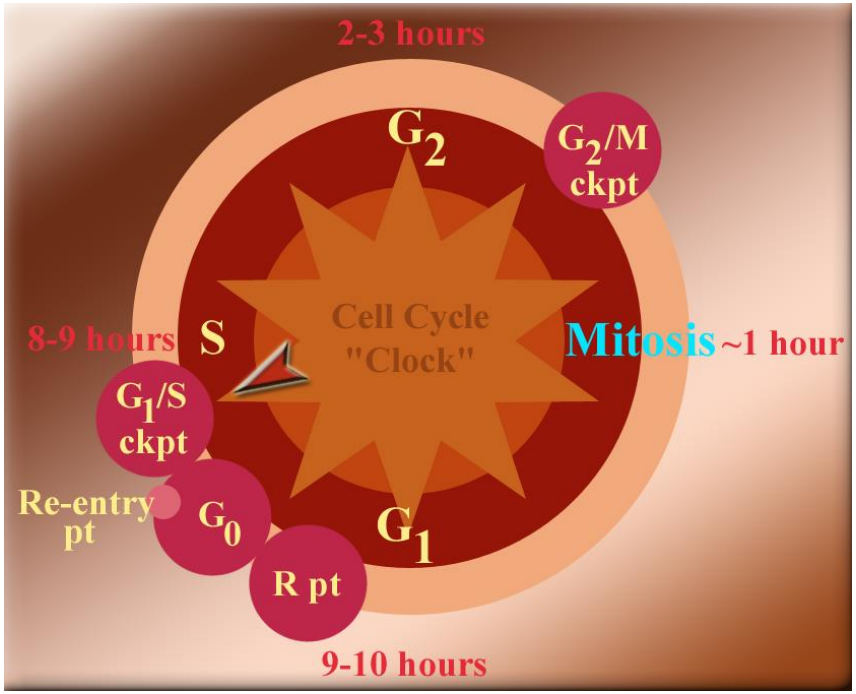
Re-entry Point

Re-entry point
The point where previously quiescent cells are stimulated to leave G_0 and re-enter the cell cycle



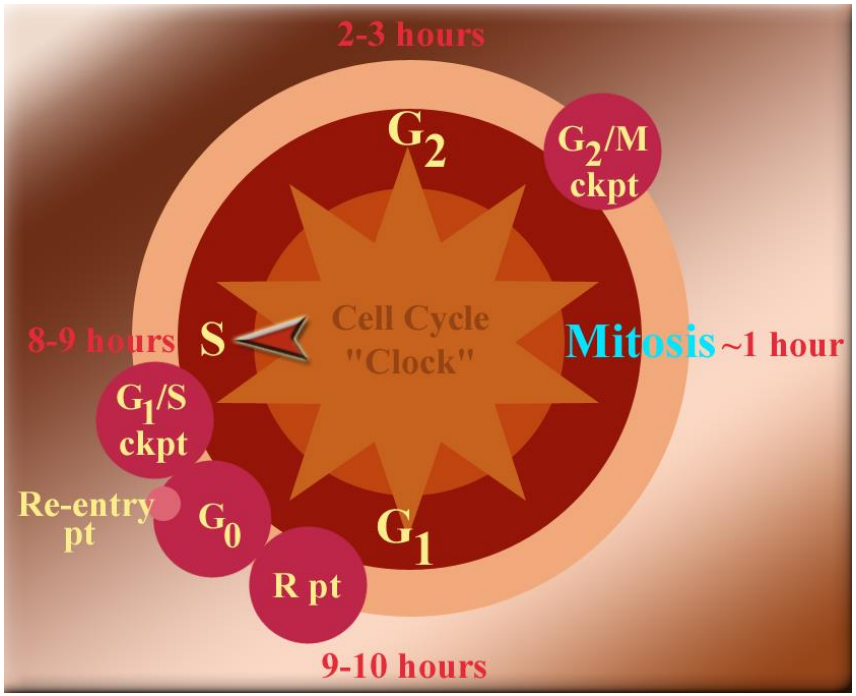
G_1/S Checkpoint

G_1/S checkpoint
A transition point; 1) to make certain enough time has passed since last mitosis, OR 2) cell is big enough to cause DNA synthesis, THEN go to S phase (uses a protein kinase)



S Phase

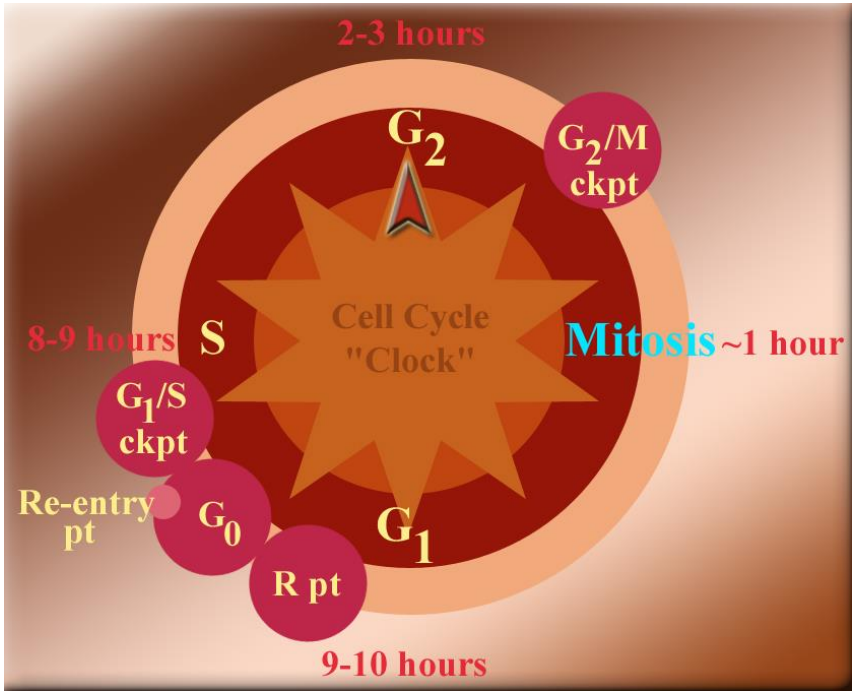
S phase
~ 6-9 hours in length
Synthesis phase
Chromosomes replicated
Once a cell is in this phase, it is committed to replicate



G_1, S and G_2 phases are collectively known as Interphase. During these three phases, chromosomes replicate, centrosomes and centrioles replicate, RNA synthesis and protein synthesis increase.

G_2 Phase

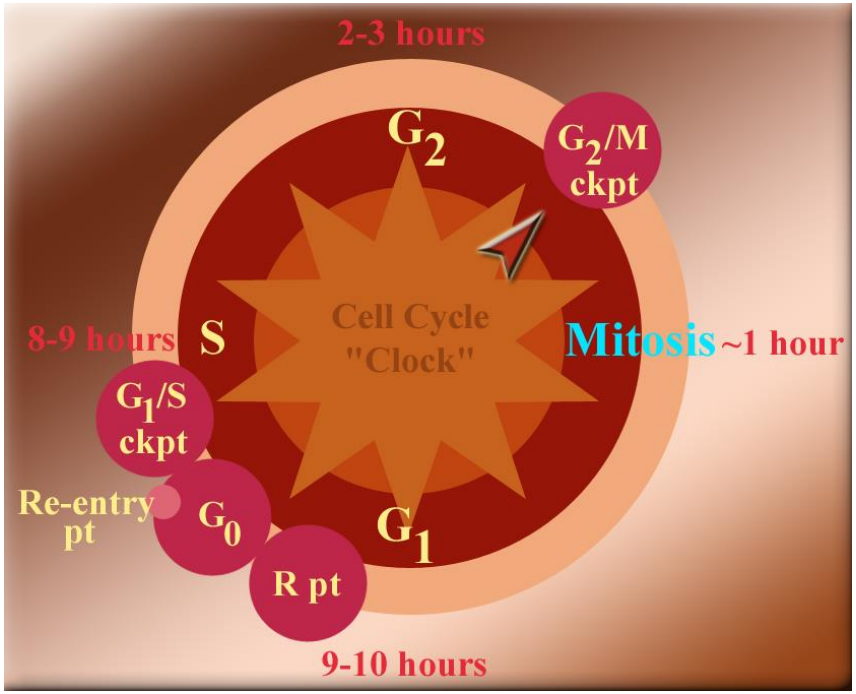
G_2 phase
~ 2-6 hours in length
Growth phase
Increased metabolism occurs; Gaps in DNA synthesis filled in
Cell volume increases about two-fold greater than it was in G1



G_1, S and G_2 phases are collectively known as Interphase. During these three phases, chromosomes replicate, centrosomes and centrioles replicate, RNA synthesis and protein synthesis increase.

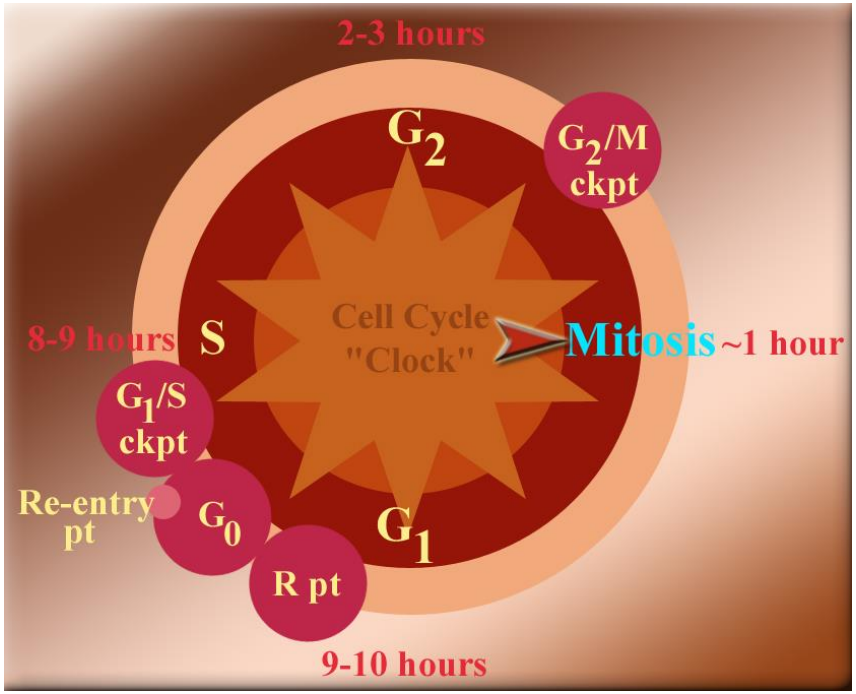
G_2/M Checkpoint

G_2/M checkpoint
This is another transition point where: 1) DNA synthesis is required to be completed and 2) When DNA repair is done in this stage, the cell goes on to mitosis (M phase) (again, uses a protein kinase for this function).



Mitosis

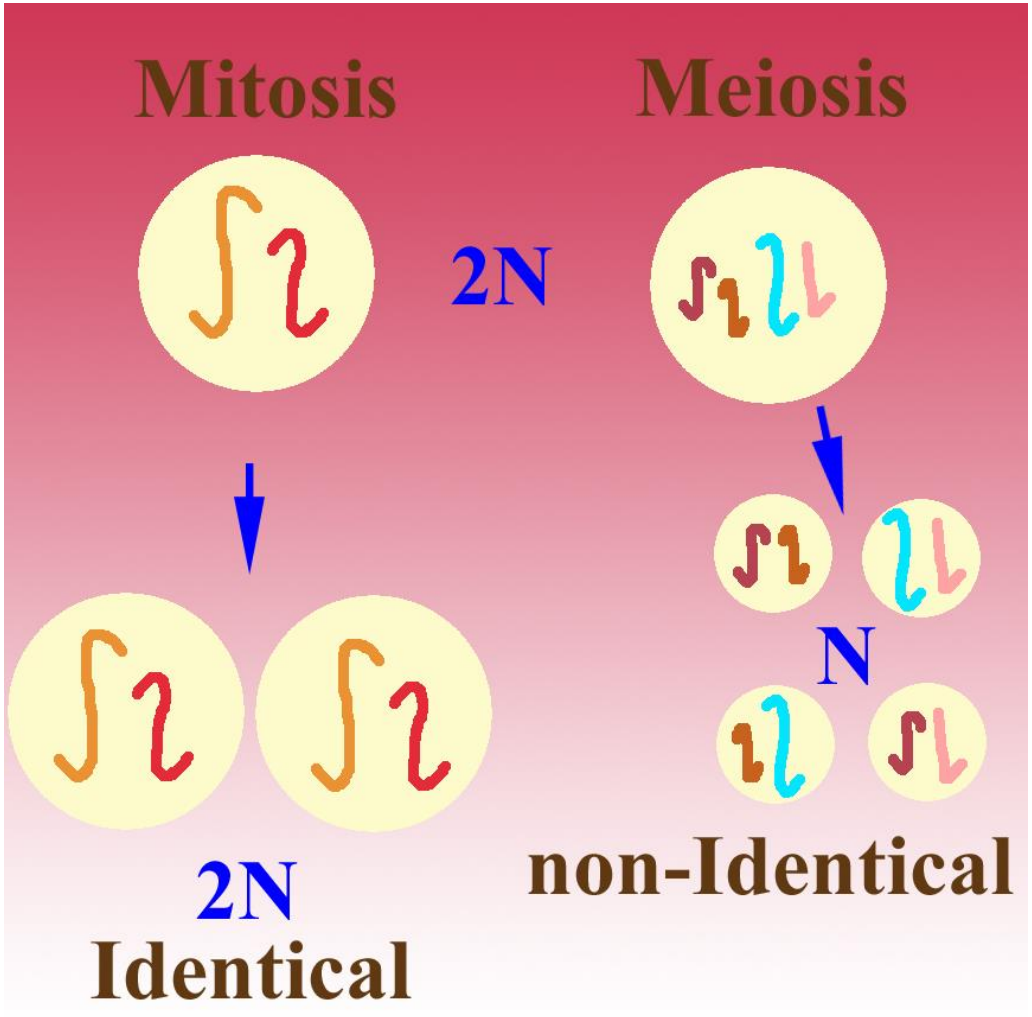
Mitosis and cytokinesis
~ 1-2 hours in length
Cell division
Cells reproduce



- There are four stages in mitosis: prophase (P), metaphase (M), anaphase (A) and telophase (T). The approximate time ratio in minutes for each stage is P: M: A: T -- 12: 1: 1: 6.
- Once the chromosomes are capped off, they are ready to undergo division via either
  - mitosis (all cells in the human) or
  - meiosis (only the immature sex cells in the human, i.e., spermatogonia and oogonia in the male and female, respectively).

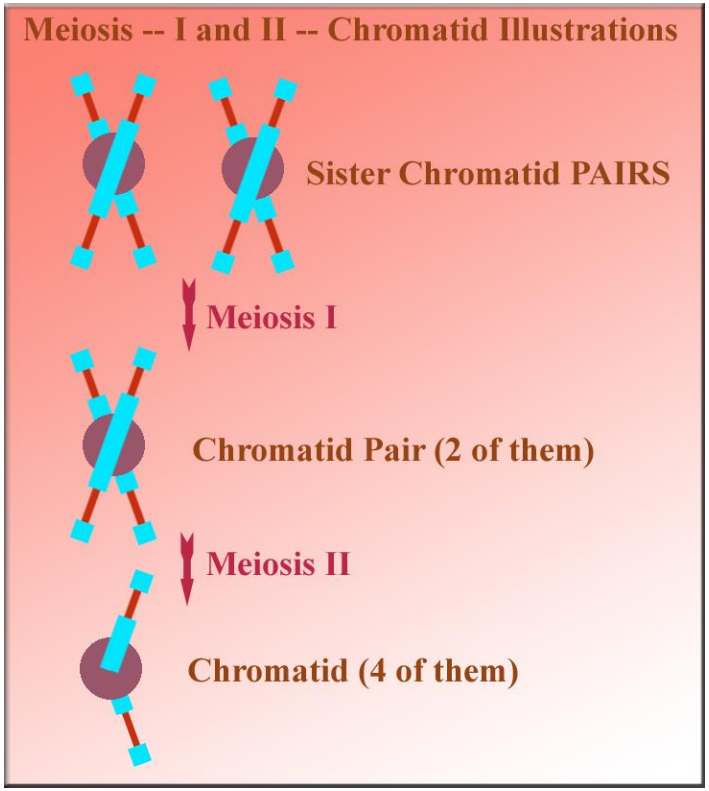
- Summary
- Cells undergoing mitosis have daughter cells that are genetically identical with identical chromosomes (2N);
- Cells that undergo meiosis have daughter cells that are non-identical and have only half the number of chromosomes (N) of the parent cells (2N).

Mitosis vs Meiosis



A Lower Hierarchical Method of Naming Chromosomes

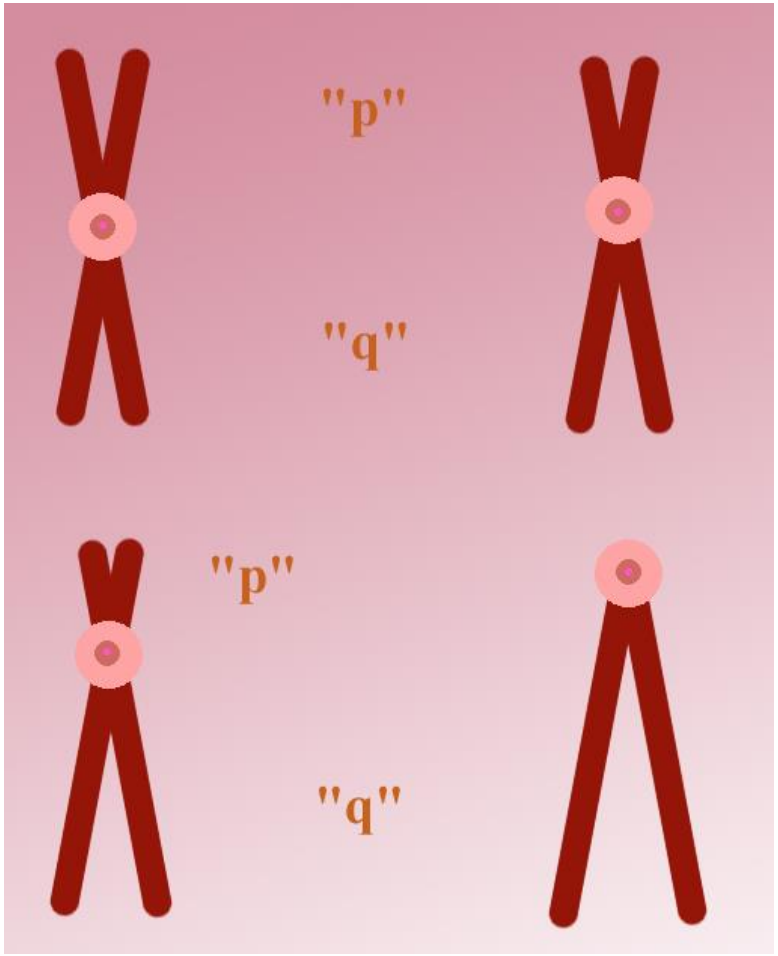
Sister chromatid pairs	Chromatid pair	Chromatid
a.k.a.	a.k.a.	A.k.a.
--tetrad (4 strands of double stranded DNA) --bivalent (1 pair) --chromosome pair --homologous chromosomes	--dyad (2 strands of double stranded DNA) --monovalent (1/2 pair) --chromosome	--monad (1 strand of double stranded DNA) --hemivalent (1/4 pair) --hemichromosome



- Chromosomes contain genes.
- Each identical gene site is called a *locus*. Plural is *loci*.
- Alternate forms of the same gene are called *alleles*.
- HAPLOIDY is N number of chromosomes, i.e., 1/2 the number of chromosomes and come from successful meiosis;
- DIPLOIDY is 2N number of chromosomes, i.e., all the chromosomes that are supposed to be there and come from successful mitosis.
- In the human, haploidy is 23 chromosomes and diploidy is 46 chromosomes or 23 pairs of chromosomes.

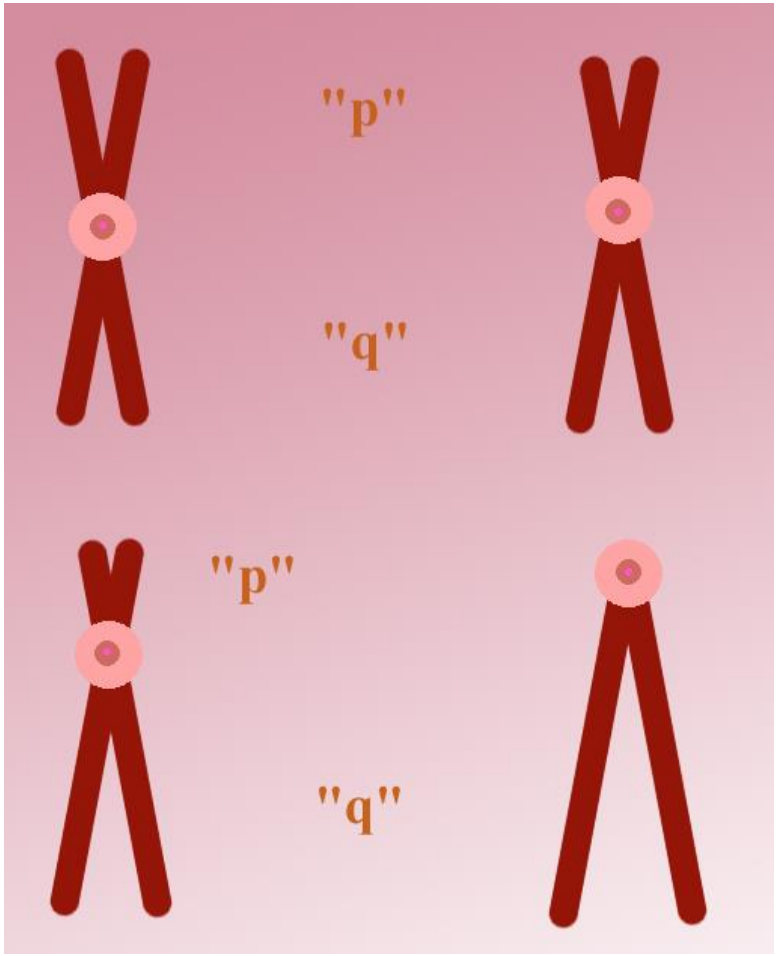
Centromere Location

- When describing chromosomes, particularly those in metaphase, it is helpful to describe them in terms of the location of the centromere on the chromosome. Figure, right, illustrates how the location of the centromere may be used to name chromosomes. As you can see in this figure, we also have names for the two arms (one above and one below the centromere): "p" for petite arm or the short arm (by convention this arm is ABOVE the centromere) and the "q" arm or long arm ("q" comes after "p" in the alphabet; by convention it is the arm BELOW the centromere).



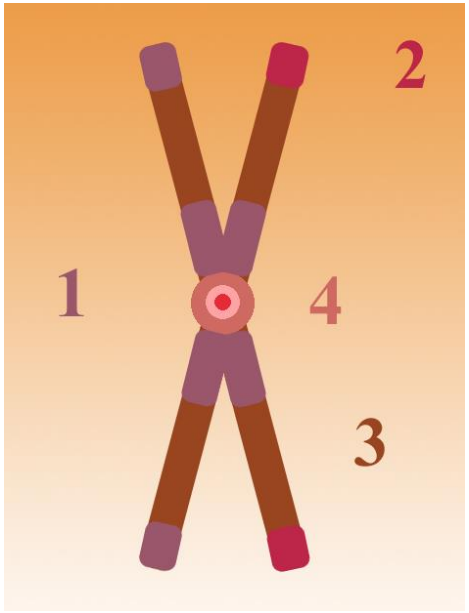
Centromere Location

- Top Left: metacentric – center of chromosome
- Top Right: submetacentric – slightly off (“above”) center of chromosome
- Bottom Left: acrocentric – closer to the “top” of the chromosome than the center
- Bottom Right: telocentric – AT the “top” of the chromosome



The Metaphase Chromosome

1. Heterochromatin
2. Telomeres
3. Euchromatin
4. Centromere



1. Heterochromatin

•The heterochromatin is dense, compact chromatin.

•It contains very low numbers of protein coding genes, i.e., genetically inert (sort of like a "spacer").

•It does NOT effect the phenotype and is capable of being stained.

•Repeated sequences within the heterochromatin with high frequencies are called satellite DNA.

•Heterochromatin contains telomeres (at the ends of the arms of the chromosomes) and centromeres (at the junction of the arms).

•There are two types of heterochromatin:

- constitutive and
- facultative.

Constitutive Heterochromatin

- Constitutive heterochromatin is associated with centromeric regions that are compact in interphase.
- They are also known as chromocenters.

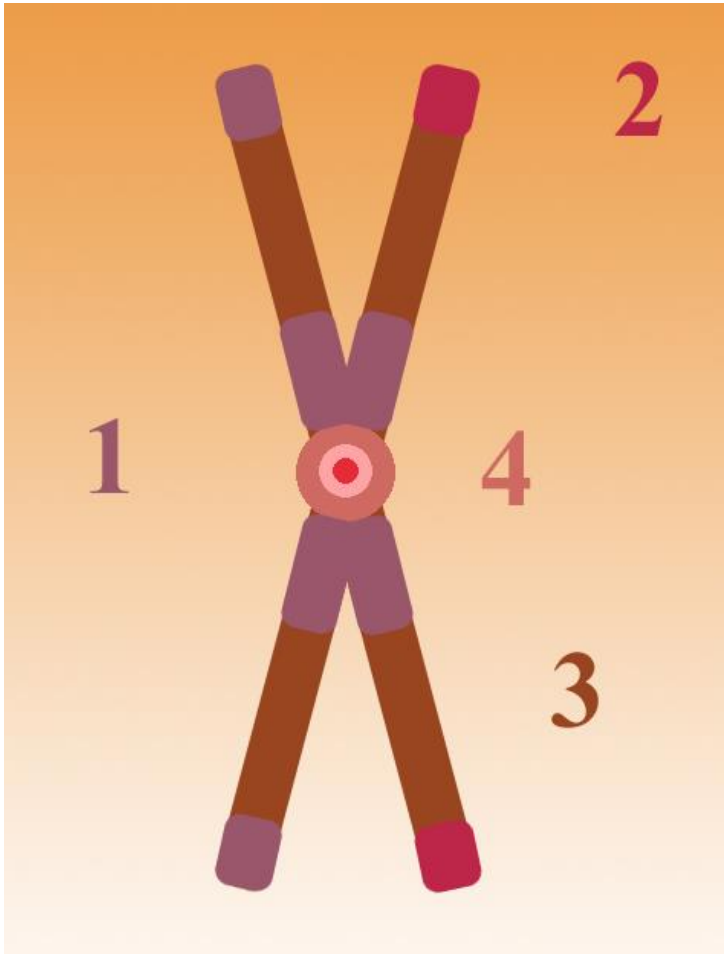
Facultative Heterochromatin

- Facultative heterochromatin condenses ONLY at a specific stage.
- It is generally switched OFF, but can be reversed.
- Facultative heterochromatin is used as a switching mechanism during development.

The Metaphase Chromosome

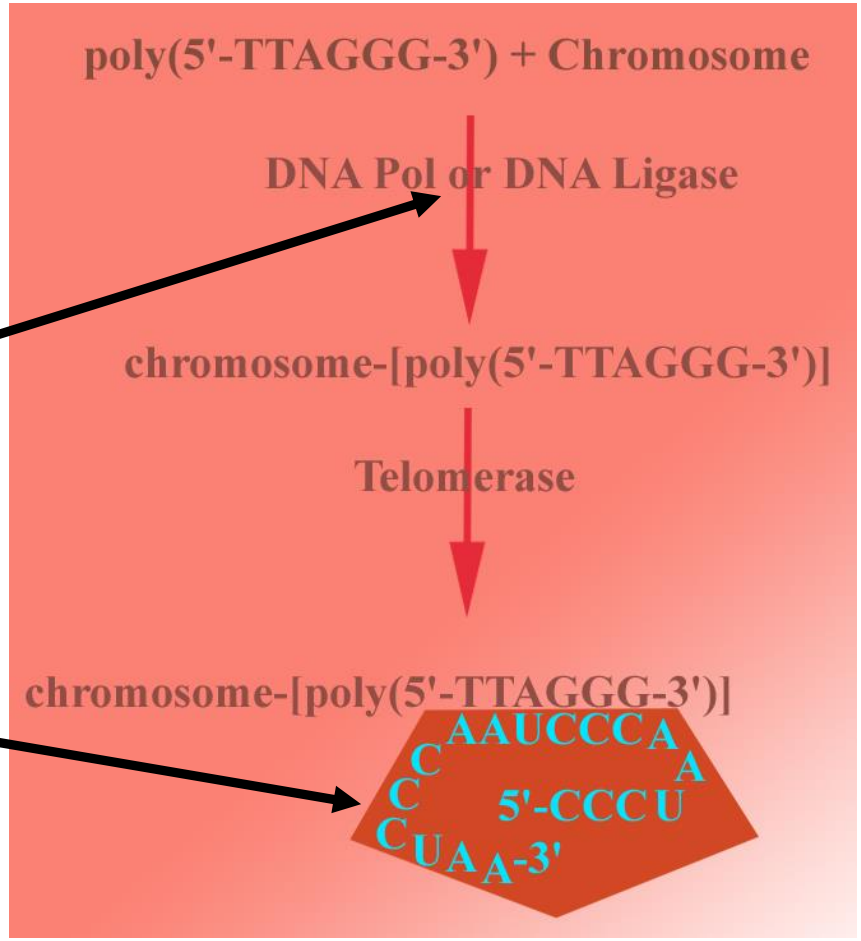
2.Telomeres

- The very ends of the facultative heterochromatin are called telomeres.
- They give the chromosomes stability by "capping off" the ends of the chromosomes.
- There are 4 telomeres per chromosome.
- They are added by the enzyme, telomerase.



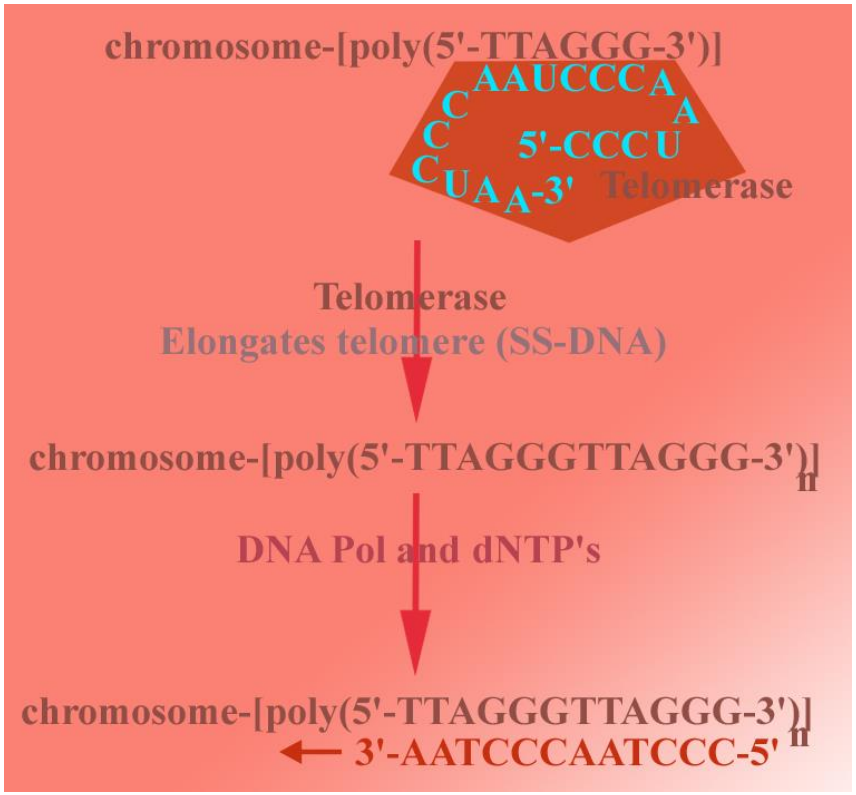
Telomerase

- In short, there is a sequence (single stranded; SS) of nucleotides that codes for the telomeres.
- It must be added onto the chromosomes under the influence of DNA polymerase or DNA ligase.
- Once the SS DNA sequence is added to the chromosome, telomerase (which has a built-in RNA sequence that is used as a complimentary DNA template) elongates the telomere as a longer strand of SS DNA.



Telomerase, Cont'd

- The chromosome with the elongated SS DNA (telomere) sequence then is acted upon by DNA polymerase with nucleotides to fill in the SS telomere with a complimentary strand of DNA and the chromosome is "capped off".
- Note in the figures the base sequences in the RNA and in the SS DNA.
- What differences do you observe?, e.g., what bases are present in DNA but not RNA and *vice versa*?



- Once the chromosomes are capped off, they are ready to undergo division via either mitosis (all cells in the human) or meiosis (only the immature sex cells in the human, i.e., spermatogonia and oogonia in the male and female, respectively).

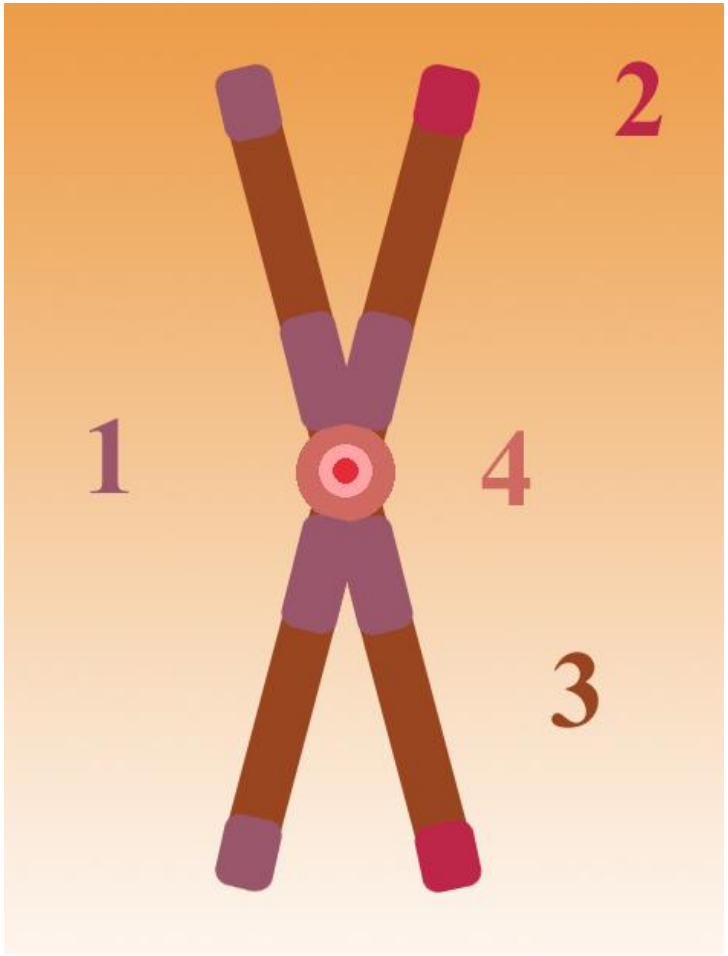
The Metaphase Chromosome

3. Euchromatin

- The chromatin between the heterochromatin is called euchromatin.
- It is loose, uncoiled chromatin.
- It contains very high numbers of protein-coding genes, i.e., genetically reactive ("key").
- It effects phenotype, but does not take stain after it compacts in mitosis or meiosis.

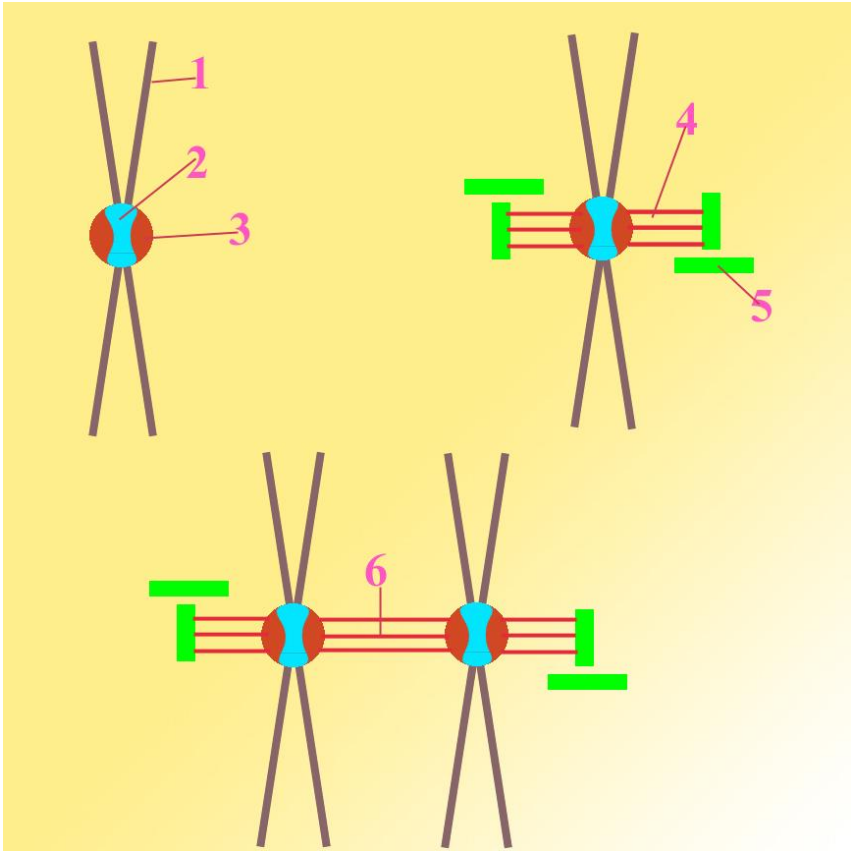
4. Centromere

- The centromere is also sometimes known as the kinetochore.



Kinetochore

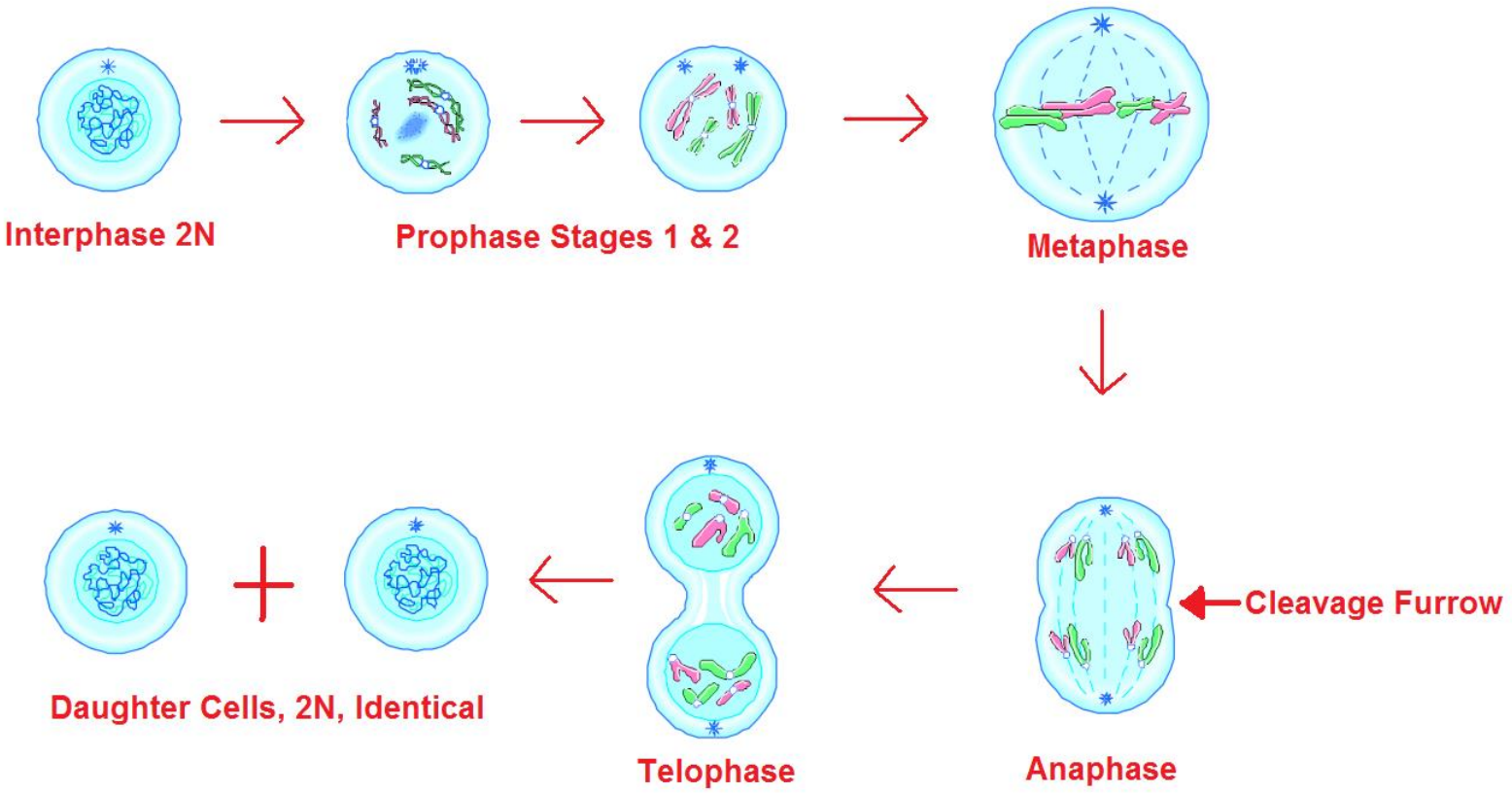
1. Chromosome
2. Centromere
3. Kinetochore
4. Kinetochore fibers
5. Centrioles
6. Kinetochore fibers between sisters



Kinetochores, Cont’d

- The kinetochore is really granules within the centromere used to attach to spindle fibers (kinetochore fibers).
- There are 2 kinetochores per 1 centromere.
- The centromere also attaches to sister chromatids.
- It is highly compact, organized chromatin and attaches, as well, to spindle fibers.
- This region of the chromosome does contain proteins.
- The proteins help protect the centromeric region resistant to DNA'ase (an enzyme used to hydrolyze DNA).

Mitosis Summary



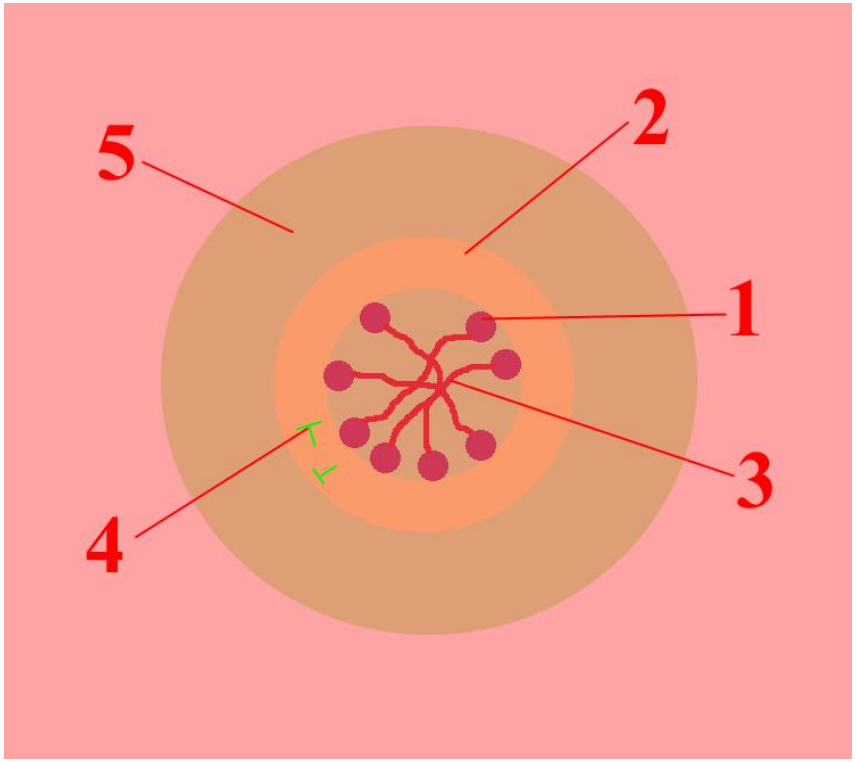
Meiosis

- We have to expand upon your fundamental knowledge of meiosis.
- There are two cycles of PMAT in meiosis.
- PMAT I and PMAT II.
- Prophase I is the stage we must expand.
- It consists of 7 distinct, more or less, stages: preleptotene, leptotene, zygotene, zygopachytene, pachytene, diplotene and diakinesis.

Preleptotene

- 2N chromosomes; fragile, threadlike chromosomes beginning to appear with "knotted" genes; nucleolus beginning to lighten

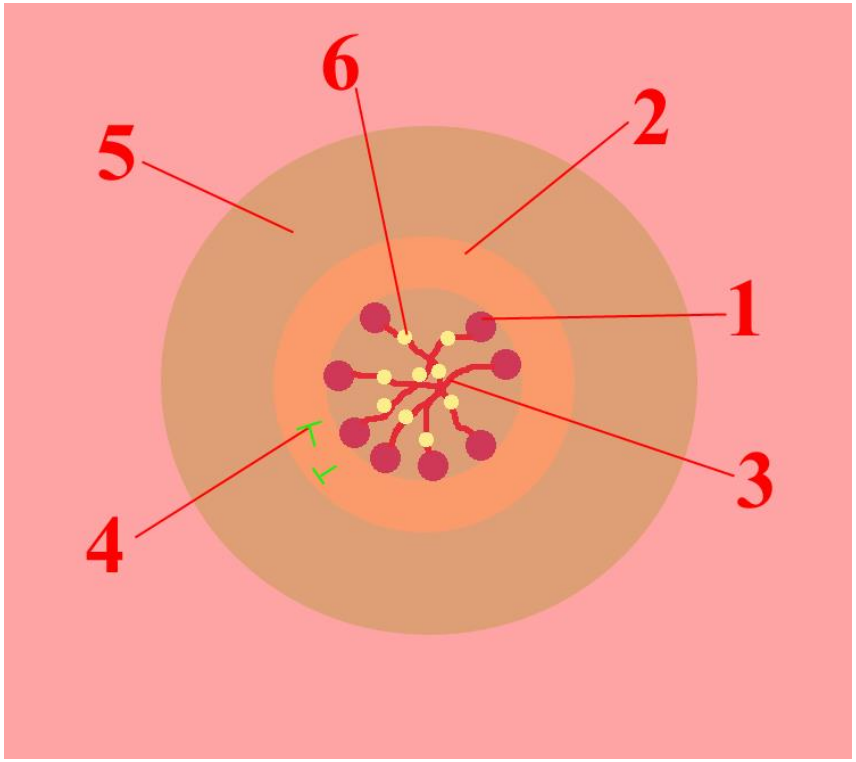
1. Telomeres (anchors)
2. Nuclear envelope
3. Chromosomes
4. Centrioles
5. Cytosol



Leptotene

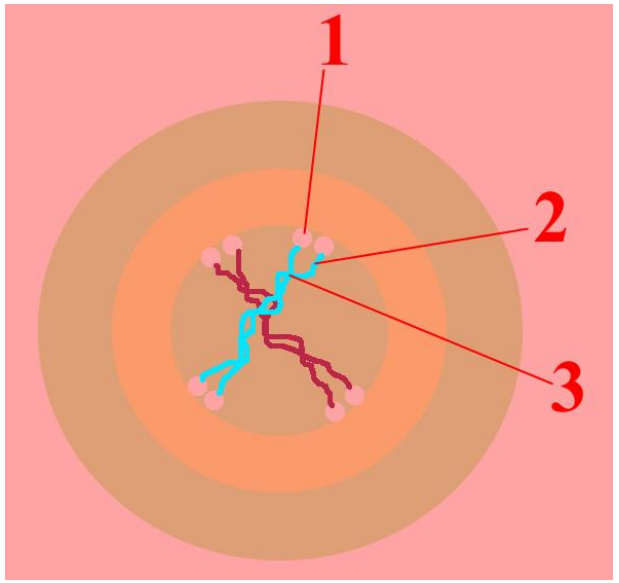
- "chromosomes" (knotted-up genes [supercoiled DNA]) appear best; nucleolus GONE

1. Telomeres
2. Nuclear envelope
3. Chromosomes
4. Centrioles
5. Cytosol
6. Supercoiled DNA



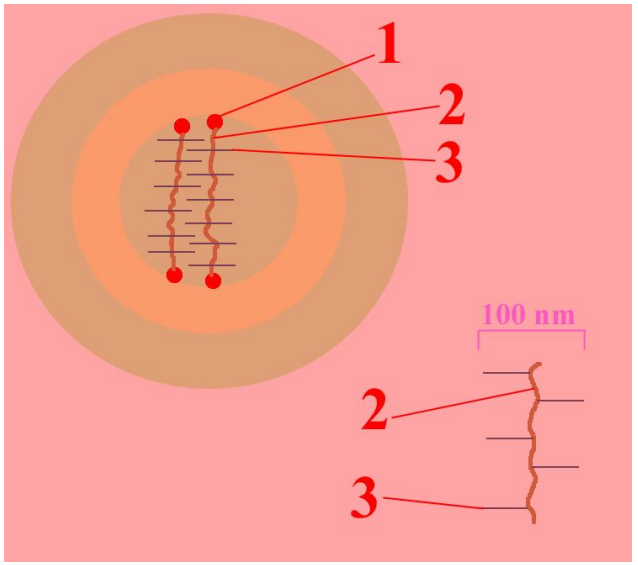
Zygotene

1. Telomeres
2. Chromosomes
3. Synaptinemal complexes



- homologous chromosomes align (called "synapsis"); synaptinemal complexes form (proteins which anneal with each pair of homologues);

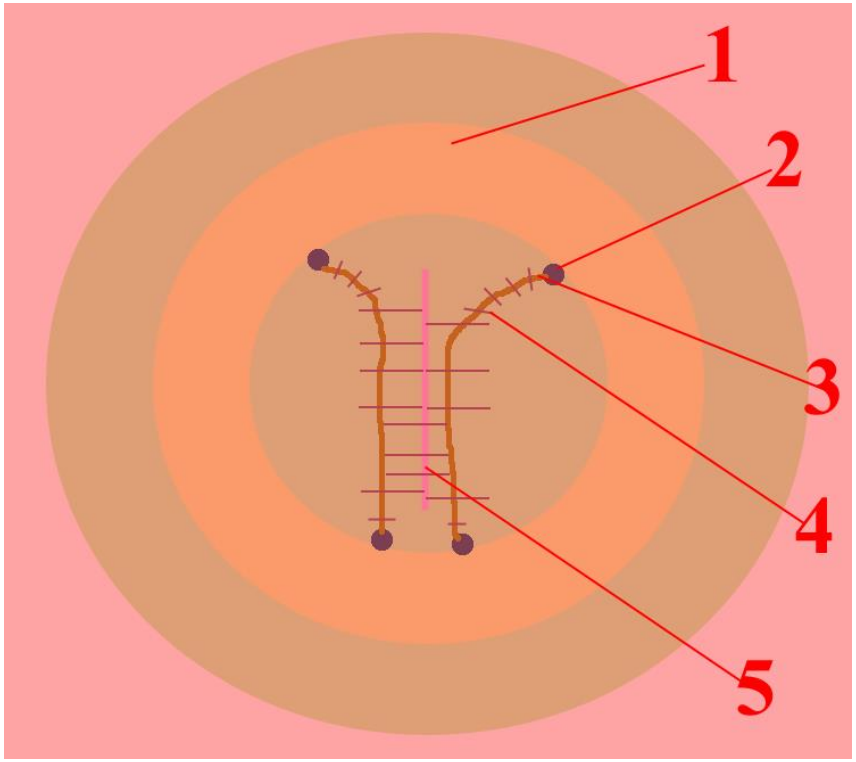
- also 0.3% of DNA required for meiosis is synthesized here to complete zygotene and the synaptinemal complexes;
- lateral elements form and are 50 nm wide **per half** side of chromosome; width of chromosomes with both lateral elements is 100 nm
- 2 chromatid pairs



Zygopachytene

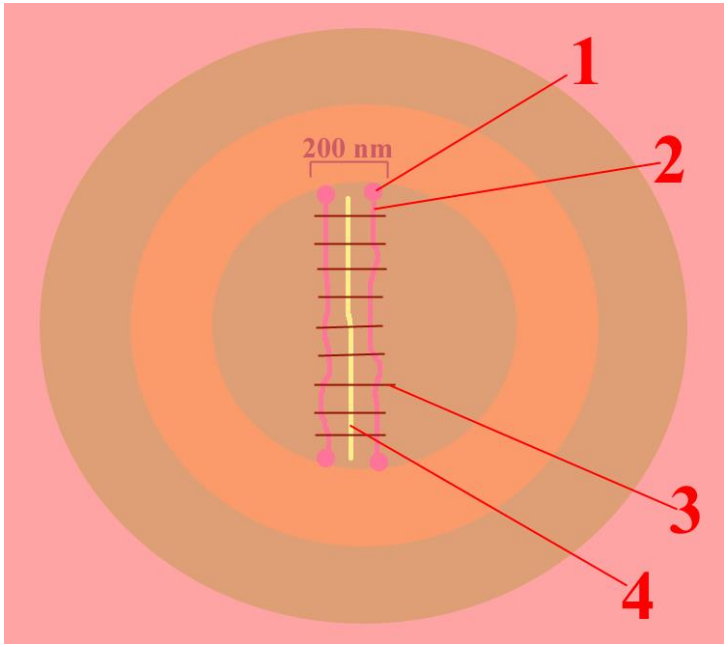
- central element forms (of protein) and telomeres re-arrange; lateral elements begin to "zip-up" each pair of homologous chromosomes

1. Nuclear envelope
2. Telomeres
3. Chromosome
4. Lateral element
5. Central element



Pachytene

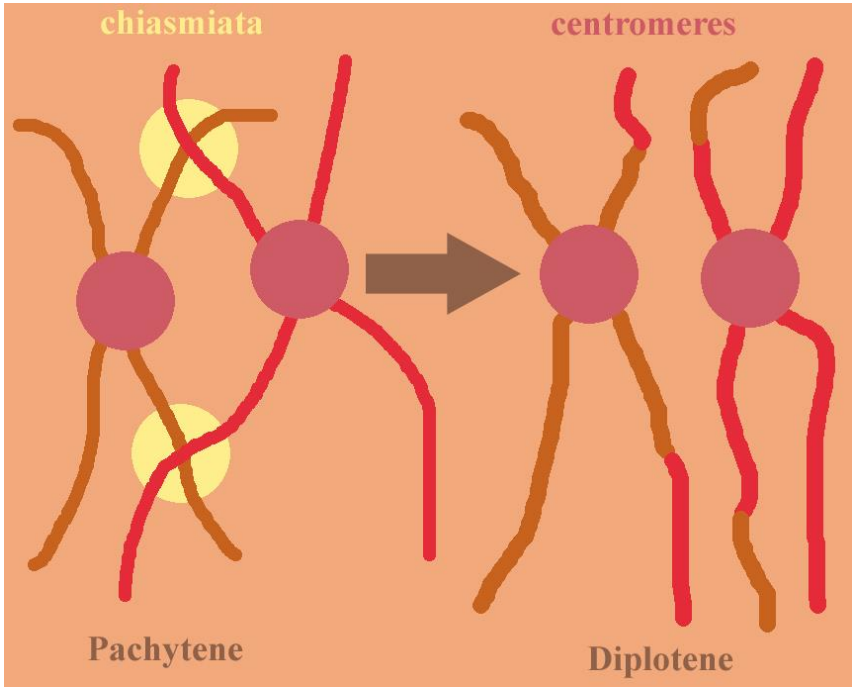
1. Telomere
2. Chromosome
3. Lateral element
4. Central element



- Synapsis completed in homologous regions; NOT so in heterologous regions, e.g., X and Y chromosomes;
- "crossing over" occurs in this stage;
- width of synaptinemal complex is 200 nm (sum of width of both chromosomes with their lateral elements) -- there is little deviation in this distance between species, i.e., a constant dimension, a.k.a. it is highly conserved in nature.
- Bivalent (paired) homologues = tetrad

Diplotene

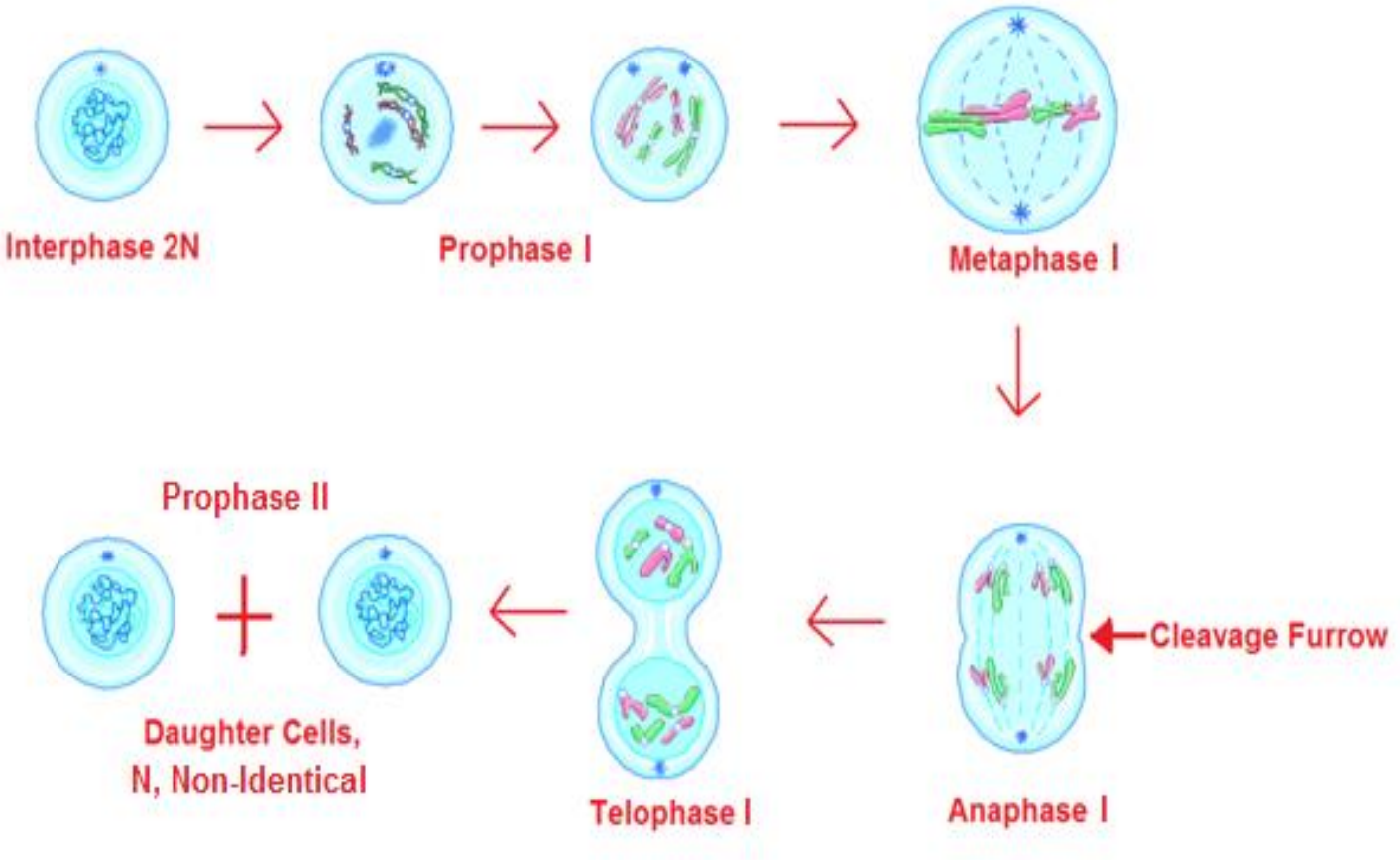
- Bivalents shorten and thicken; homologues begin to repel each other; complete separation blocked by chiasmiata.
- Figure, right,
- There is AT LEAST 1 chiasma per homologous chromosome; long chromosomes may have more than 3 chiasma



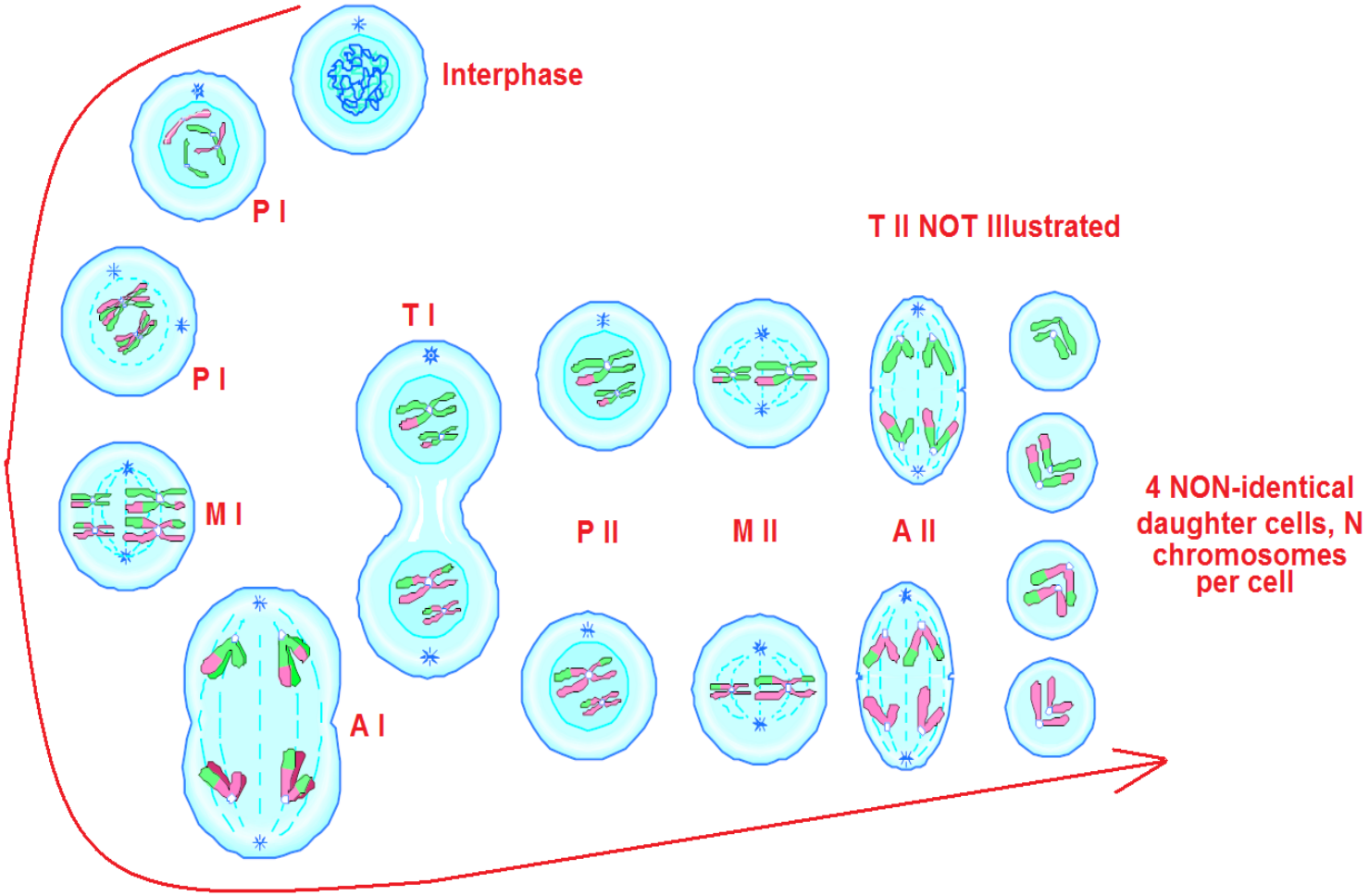
Diakinesis

- Continued compaction of chromosomes;
- spindle fibers form;
- lose nuclear envelope;
- moves into metaphase 1

Meiosis I – Reduction Division



Meiosis II -- Equatorial (Equational) Division



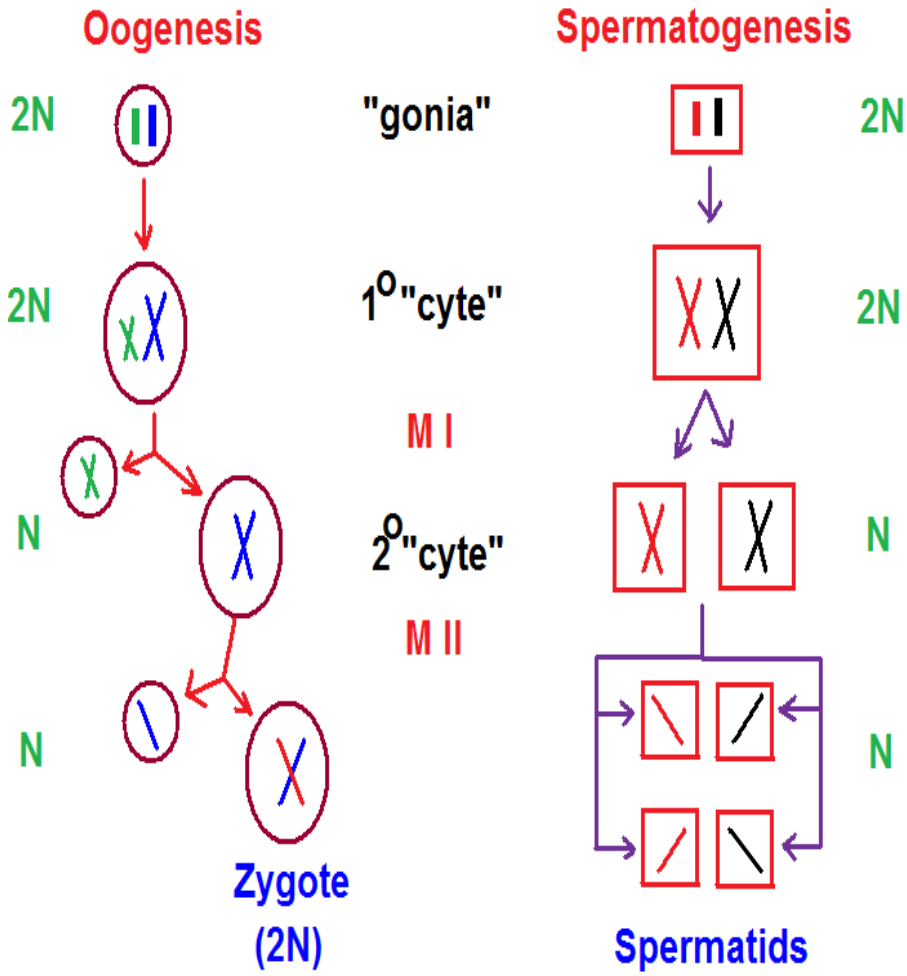
Applications of Cell Division

In the previous section, we discussed how the cell or cells undergo[es] reproduction.

In this section, we will discuss some of the applications of the cell reproductive cycle to human.

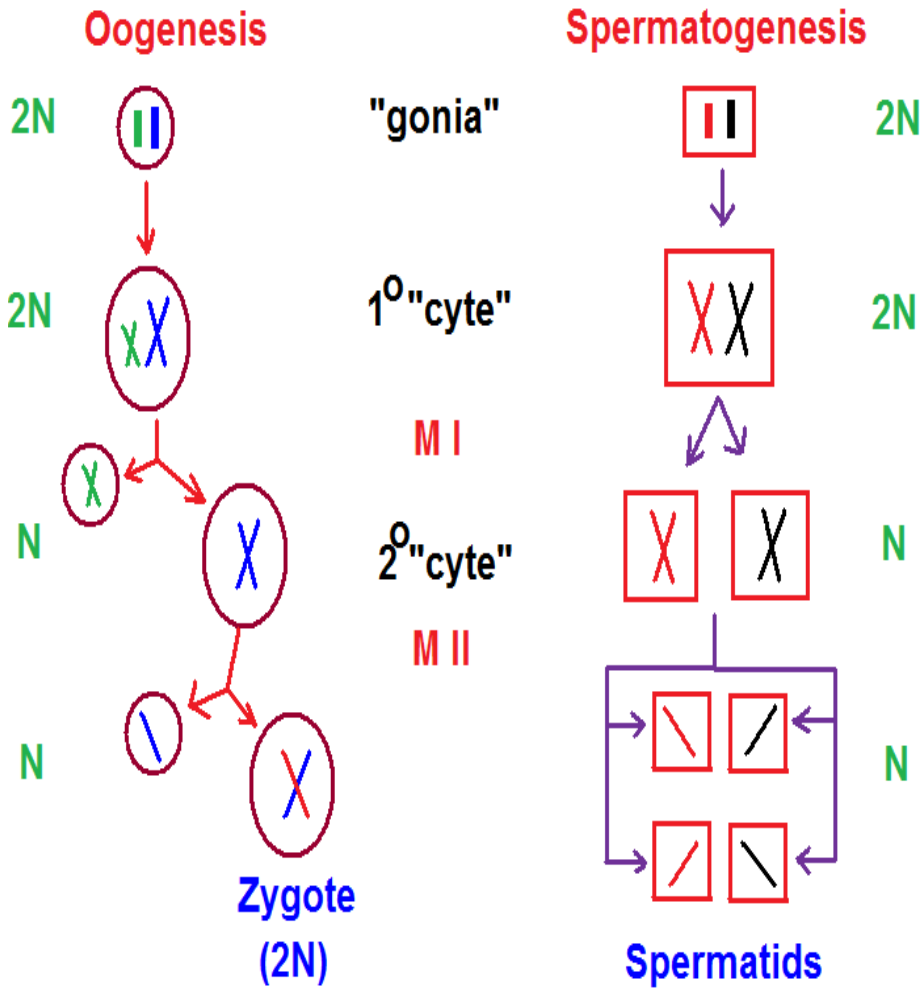
We want to tackle the production of gametes in both the male and female of our species: spermatogenesis and oogenesis, respectively.

Where Gametes Come from



- In spermatogenesis, a 2N spermatogonium (stem cell before birth) undergoes mitosis to form a primary spermatocyte and is arrested in prophase I at birth.
- When puberty kicks in, this 2N cell undergoes meiosis I to form two secondary spermatocytes.
- These cells then undergo meiosis II to form four early spermatids which mature to late spermatids, then to spermatozoa.
- From the formation of the secondary spermatocytes on, the cells are N cells, i.e., have 23 chromosomes.

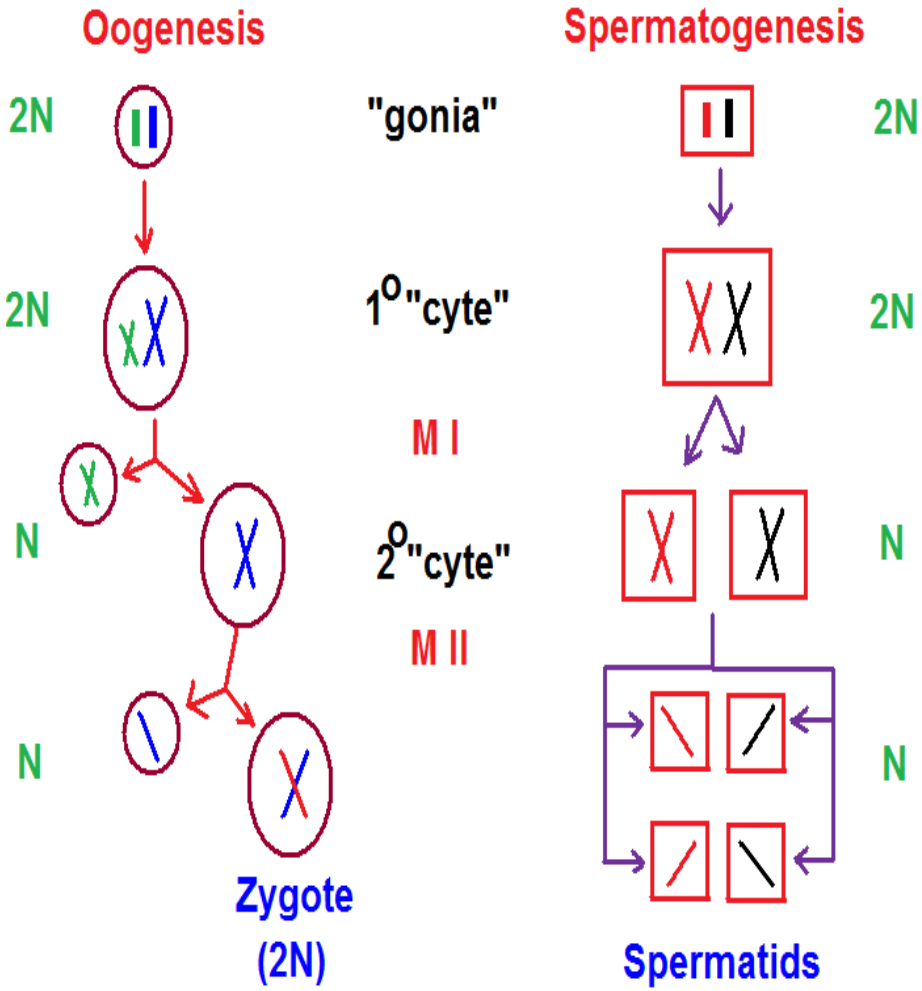
Where Gametes Come from



- In oogenesis, the 2N cells (oogonium/stem cells before birth) are arrested as primary oocytes in prophase I at birth.
- When puberty kicks in, the primary oocyte (primary follicle) grows and undergoes meiosis I to form a polar body and a secondary oocyte (the mature Graafian follicle).
- Once the Graafian follicle is ovulated, it must be fertilized by a sperm BEFORE it can undergo meiosis II.
- If that happens, then a zygote is formed that will differentiate into an embryo and then into a fetus.

Compare and Contrast

- One note of significance is that spermatogenesis (production of spermatozoa) occurs in the male reproductive tract PRIOR to entering the epididymis. The process of sperm maturation, spermiogenesis (spur mee oh GENN uh siss), occurs IN the epididymis.

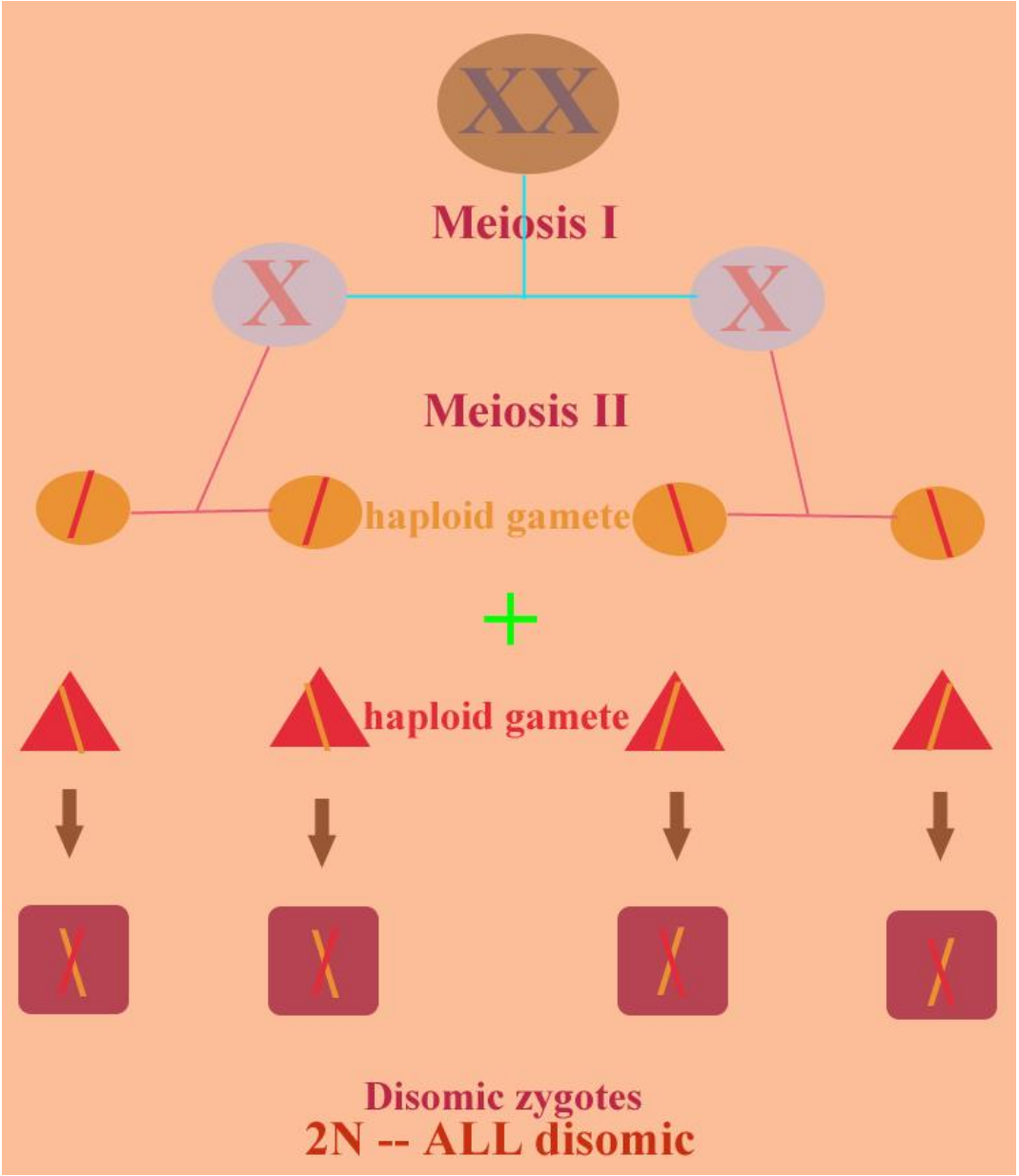


4 Chromosome Movements that are Significant Pre-, Peri- and Post-Meiosis.

Dysjunction	Non-dysjunction	Translocation	Reciprocal Translocation
Separation of a tetrad in anaphase I to 2 dyads; in anaphase II to 2 monads NORMAL	Error in separation; failure of a pair of chromosomes to separate at meiosis; move to the same pole in anaphase; if in anaphase I = primary event; if in anaphase II = secondary event. NOT normal	Movement of a chromosome segment to a different genomic site; may occur within 1 chromosome OR between non-homologous chromosomes NOT normal	Exchange of segments between 2 NON-homologous chromosomes NOT Normal

Dysjunction: NORMAL

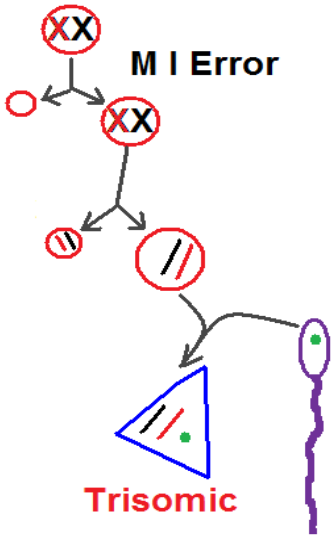
- Bottom line: all secondary oocytes and spermatozoa are supposed to have N numbers of chromosomes.

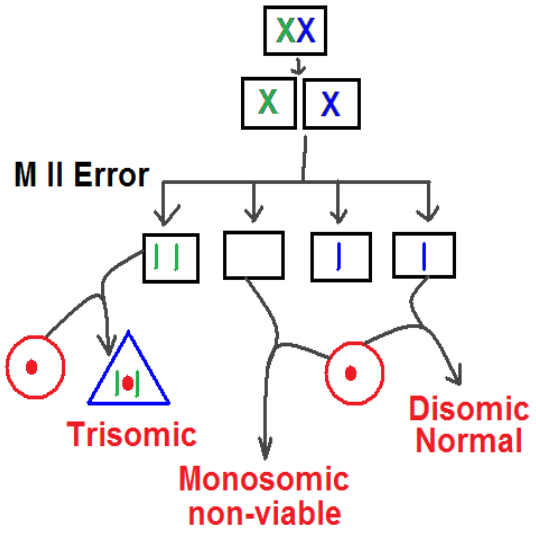


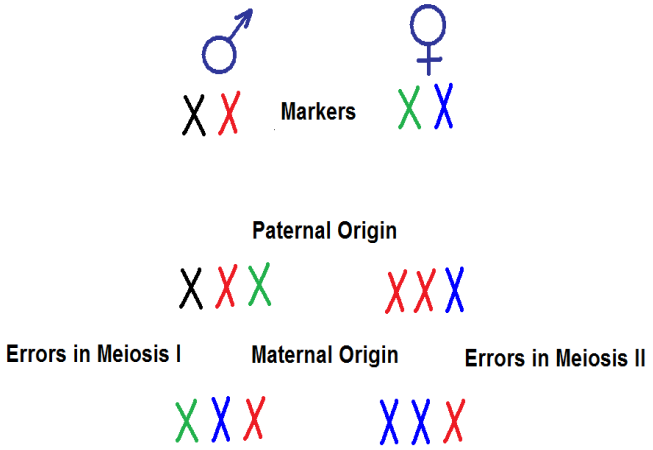
NON-Dysjunction: ABNORMAL

•Specifically, non-dysjunction is the failure of a pair of chromosomes to separate at meiosis.
•Of interest are three items:
1) errors in meiosis I and II occur in both genders,
•In the case of meiosis I non-dysjunction, this may result in a trisomic zygote.
•If it were to happen in the case of meiosis II in spermatogenesis, the resulting zygote could be monosomic, normal or trisomic. (I.e., the results, whether the error occurs in meiosis I or II are **trisomic** zygotes (three copies of the chromosome), **disomic** (normal; 2 copies of the chromosome) or **monosomic** (one copy of the chromosome) zygotes (images at right). The latter tends to be a lethal "combination"; the first not necessarily lethal, but causes severe developmental abnormalities. The disomic individual is the one we refer to as "normal".)

- •The monosomic zygote is not viable.
- •In the case of trisomic zygotes that are carried to term, it is possible to determine the origin of the extra chromosome by using stains or fluorescent antibody techniques.
- •By walking through the errors, lower right, in either stage of meiosis, you can see how the following illustration takes advantage of these errors by the color coding of the extra chromosome using trisomy 21 as an example.

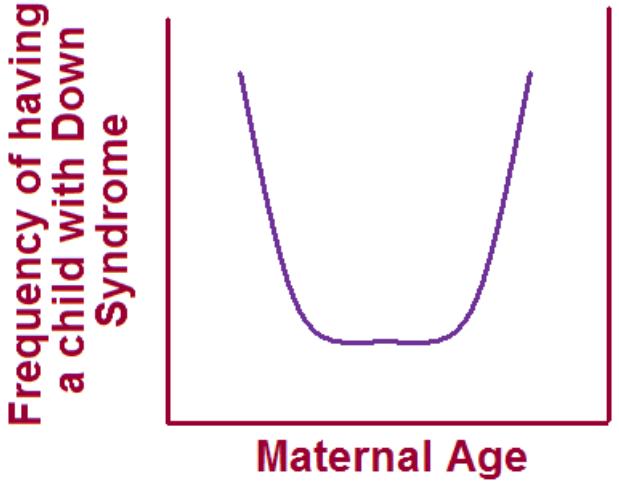






Trisomy 21 – Down Symdrome

2) **studies have shown that for women**, the ages of greatest frequency of having a child with Down Syndrome are the very young and the older mother, i.e., a "U" shaped curve, have the highest risks of having a child with Down Syndrome, and

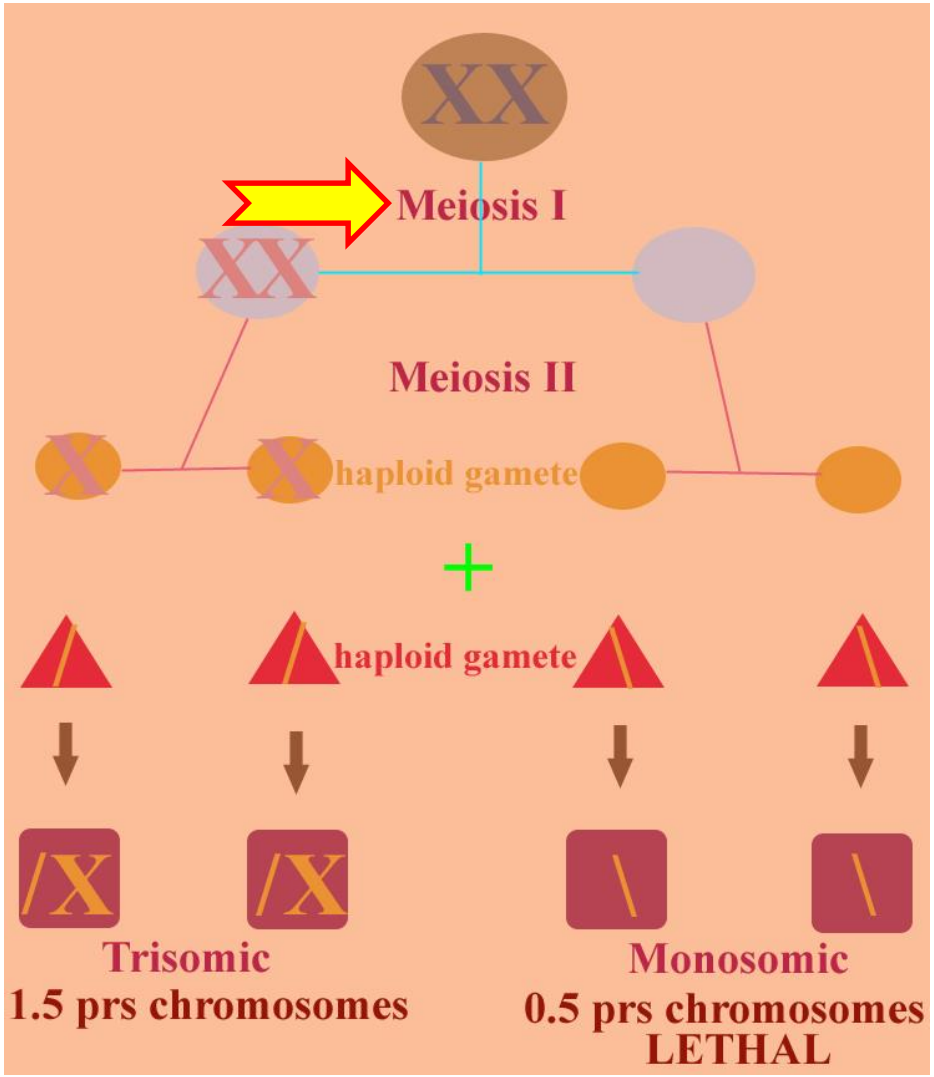


3) **recent research has shown that at least a third of all cases of children born with trisomy 21 are traceable to the paternal side of that family**, i.e., 1/3 d of these cases are paternal in origin.

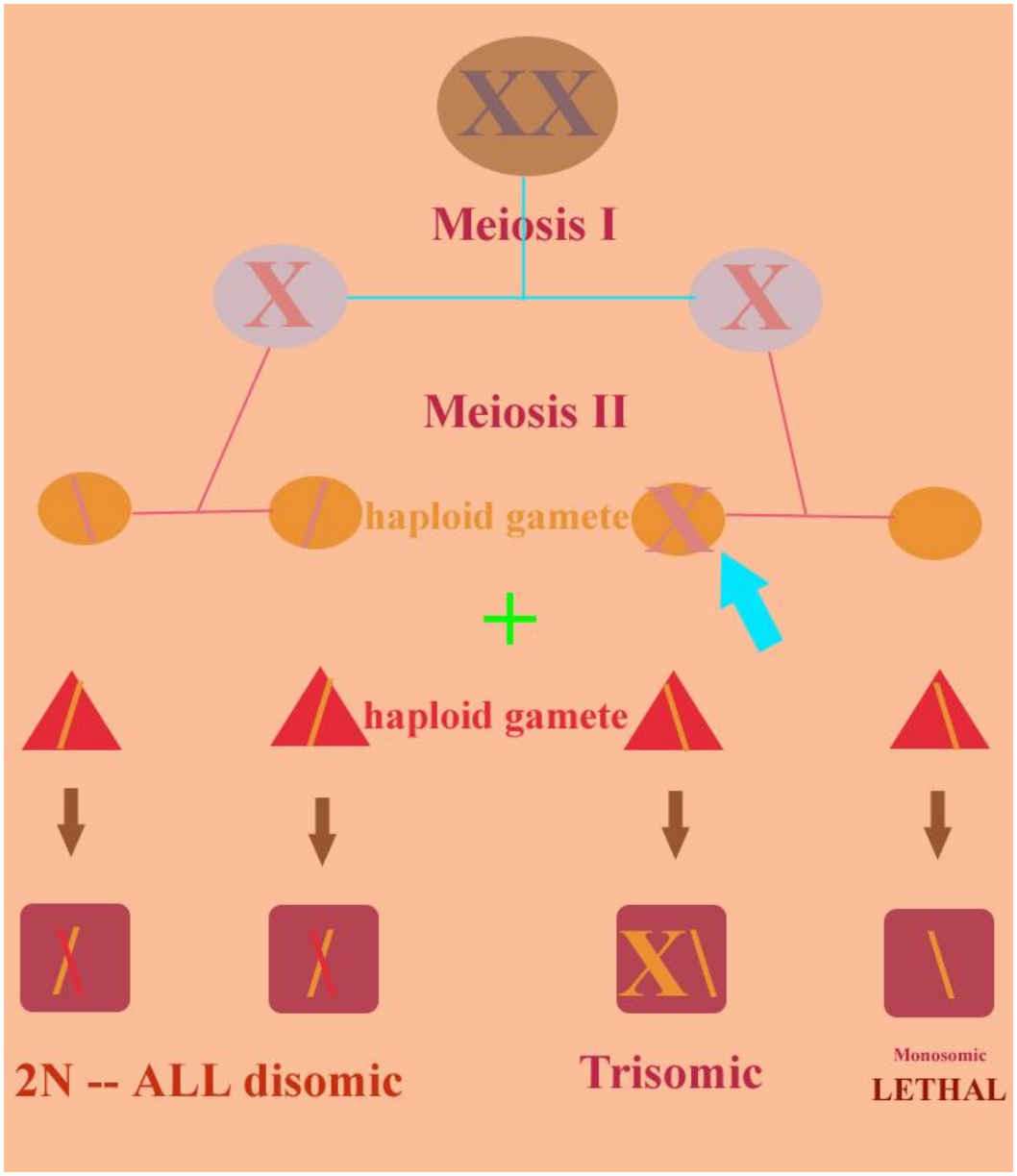
Bottom line: I suspect that in the next 50 years, or so, research will show that the likelihood of a male or a female providing a sperm or ovum with the potential to cause trisomy 21 - and possibly other trisomic disorders - will be equal, as will the source of the extra chromosome in children with the trisomies.

Primary Translocation: ABNORMAL

- Primary and secondary events in Non-dysjunction.
- In short, for some reason, mostly unknown, the chromosomes seem to be sticky and do not want to separate.
- One instance of stickiness that is known to occur is that chronically alcoholic women who get pregnant tend to give birth to babies that have trisomies, i.e., there is something about the chronically high dose of grain alcohol that makes their chromosomes (seems to be one pair of chromosomes rather than all of the chromosomes) not want to "unstick" from each other.
- Given time and funding, I suspect that we'll find the same sort of thing happening in the male of our species, as well.

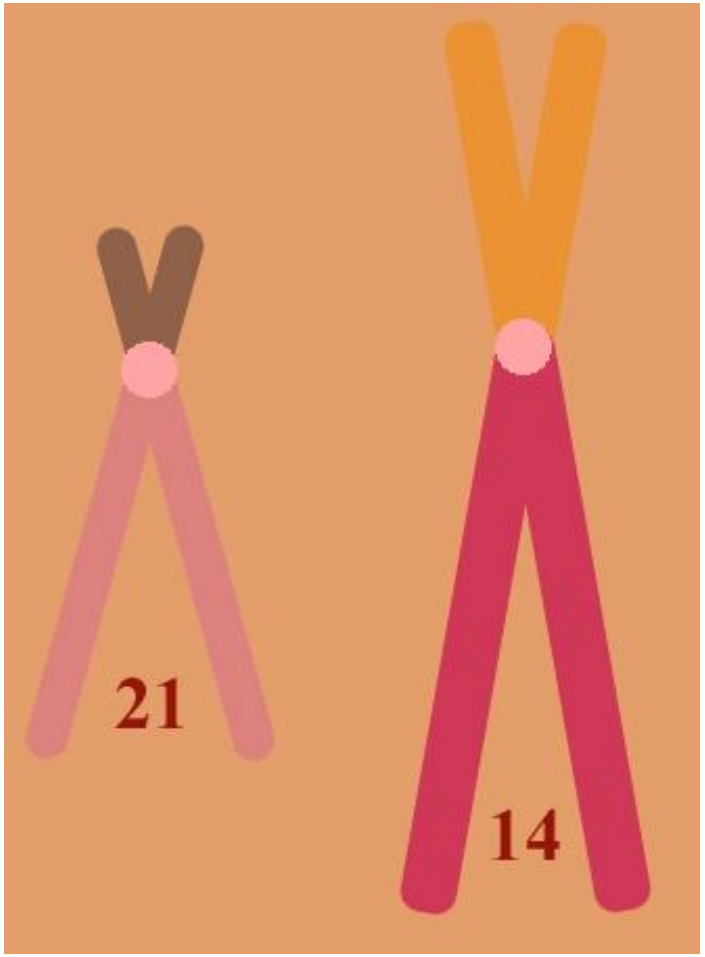


Secondary Translocation: ABNORMAL



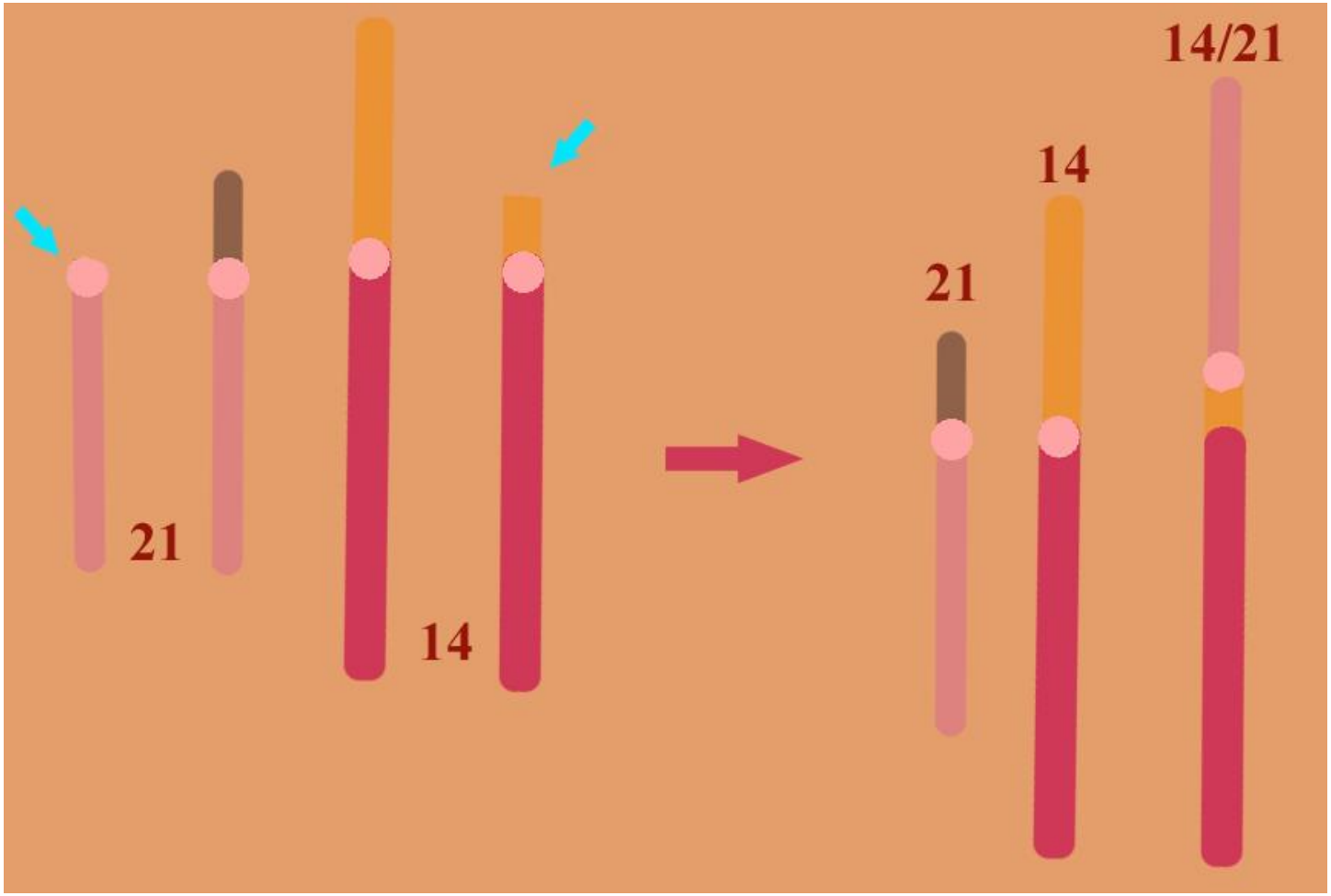
Reciprocal Translocation: ABNORMAL – Stage 1

- “normal" acrocentric chromosomes 14 and 21 in the human.
- Sometimes the "p" arms are lost (more or less) on one of the two of these chromosomes leaving a short 21 and a short 14.
- The two short chromosomes then anneal to make a sort of "normal" appearing chromosome to our cells.



Reciprocal Translocation: ABNORMAL – Stage 2

- This hybrid chromosome is called chromosome 14/21, and tends to act as a 21st chromosome.



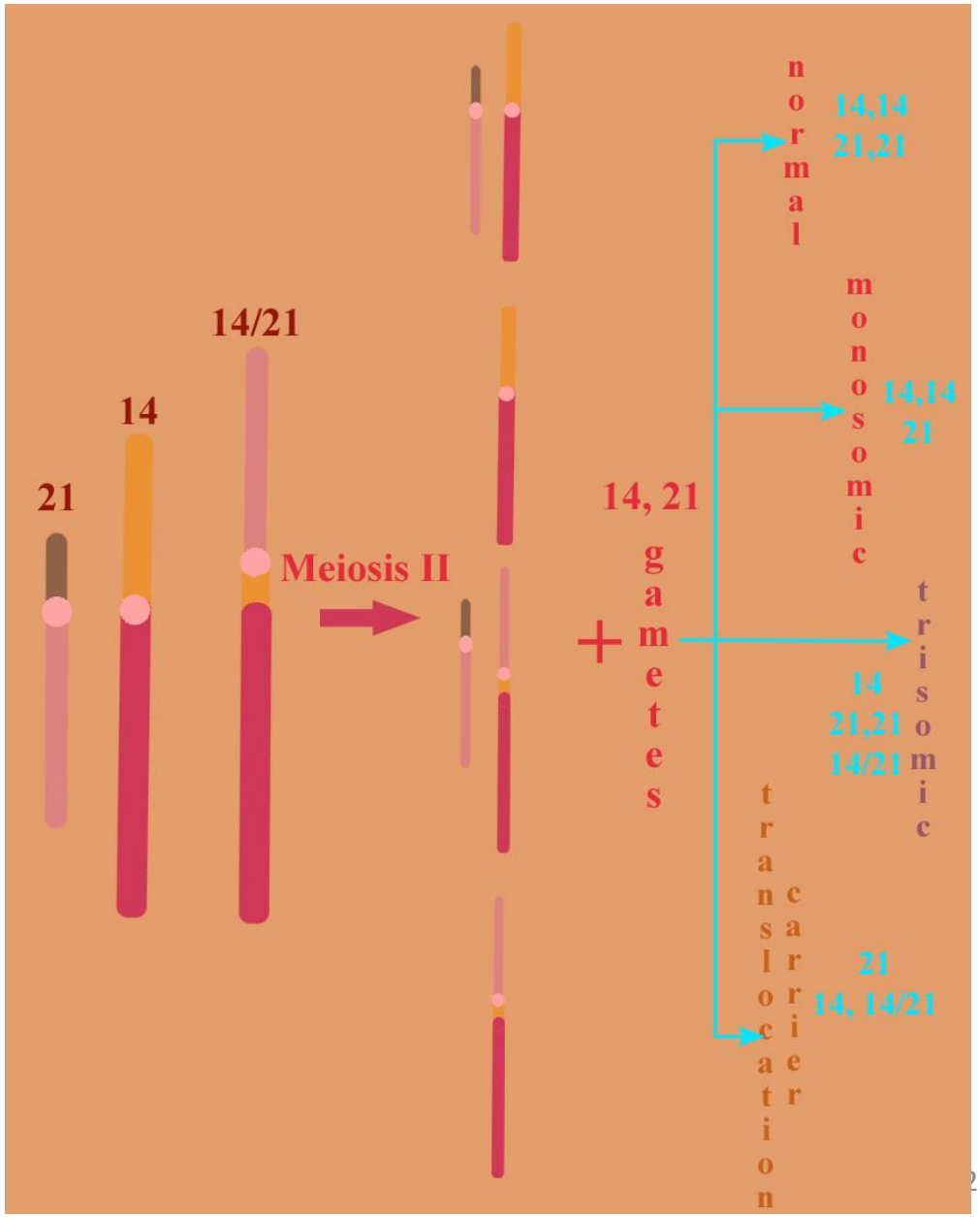
Reciprocal Translocation: ABNORMAL

- you will find 4 possible combinations of gametes and the zygotes they may produce in the following slide:

- NOTE: This sort of translocation is called Robertsonian Translocation.

Reciprocal Translocation: ABNORMAL – Stage 3

- If a male or female carry the genetic combination 14, 21, 14/21 (left) as their genetic makeup, they will produce 4 gametes in meiosis II that will have 14, 21 (top) and 14 (2d from top) and 21, 14/21 (2d from bottom)and 14/21 (bottom) as the genetic makeup.



Robertsonian Translocation

Gamete 1	14, 21	14,0	14/21, 21	14/21
Gamete 2	14, 21	14, 21	14, 21	14, 21
Zygote	14, 14, 21, 21	14, 14, 21, 0	14, 14/21, 21, 21	14, 14/21, 21
Comment	Normal, disomic	monosomic 21	Trisomic for 21	Disomic, carrier for 14/21

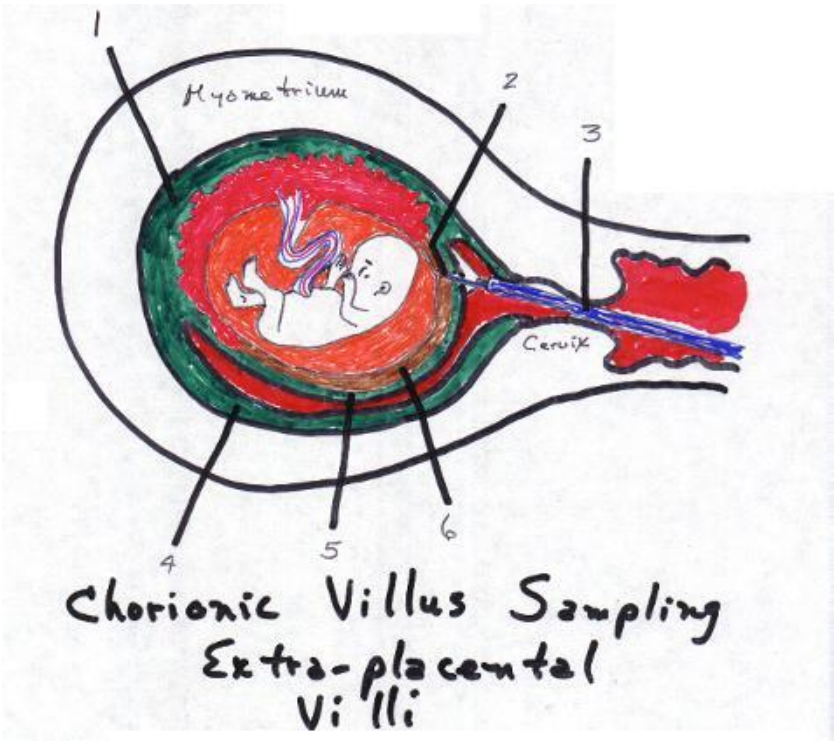
Robertsonian Translocation

- Trisomy 21 explains about 95% of cases of Down Syndrome.
- Parents of children with TRUE trisomy 21 have much reduced odds of having another child with Trisomy 21 the second or more children they have.
- Parents with the 14/21 carrier state have much greater odds of having many children with Down Syndrome over several generations, hence, the carrier (14, 21, 14/21) is the contributor to FAMILIAL Down Syndrome.
- It also follows that NOT ALL Tri 21 are truly 21, 21, 21: they may also be 14, 14/21, 21, 21.

Karyotyping

- How may one determine the presence of one, two or three or more sets of chromosomes for one individual?
- How does one determine the sex of an unborn baby?
- All of these may initially be studied by karyotyping. Karyotyping is the process of taking some cells, synchronize them all so that they reach metaphase at the same time, introduce a drug called colchicine to kill the cells, then examine the chromosomes microscopically.
- Now this sounds easier than it is.
- Once the cells are dead, one must find a good field to photograph.
- Once the photo is developed and enlarged, the chromosomes are cut out and laid in the order of biggest to smallest (1st to 23d chromosome pairs) and by the location of the centromere and satellite regions on the chromosomes.

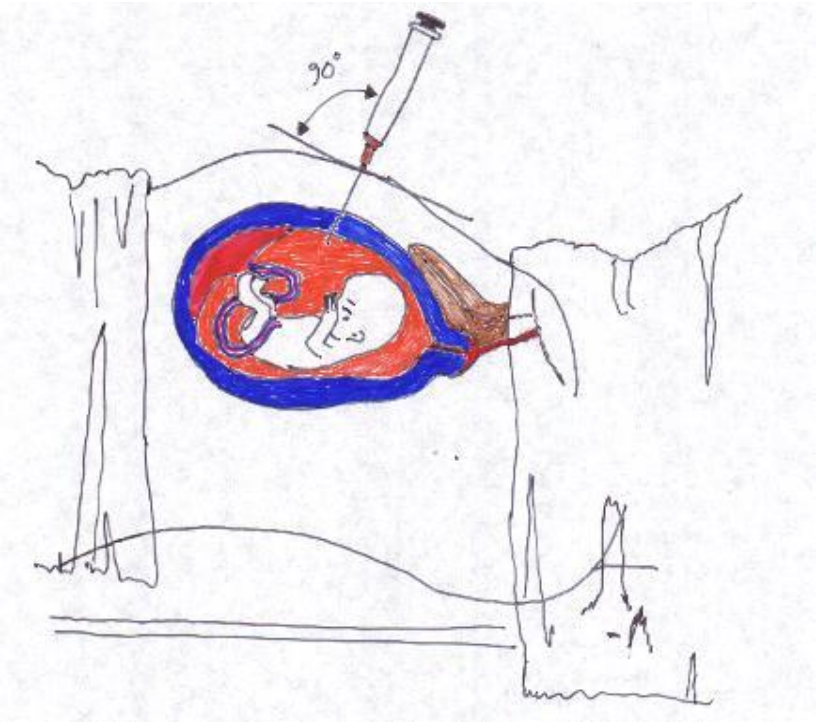
Chorionic Villus Sampling



- The significance of these chorionic villi, besides fetal well-being, is that extra-placental villi samples may be obtained between 8-12 weeks of gestation.
- This is called chorionic villus sampling.
- The graphic at right shows the approximate procedure.
- An endoscope (#3) is inserted through the vagina into the cervix so that the aspiration needle (#2) may obtain a sample of these villi from the chorion (#6).
- #1 is the decidua basalis, #4 is the decidua parietalis and #5 is the decidua capsularis.

- Although this is riskier to the fetus than amniocentesis, cells may be immediately karyotyped and anomalies detected sooner so that the parents may make decisions regarding the pregnancy.

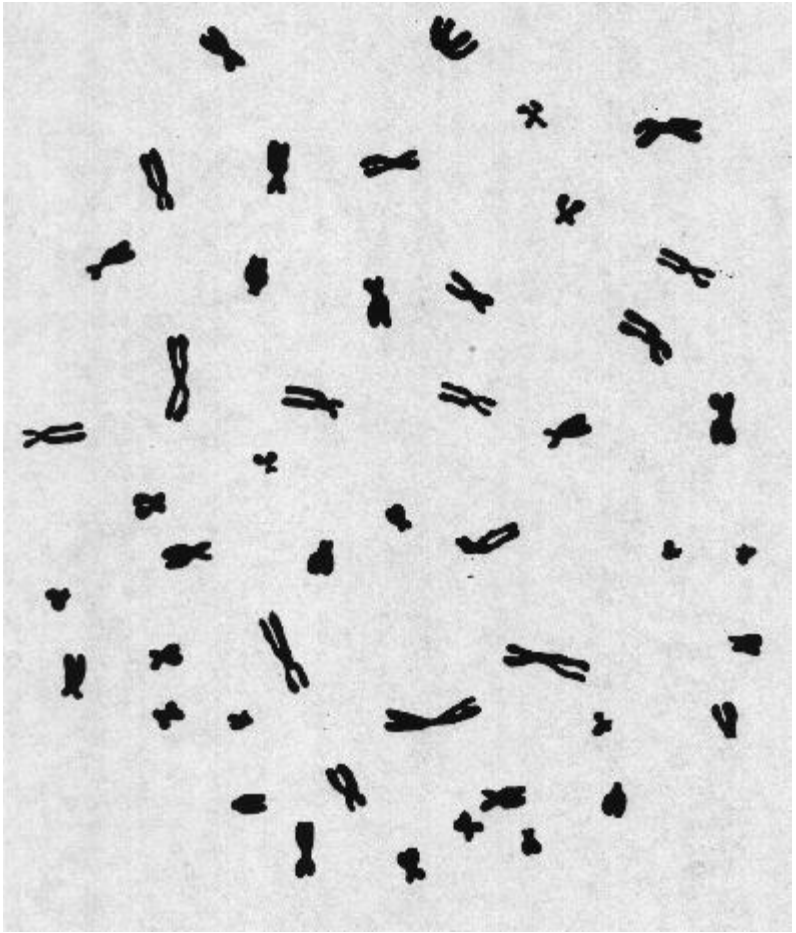
Amniocentesis



- The graphic at left illustrates amniocentesis: the removal of amniotic fluid for diagnostic purposes.
- In general, this is coupled with sonography for placental localization so that it is not inadvertently damaged.
- The needle and syringe are held at 90° to the abdominal wall and inserted into the amniotic sac.
- A sample is withdrawn for diagnostic studies.
- There is general agreement in the literature that 16 weeks of gestation is adequate for this procedure, although there are some references that indicate that amniocentesis **may be performed** at 14 weeks of gestation.
- The drawback to amniocentesis is that it takes several weeks to get back the results of karyotypes.

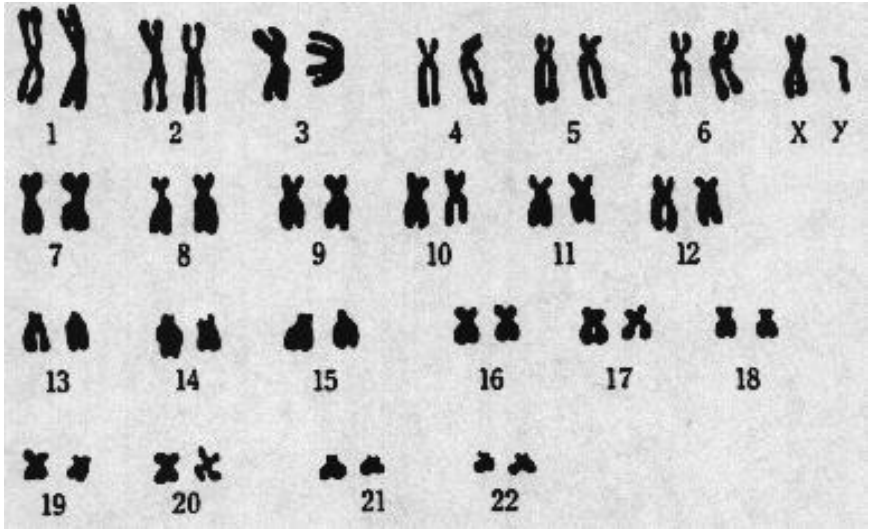
Karyotyping after Obtaining Samples

- Can you tell if this set of chromosomes is normal? Trisomic? Male? Female? NO! You have to cut and paste them onto a karyotyping form to examine and analyze them to answer this burning question.

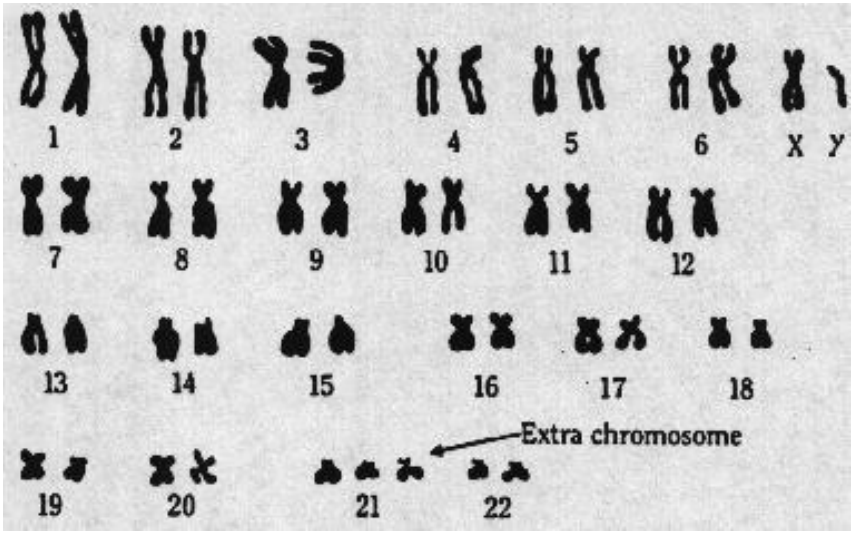


Male Karyotypes

- Normal

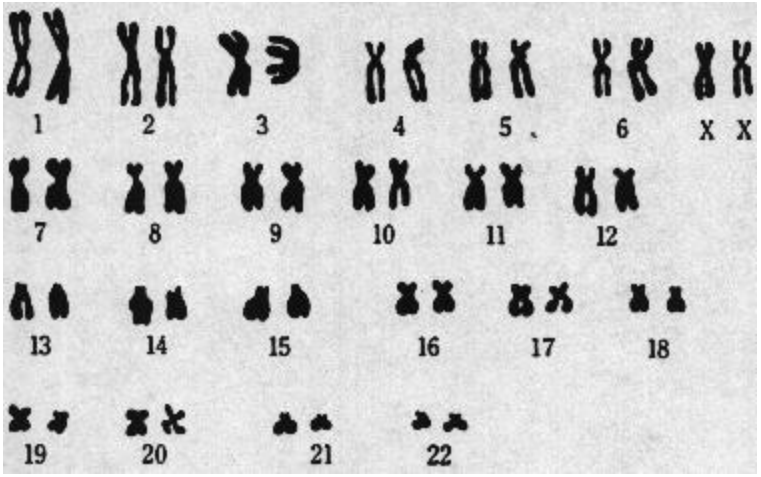


- Down Syndrome

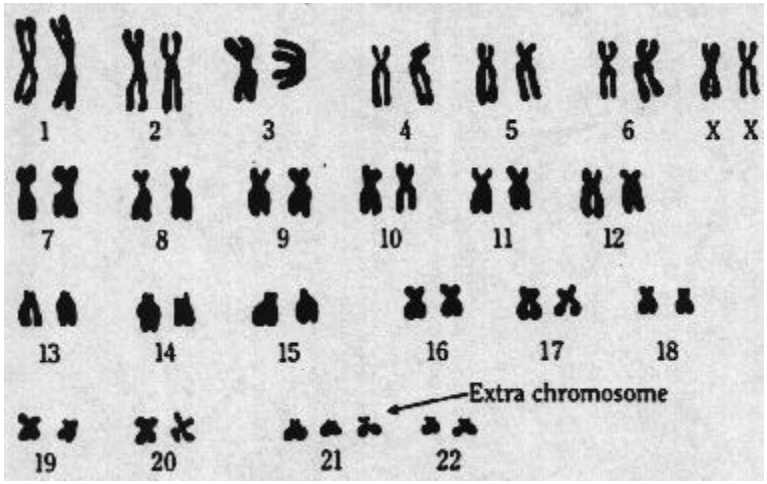


Female Karyotypes

- Normal



- Down Syndrome



Aging Theories

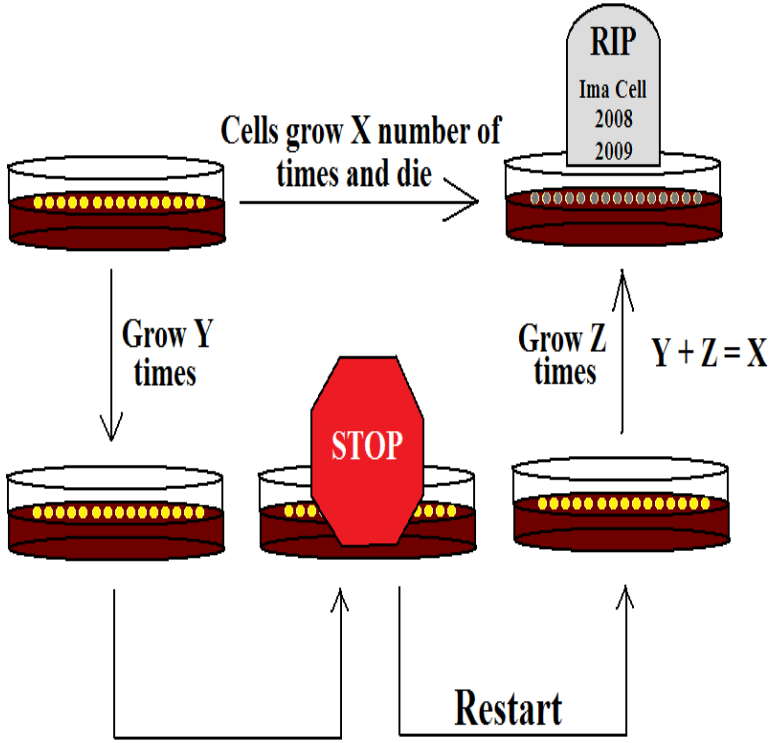
There are 8 aging theories for discussion.

In all likelihood, though, each one is correct to a point on its own merit and all are fully correct when "mixed" together, i.e., when they are all combined.

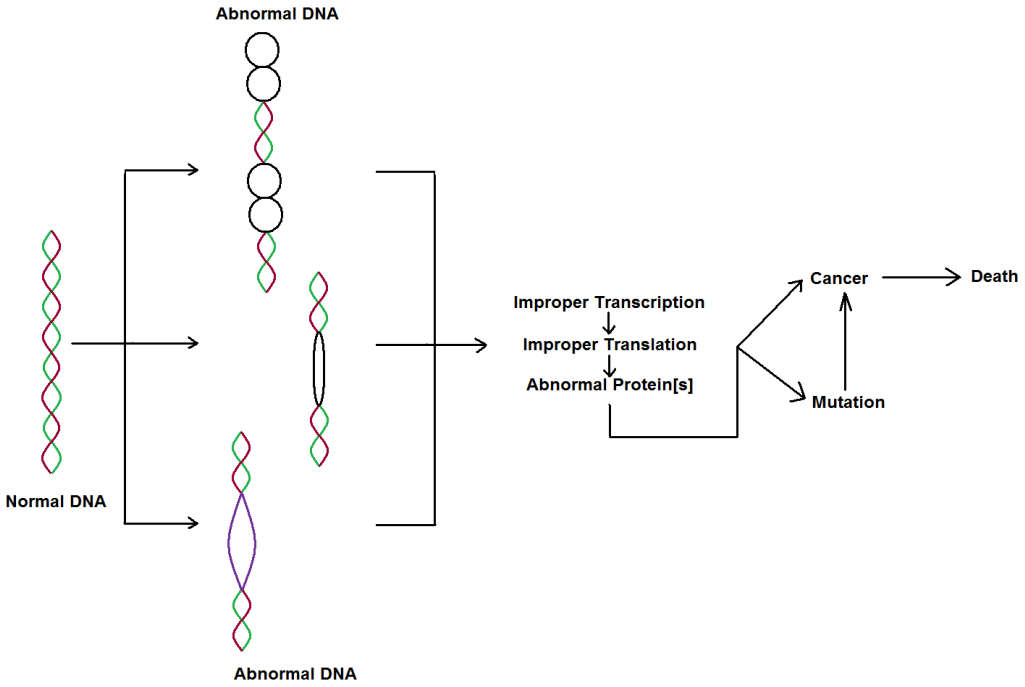
Another way of viewing this is that individually, there are problems with all of these theories. Together, they make pretty good sense.

Program Theory

- When cells are grown in culture, they will replicate "X" number of times and then die.
- This has been shown in embryonic (emm bree AWN ick) cells grown in culture, then taking clones and doing the next experiment: start and stop the growth of these cells and see how many times they will replicate.
- Interestingly enough, no matter how many times the cells were started and stopped, when the calculations were complete, the cells in both cases replicated the same number of times.



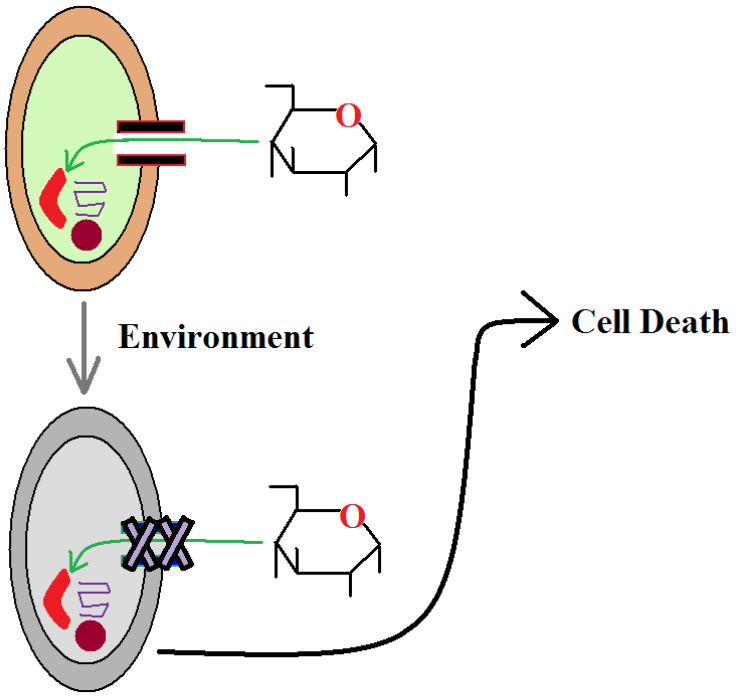
Error Theory



- Normal DNA under normal conditions alters its structure as we age.
- Due to these alterations, the DNA is not read correctly so that transcription and translation are malfunctioning which leads to a malfunctioning (abnormal) protein that either directly causes cancer or indirectly causes cancer through a mutation.
- Either way, the cell dies.

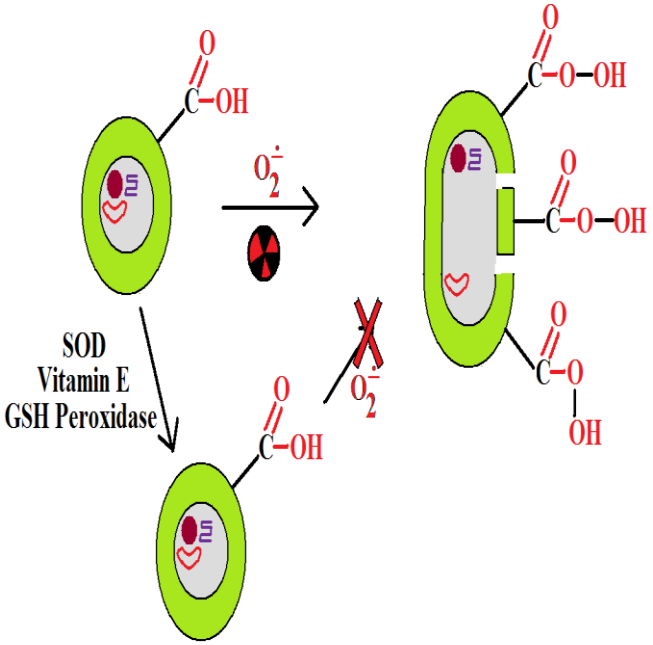
Cellular Theory

- Under normal cellular "wear and tear", the cells become debilitated and do not function as well while we age.
- It tends to support the idea that if we increase our metabolic processes, the increase causes our cells to age faster and reduce our life span.
- Probably a part of this is correct, however, the reduction in life span we think about probably amounts to only a few years, at most, on the far end of the life span, i.e., we're probably not gonna notice the loss of those few years.



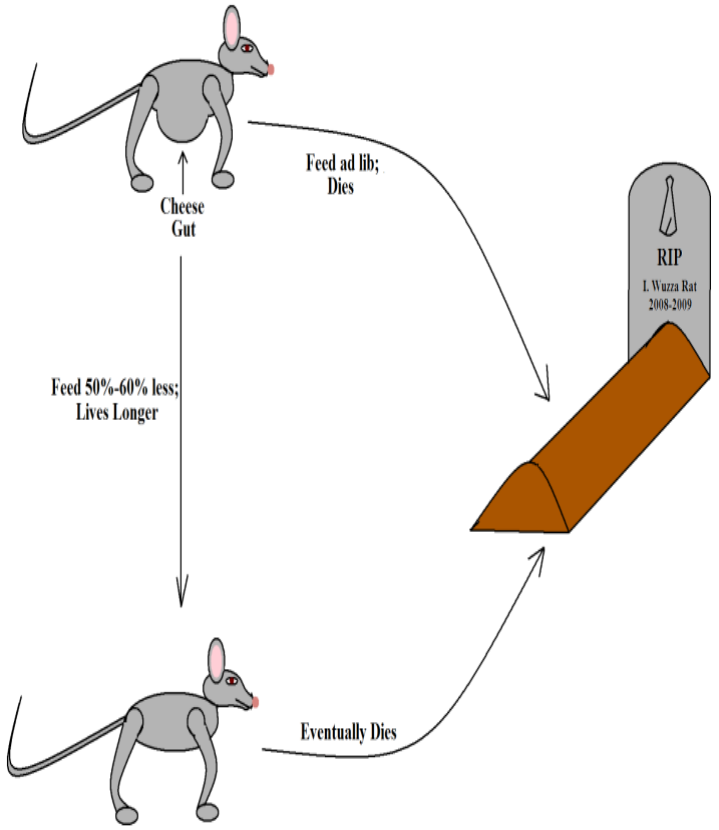
Free Radical Theory

- When lipids in our cell membranes are exposed to free radicals, e.g., superoxide anion (O_2^-) or radiation, the free carboxyl groups are oxidized to COOOH groups from the COOH groups normally present.
- The COOOH groups are called lipid peroxides.
- These lipid peroxides are quite reactive and will cause the cell membrane to rupture, causing the demise of the cell.
- We do know that when cells are exposed to free radicals or radiation in a test tube and we've added
  - Vitamin E or
  - superoxide dismutase (SOD; enzyme that hydrolyzes superoxide to water and oxygen) or
  - glutathione peroxidase (GSH peroxidase; another enzyme that protects against lipid peroxidation)
- that the life span of the cells are prolonged.
- The key is to remember that, thus far, it only works in the test tube.



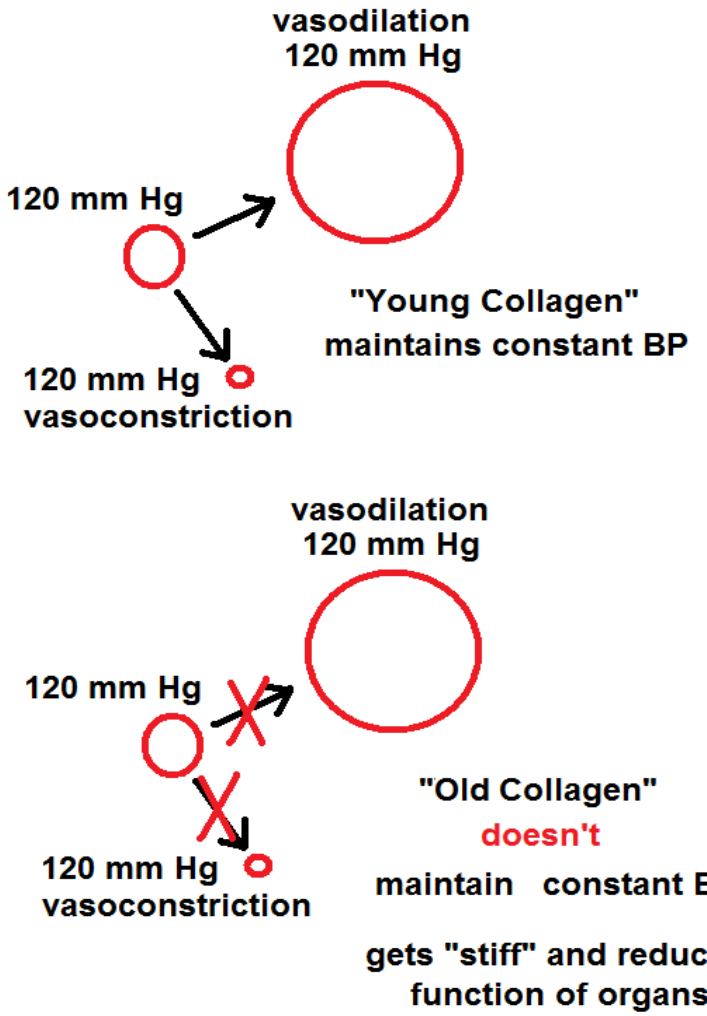
Nutritional Model Theory

- If an animal is fed 50-60% energy less than what it will normally obtain on its own that it will live longer and be healthier.
- This is the only model that actually works by itself - BUT!
- Remember: animals are much different from humans so it may not apply to humans.
- In addition, just because one has a great deal of lean muscle mass, as opposed to adipose tissue, this does not mean that that person will live longer than someone with the opposite physical characteristics.



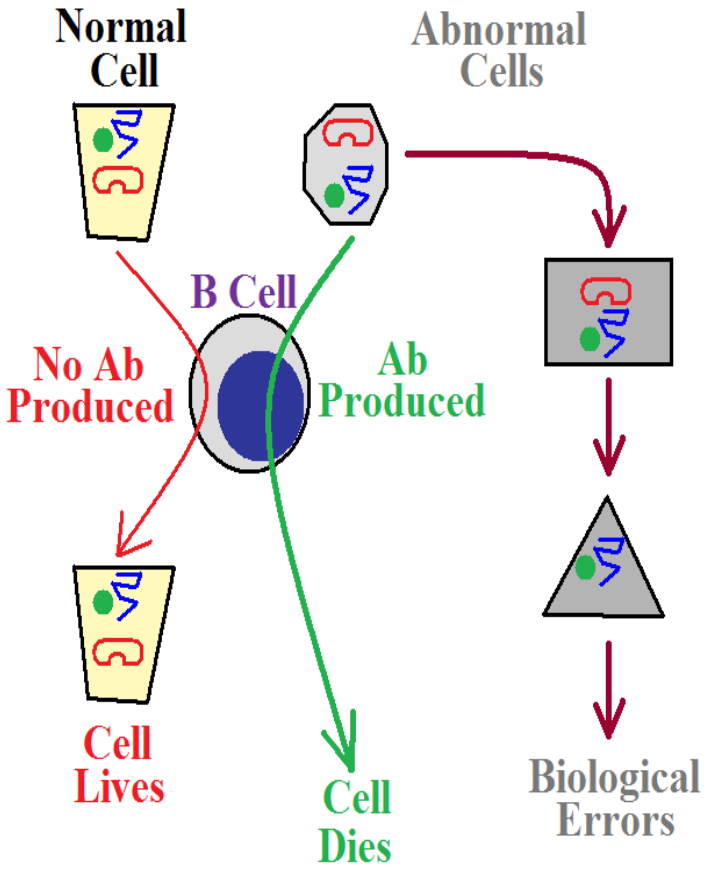
Collagen Theory of Aging

- As we age, our collagen (CALL uh junn) in our bodies gets older.
- When that happens the old collagen gets stiff and does not act as flexibly, causing problems, e.g.,
  - causes hypertension by not expanding to accomodate the flow of blood through the vessels,
  - stiff collagen causes organs to malfunction as they seem to be "crispy" and hinder metabolic reactions.



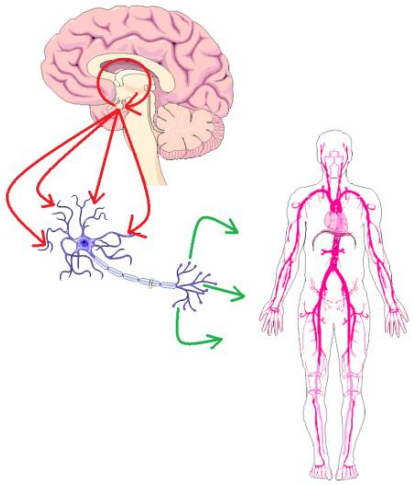
Mutating Autoimmune Theory of Aging

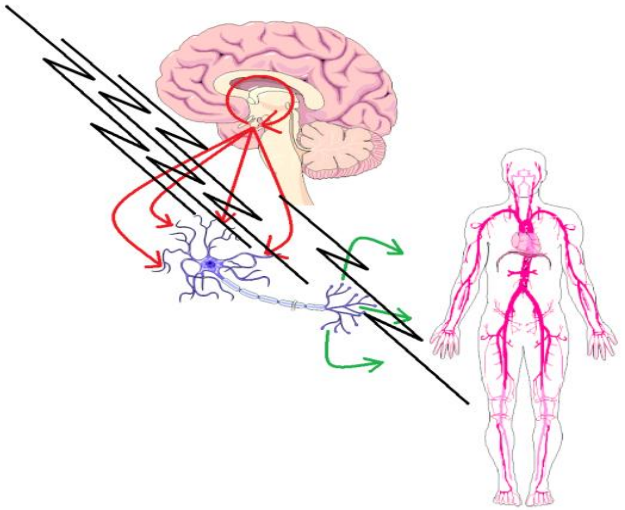
- Normal cells have normal functions and secrete normal proteins in, on or through the cell membrane.
- None of which ought to cause any sort of immune response.
- When, though, these cells mutate with time, they secrete foreign proteins in on or through the cell membrane which DOES solicit an immune response by the body.
- This response shuts down the cell.
- Alternatively, this theory also suggests that whole cells mutate over time and cause biological errors leading to the demise of the organism.



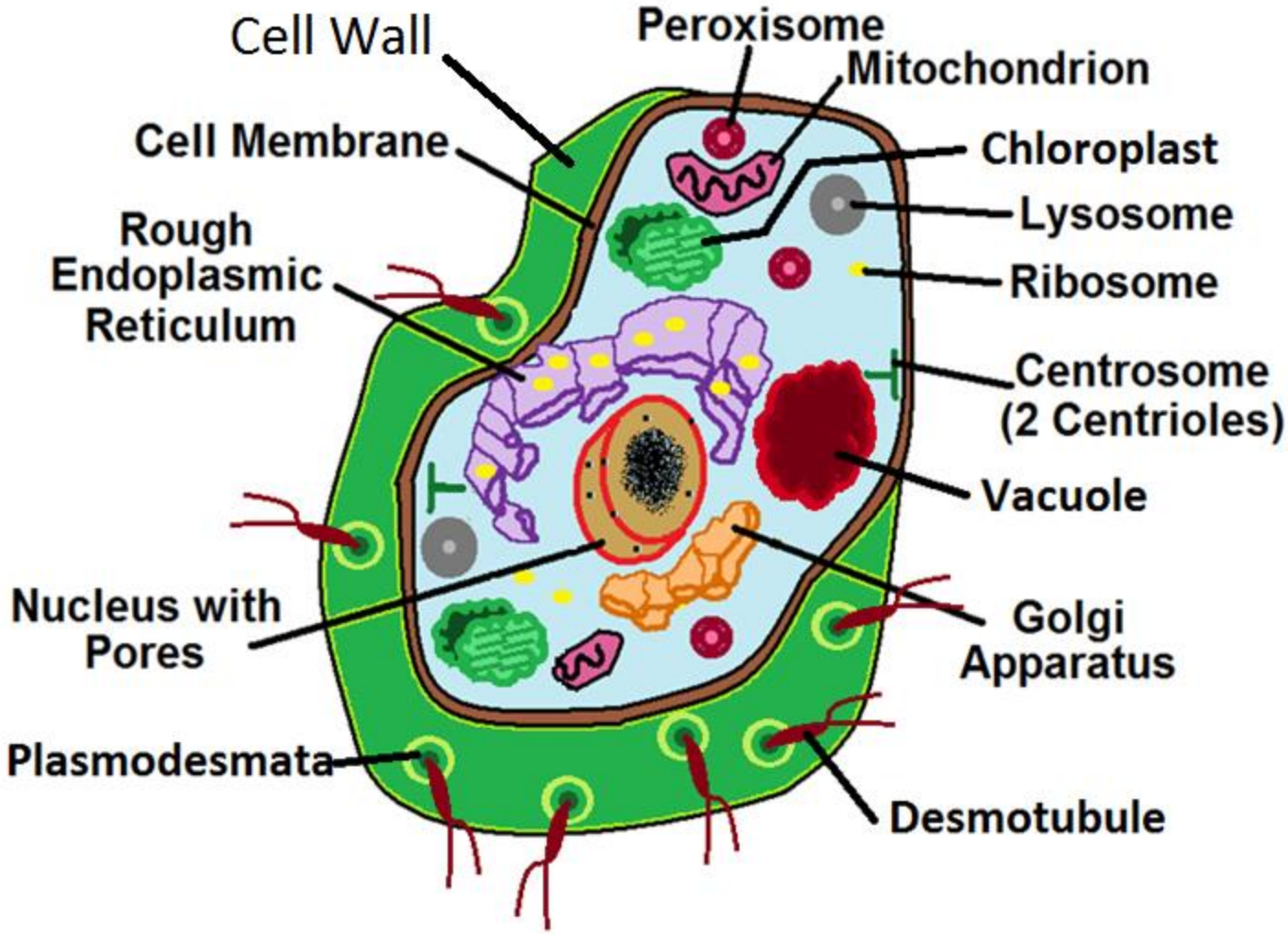
Neuroaging Theory

- As we age, we undergo thalamo-hypothalamo-pituitary (thuh LAMM oh HIGH poe thuh LAMM oh pi TOO uh tear ee; THP Axis) and neuronal degeneration.
- The THP axis is the "natural pacemaker" for all cellular aging and the concurrent effects on physiological processes.
- As we age, then there are alterations in hormonal release (lowered levels as we age) and effect (reduced numbers of receptors and/or increased peripheral resistance to the hormone by its target cells).
- All of these effects lead to the decline in cell function we call "aging" throughout the organism.

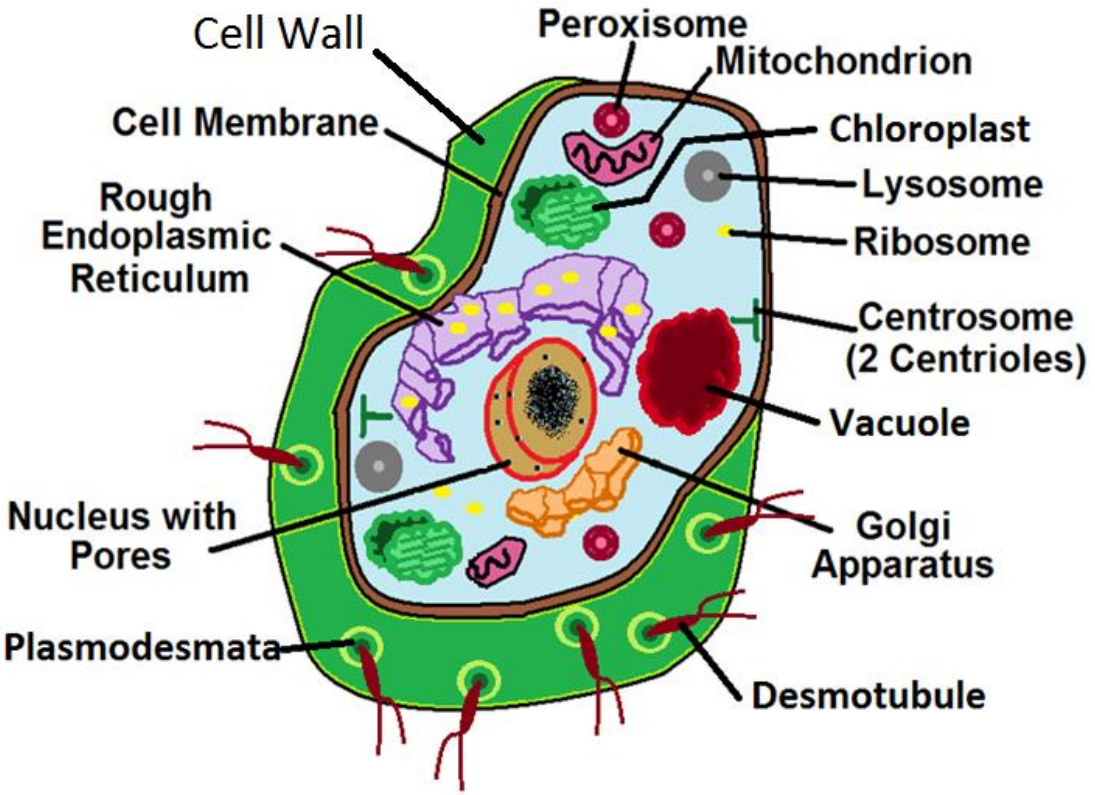




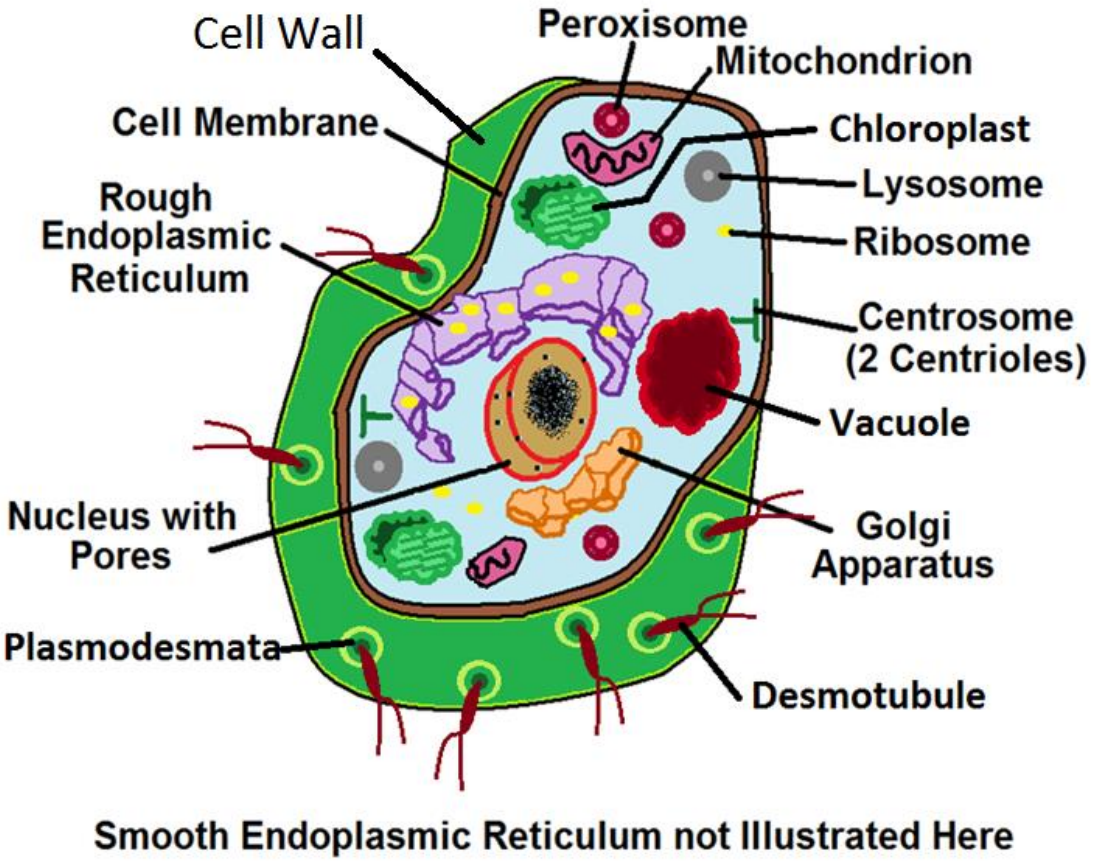
Plant Cells: Anatomy



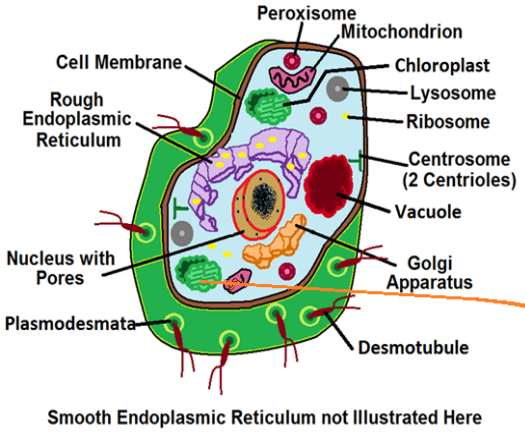
- Plasmodesmata: are narrow channels that act as intercellular cytoplasmic bridges to facilitate communication and transport of materials between plant cells.
- Desmotubule: Cylindrical membrane-lined channel through a plasmodesma, linking the smooth endoplasmic reticulum in the two cells.
- Chloroplast:
- Vacuole: Vacuoles are membrane-bound sacs within the cytoplasm of a cell that function in several different ways. In mature plant cells, vacuoles tend to be very large and are extremely important in providing structural support, as well as serving functions such as storage, waste disposal, protection, and growth. Many plant cells have a large, single **central vacuole** that typically takes up most of the room in the cell (80 percent or more).
- Tonoplast: Membrane around vacuole.

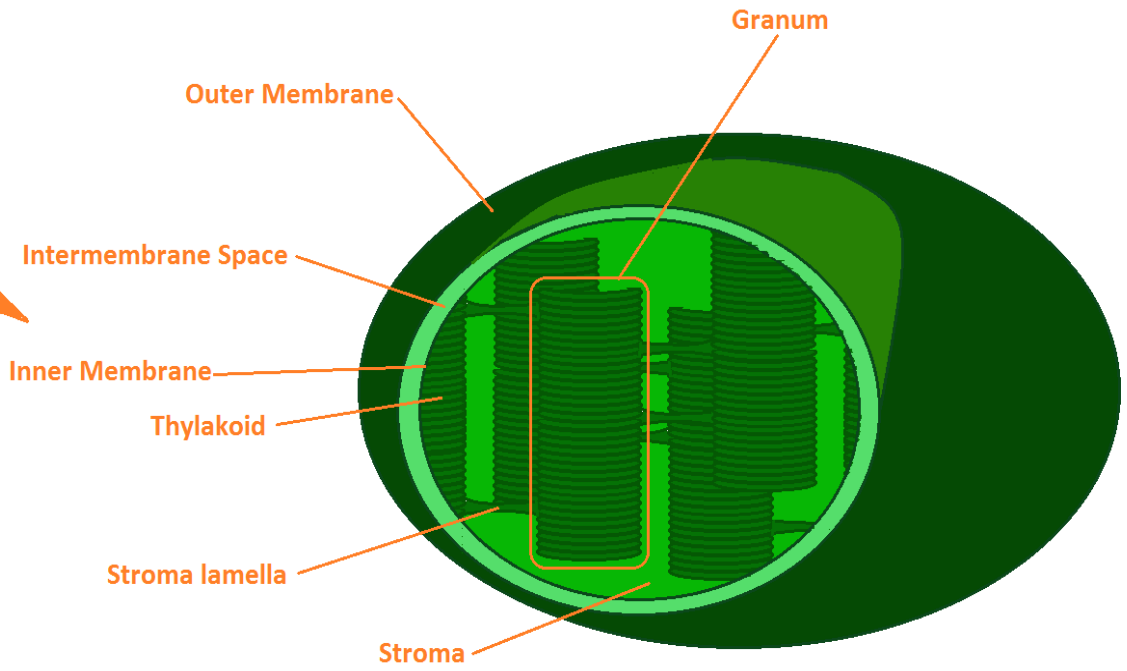


- Chloroplasts: the organelles responsible for photosynthesis, are in many respects similar to mitochondria. Both chloroplasts and mitochondria function to generate metabolic energy, contain their own genetic systems, and replicate by division. However, chloroplasts are larger and more complex than mitochondria, and they perform several critical tasks in addition to the generation of ATP. Most importantly, chloroplasts are responsible for the photosynthetic conversion of CO_2 to carbohydrates.
- In addition, chloroplasts synthesize amino acids, fatty acids, and the lipid components of their own membranes.
- The reduction of nitrite (NO_2^-) to ammonia (NH_3), an essential step in the incorporation of nitrogen into organic compounds, also occurs in chloroplasts.



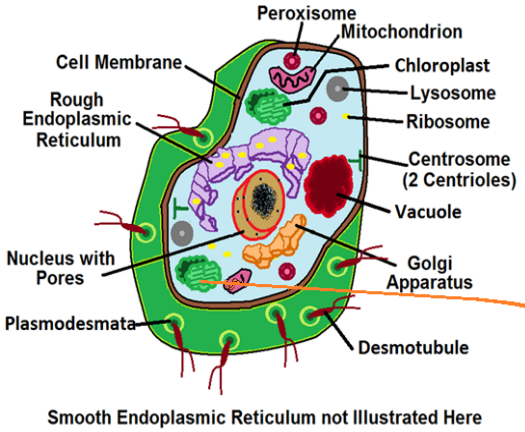
Chloroplast

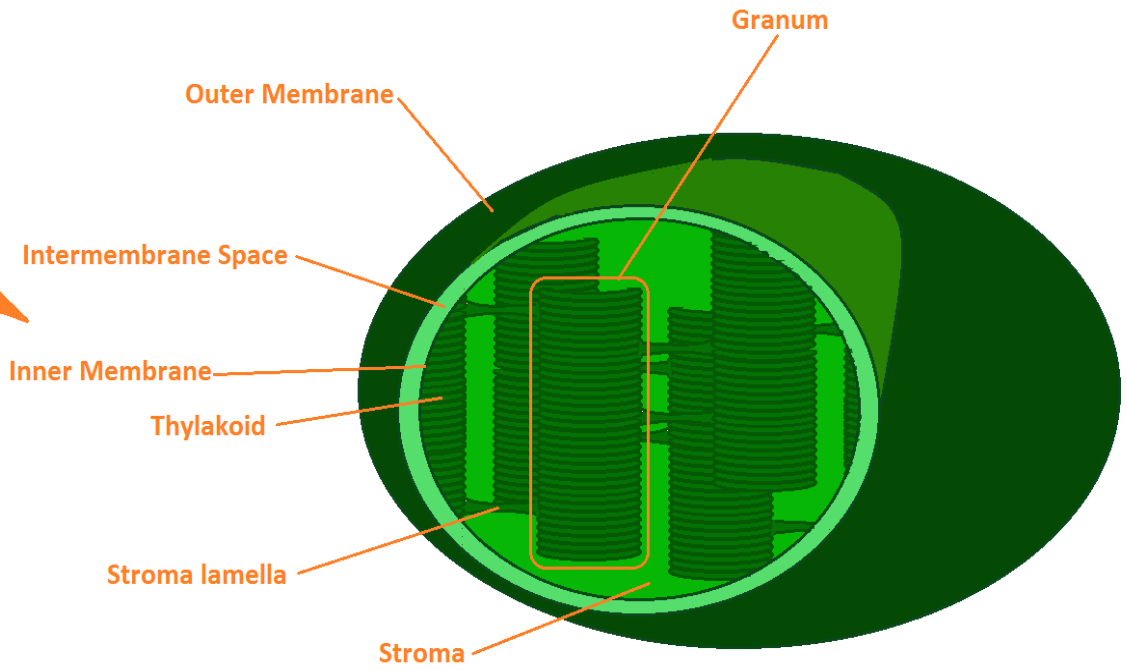




- Thylakoid: Thylakoids are membrane-bound structures embedded into the chloroplast stroma.
- Stroma Lamella: Grana (pl.) are connected by lamellae.
- Stroma: the gel-like matrix of chloroplasts.
- Granum: A stack of thylakoids; like a stack of coins.

Chloroplast

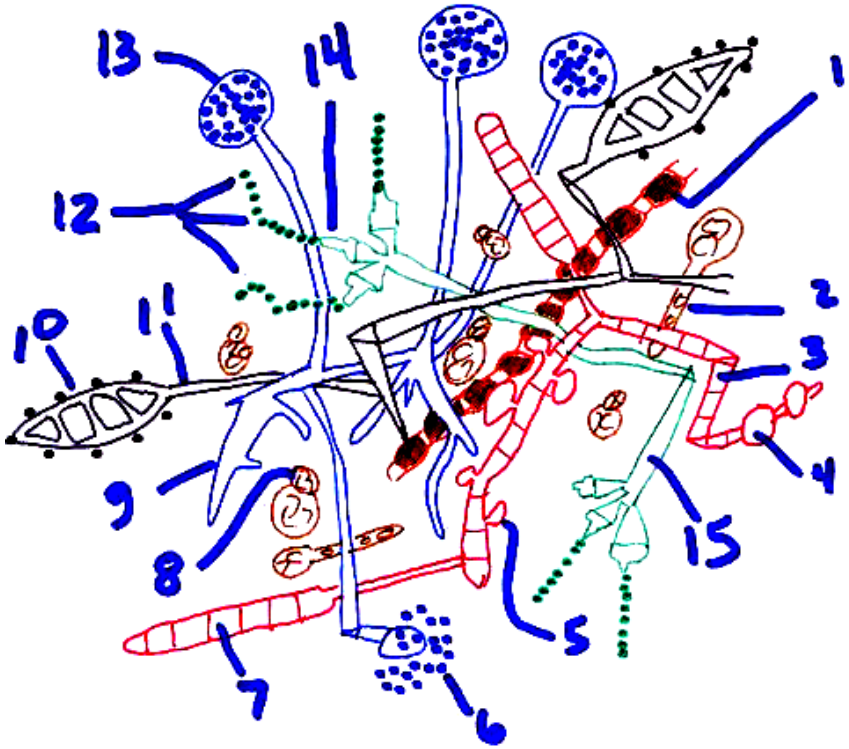




- The **thylakoid membrane** is the site of the light-dependent reactions of photosynthesis with the photosynthetic pigments embedded directly in the membrane.
- The **thylakoid lumen** is a continuous aqueous phase enclosed by the thylakoid membrane. It plays a vital role for photophosphorylation during photosynthesis. During the light-dependent reaction, protons are pumped across the thylakoid membrane into the lumen making it acidic down to pH 4.

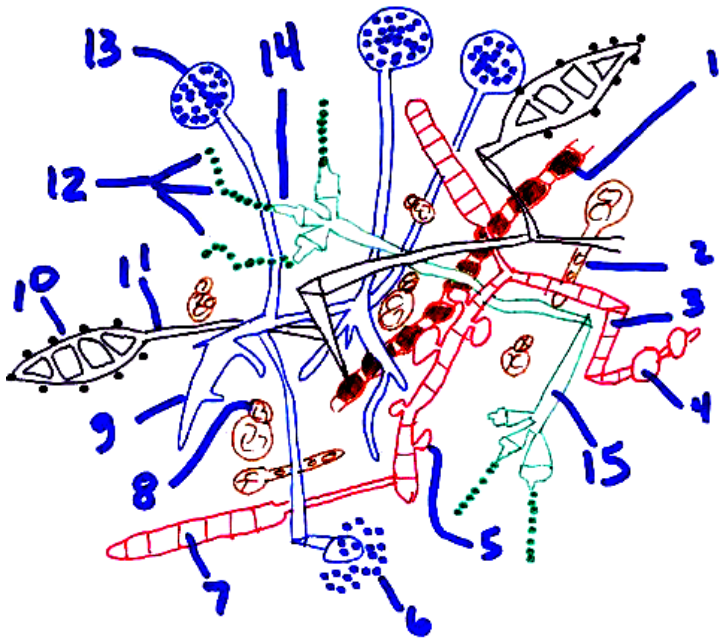
Fungal Anatomy

1. Arthroconidia
2. Pseudohypha
3. Septate hypha
4. Chlamydoconidia
5. Microconidia
6. Sporangiospore
7. Macroconidia
8. Blastoconidium
9. Vegatative mycelium
10. Macroconidium
11. Hypha
12. Conidia
13. Sporangium/spherule
14. Conidiophore
15. Non-septate hypha



Fungal Anatomy

- Blastoconidia (8): buds; yeasts
- Hypha (11): tubelike extensions of the cell with thick parallel cells
- Mycelium (9): intertwined hyphae – the fuzzy part of the mold you can see; anchors the mold and absorbs nutrients
- Pseudohyphae (2): less rigid walls than hypha
- Conidiophores (14): stalk-like structures that support
- Macro/microconidia (5, 7, 10): size of conidia
  - Imperfect fungi are called "imperfect" because no one has witnessed sexual stages among these fungi. Reproduction is only carried out asexually by reproductive structures called **conidia** produced on modified hyphae (**conidiophores**).
- Chlamydo/arthroconidia (1, 4): conidia in hyphae

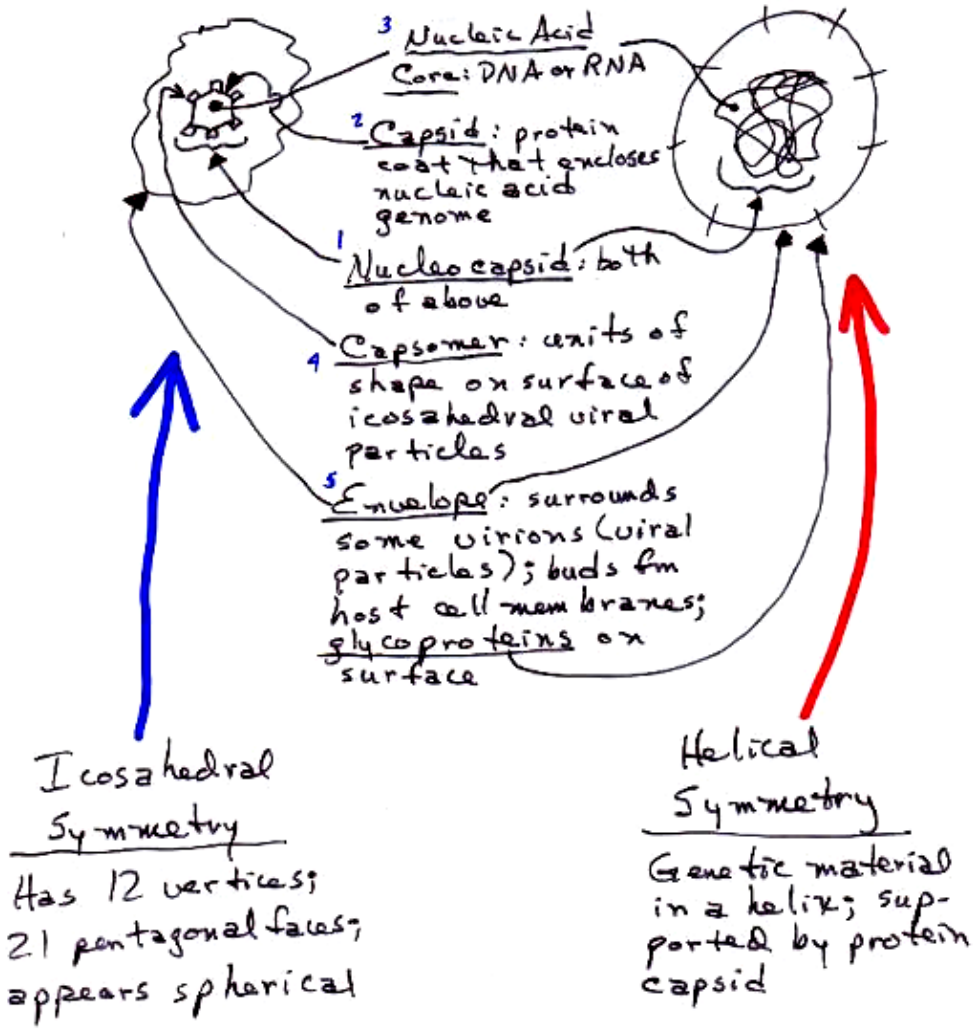


- Fungi are nature's decomposers
- Occasionally fungi from the non-pathogenic Phyla ARE pathogenic, e.g.,
  - Ascomycota: Candida, Trichophyton
  - Basidiomycota: Cryptococcus
- Generally under some sort of immunocompromisation that is either acquired "naturally",nosocomially or iatrogenically

Viruses

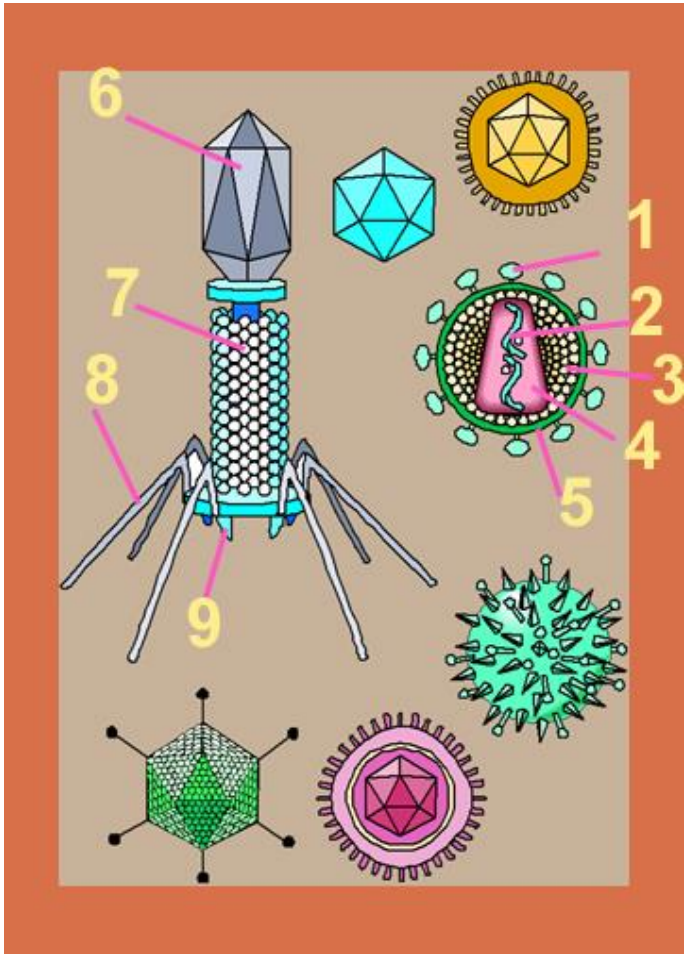
- One of the most important things to remember about viruses is that they are not living organisms.
- They are particles that have the capability of being reproduced by our own cellular machinery and contain some of the necessary elements for that replication, e.g., reverse transcriptase in HIV.
- Whenever a virus is referred to as "live", it means that the virus is capable of causing disease.
- An attenuated "live" virus is a virus that is capable of eliciting an immune response in the body, may cause a lighter form of the disease or may cause no noticeable form of disease, at all.

- Figure, right, illustrates very crudely two of the symmetries that viruses may attain: Icosahedral and helical symmetries. The former is characterized by having 12 vertices, 21 pentagonal faces and appears spherical. The latter contains its genetic material in a helix and is supported by a protein capsid.

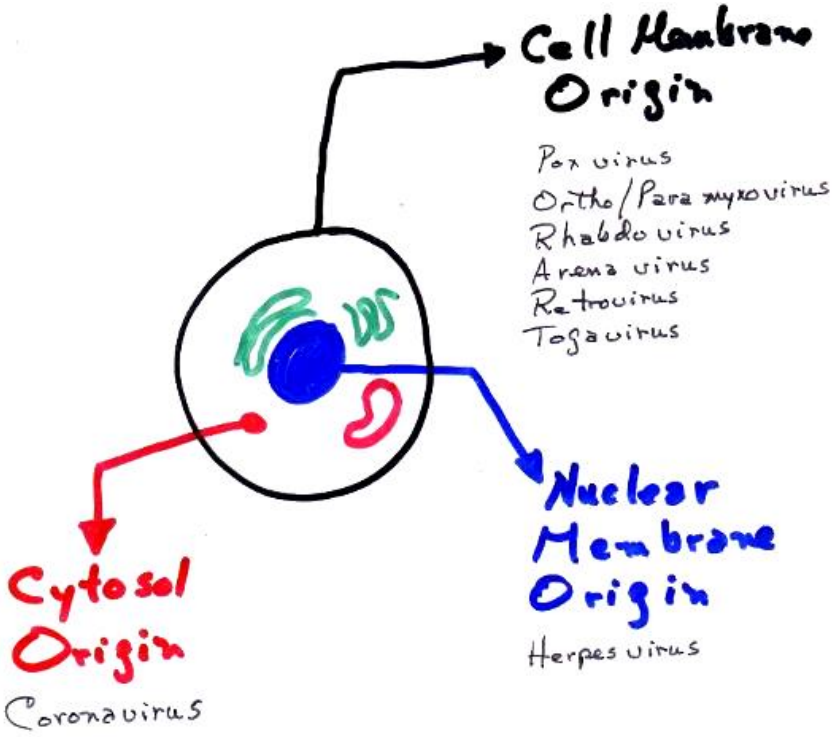


Viruses -- Anatomy

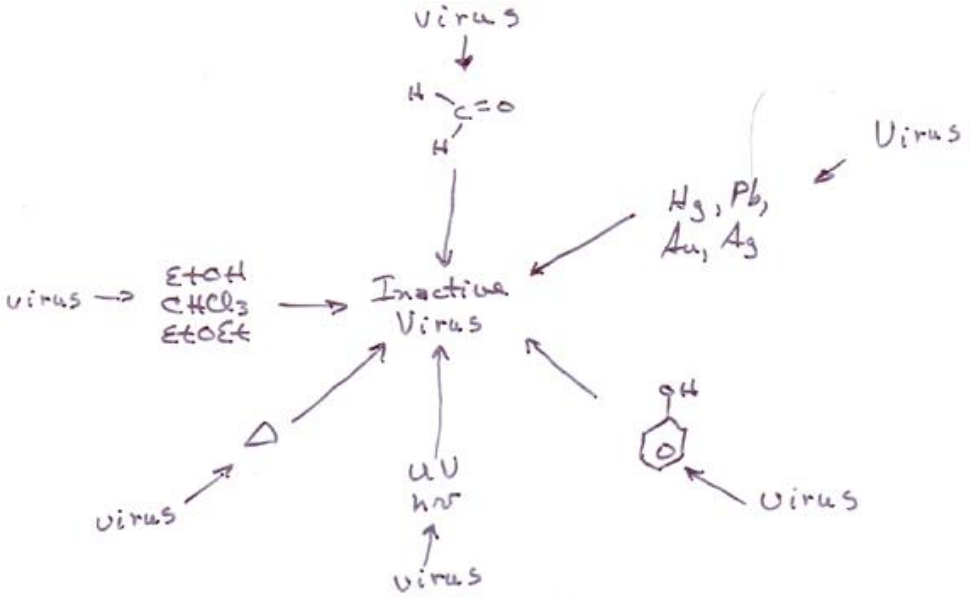
1. Glycoproteins/spikes
2. Nucleic acid core (may be DNA or RNA)
3. Capsid
4. Nuclear core
5. Viral envelope
6. Head
7. Tail sheath
8. Tail fibers
9. Pin



- Figure, right, illustrates that when many viruses are released from the cell that they receive a portion of their membranes from parts of our cells. For example,
  - Coronavirus "buds off" from the cytosol;
  - Herpes viruses "bud off" from the nuclear envelope;
  - Pox virus, Ortho/Paramyxoviruses, Rhabdovirus, Arena virus, Retrovirus and Togavirus "bud off" the cell membrane.



Techniques for Inactivating Viruses



- Formaldehyde reacts with amino groups on the nitrogenous bases of DNA or RNA to render the virus ineffective.
- Ethyl alcohol (EtOH), chloroform and diethyl ether dissolve lipids surrounding the virion.
- Heavy metals, e.g., Hg, Ag, Pb, Au, react with proteins on the capsid.
- Heat denatures the protein.
- Phenol, C_6H_5OH, reacts with proteins on the capsid.
- Ultraviolet light causes the formation of thymine dimers which puts "bubbles" in the DNA so it can not be "read" correctly and, hence, rendered inactive.