BIOL 230: Cell & Molecular Biology

Fall 2019 17-205 MW, Oct. 14-16

http://accounts.smccd.edu/staplesn/biol230/

1. Pre-Lab writeups due each Mon. (for both M&W!!) at the start of lab. (*briefly*, **What**? **Why**? **How**? for each expt.). Question & **Hypothesis**?!
2. **LAB this week: DNA Fingerprinting, #1!** ☺
3. **Ch. 10, PHOTOSYNTHESIS lecture IS POSTED ONLINE!!**
   - **Read the chapter, and watch the video. The Objectives and Study guide questions are DUE THURSDAY (with Ch. 9)!!**
4. **Native PAGE data** is posted under **"Add'l Materials."**
   - ❖ (Enzyme/Tyrosinase Rpt. Due 10/18 Online); Rough draft due TODAY!!!
5. **Extra Credit: STEM SPEAKER SERIES**, Weds. @ 5pm-6pm, Sept. 11- Nov. 6. (NOT Oct. 9) in 6-102. *Write 1 page summary by the following week, and upload to CANVAS*. Extra-Extra credit: Ask the speaker a scientific question, and write about the answer.
6. **THIS Wed.: Review for Midterm #2!! (Ch. 8, 9, 10, 13a?)**
7. **ALSO WED.: QUIZ #4 first attempt due!!!**

1

REVIEW

1. Diagram and describe the **forms in which energy** may be transferred between molecules and reactions in cells.
2. Outline or diagram the **energy** inputs and outputs of Glycolysis and Cellular Respiration. What types of **cofactors** and biomolecules are involved in these processes?
3. Diagram the inputs & outputs of **carbons** during Glycolysis and Cellular Respiration.
4. Explain how ATP is synthesized in mitochondria, including the electron transport process. Define **substrate-level phosphorylation, chemiosmosis, & oxidative phosphorylation.**

TODAY's Objectives: Students should be able to....

1. **Ch. 13:** Describe the separate experimental processes by which **Griffith, Avery et al., and Hershey/Chase** proved the identity of the Genetic Material.
2. Describe **five pieces of evidence** (and the scientists that produced them) that Watson and Crick used to deduce the **structure of DNA**.
3. Diagram and describe **6 structural characteristics of DNA** that are important to its function. ****
4. Using *diagrams*, describe the **functions of 9 Protein and Nucleic Acid factors involved in DNA Replication** at the leading and lagging strands…

❖ ***Objectives and Study Guide Questions are your HOMEWORK between classes!!! DUE WED. at the end of Lecture!!***

2

Chapter 13: DNA & Its Role in Heredity

1. DNA: The Genetic Material
2. The Structure of DNA
3. DNA Replication
4. The Mechanism of DNA Replication
5. DNA Proofreading and Repair
6. Practical Applications of DNA Replication

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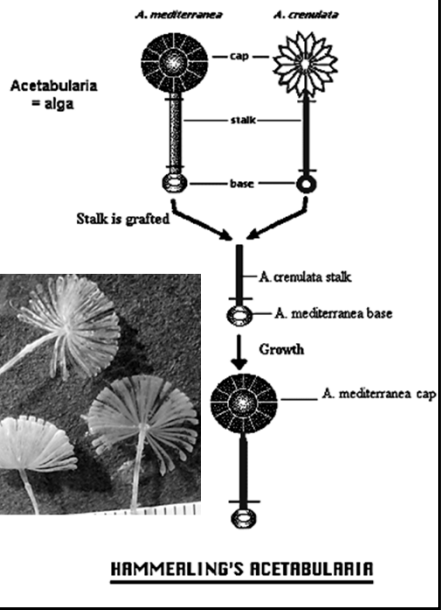
13.1) DNA: The Genetic Material

- **Nuclear transplantation experiments (1930s):**
  - **the nucleus carries the genes!!!**



❖ **Joachim Hammerling:**
- **Algae - "giant cells"**
  - ***Acetabularia…..***

- **Animals –**
  - **frogs, sheep, cattle….**

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DNA: The Genetic Material

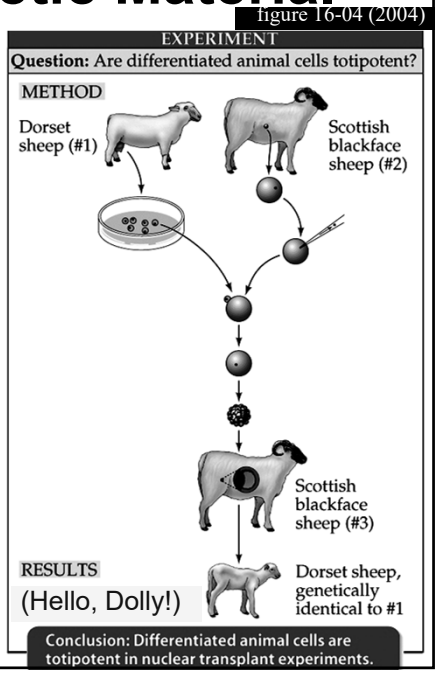
1. Nucleus from *somatic* ("body", udder) cell of Species 1

2. Implanted in enucleated, fertilized egg of Species 2

3. Offspring Genetically identical to species 1 !!

FYI: http://www.dnalc.org/cloning.html

http://learn.genetics.utah.edu/units/cloning/index.cfm



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DNA: The Genetic Material

- Nuclear transplantation showed that the nucleus carries the genes

- Staining reveals the "nucleic acids" within the nucleus (***Feulgen's Dye***)
  - Different amounts in different species
  - Half the amount in eggs and sperm
    - (***haploid*** gametes vs. ***diploid*** adult)

- *Three experiments then proved DNA is the genetic material: .....*

FYI:
http://www.wwnorton.com/college/biology/discoverbio3/core/content/ch12/animations.asp

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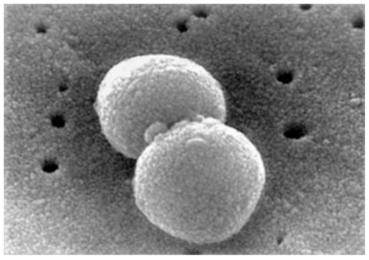
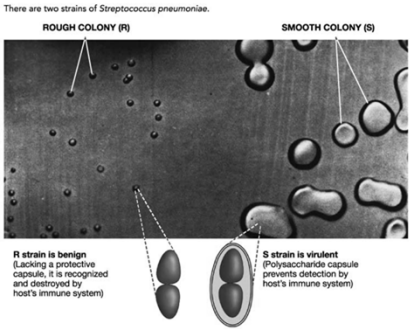
A. Griffith: The "Transforming Substance" is the Genetic Material

1. Frederick Griffith (1920s)

– DNA from a virulent strain of pneumococcus ***genetically transformed*** nonvirulent bacteria into virulent bacteria. *(Streptococcus pneumoniae)*





Tutorial: http://nortonbooks.com/college/biology/animations/ch12a01.htm

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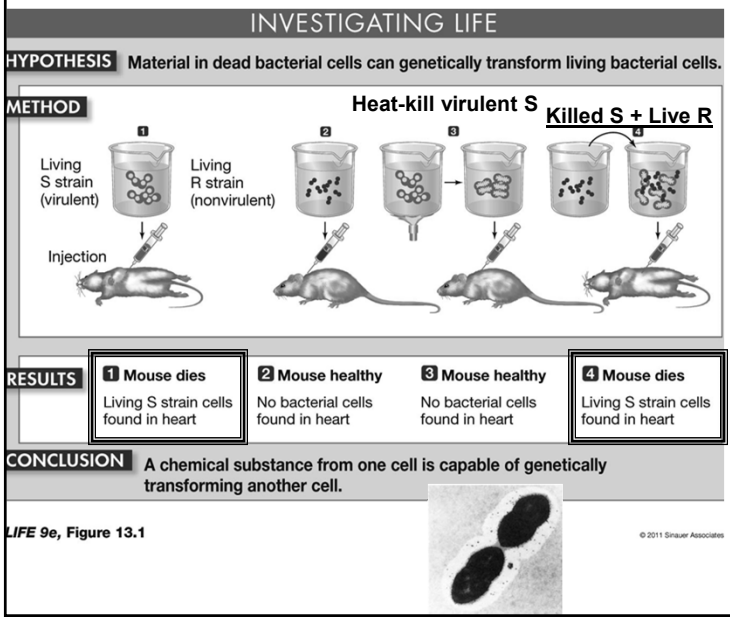
Griffith's Experiments



MOUSE INJECTIONS:

1. **Living S → death**
2. **Living R → healthy**
3. **Heat-killed S → healthy**
4. **Killed S + Live R → Dead!!**

- ***Something from the dead S cells TRANSFORMED the harmless R cells into Killers!!!***
- **(smooth with polysaccharide capsule)**

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What is the "Transforming Principle"?

1. **Griffith**: partially purified "***Transforming Substance***" caused the same transformation from R→S bacteria.
   - ***Was mostly DNA!***

2. Oswald **Avery,** Colin **MacCleod &** Maclyn **McCarty (1944):** treated "TS" with various, highly-specific, macromolecule-degrading enzymes
   - (Proteases, RNAses, DNAses, Glycosidases, Lipases)
   - ***None, except DNAses, removed the transforming ability of the Transforming Material***
   - ***Therefore, DNA Must be the Genetic Material!!!***
     - Still, many detractors remained!!!…("Still protein contaminant")….

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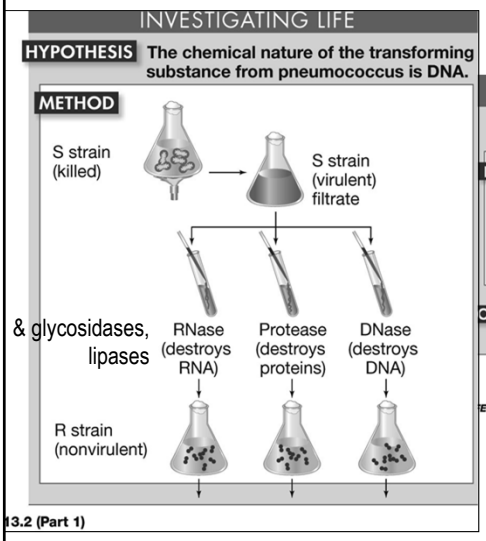
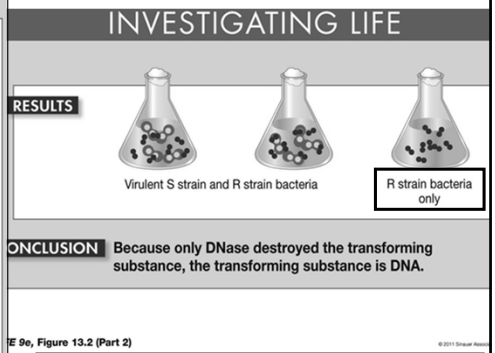
B. Avery, MacLeod, McCarty Experiment

- Individually treated the TS with different procedures to remove each known type of macromolecule…..





1. **TS = genetic material (Griffiths)**
2. **TS = DNA**
3. **Therefore, DNA = Genetic material!!**

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C. Hershey & Chase Blender Expt: Prove DNA = Genetic Material!

- **Alfred Hershey, Martha Chase (1952):**
  - Labeled viruses were incubated with host bacteria.
  - ➢ ***Labeled viral DNA entered host cells, while labeled virus protein did not.***
- Entry of the viral nucleic acids produced hundreds of label-bearing viruses.

http://highered.mcgraw-hill.com/olc/dl/120076/bio21.swf

Original paper: http://www.jgp.org/cgi/reprint/36/1/39

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T2 Bacteriophage

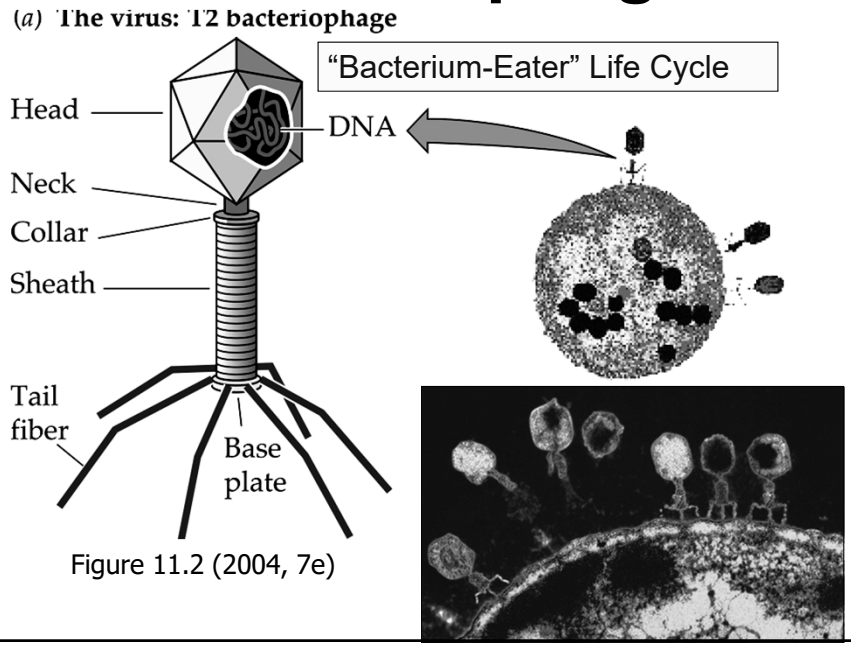

Figure 11.2 (2004, 7e)

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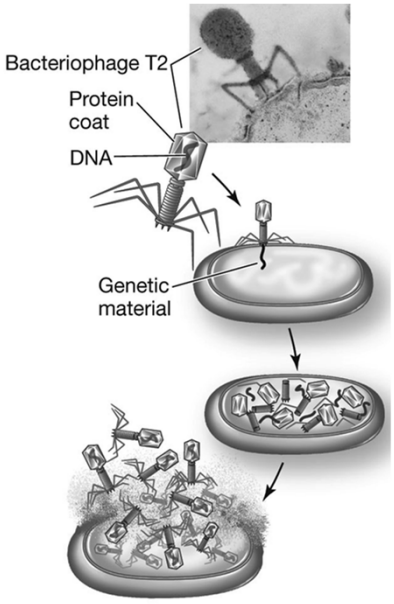
Fig. 13.3 Bacteriophage T2 Reproduction Cycle



13.3

1. **Adhesion:** Virus **attaches** at specific host surface receptor
2. **Infection:** Injects genetic material
3. **Synthesis & Assembly:** Virus particles replicate and assemble ("mature")
4. **Release:** About 100 phage particles lyse host and escape to reinitiate cycle
   - ***Which part of the virus is the genetic material that is injected into cells???***

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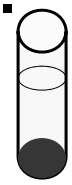
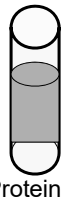
Hershey-Chase Blender Expt.

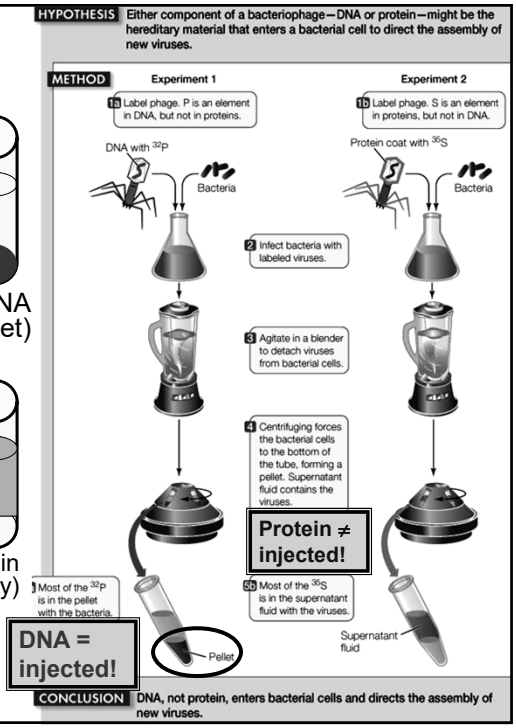
- **^{32}P-DNA** in Pellet (Cells!!)
  - Labels Phosphates
  - (In DNA, not Protein!!)
- **^{35}S-Protein** in supernatant (not in cells!).
  - Labels methionine and cysteine amino acids
  - (not in DNA!!)
- ***Thus, DNA is the injected, Genetic Material!!***



^{32}P = DNA (in pellet)



^{35}S = Protein (in sup. only)



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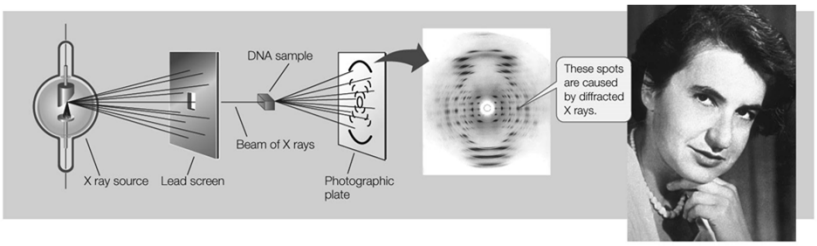
13.2) The Structure of DNA

1. X-ray crystallography showed that the DNA molecule is a ***helix (cylindrical spiral).***
   - (Rosalind Franklin, Maurice Wilkins).
2. Also, has **regular diameter** (~20 Angstroms = **20 Å**)
   - [= width of two purine/pyrimidine nucleotide pairs!! = 2 strands.]



3. Also: **Density Centrifugation data → 2 strands!!**

http://www.dnai.org/a/index.html

LIFE 9e, Figure 13.6

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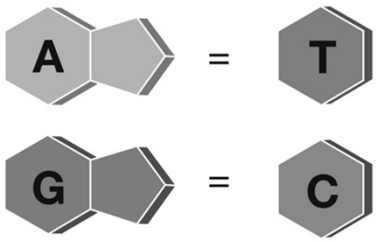
Composition of DNA was known (Edwin Chargaff, 1950)

4. DNA is composed of nucleotides
   - **("Phos-Sug-Base")**
5. Each containing **Adenine**, **Cytosine**, **Thymine**, or **Guanine**.



a) [A] = [T]

b) [G] = [C]

c) [Pur] = [Pyr]

❖ **Chargaff's Laws proven in dozens of different species**

LIFE 9e, Figure 13.7

11.1 ***Percentages of Bases in the DNA of Some Well-Studied Species***

DNA ORIGIN	AMOUNT OF BASE (PERCENTAGE OF TOTAL DNA) A	T	G	C
Human (*Homo sapiens*)	31.0	31.5	19.1	18.4
Corn (*Zea mays*)	25.6	25.3	24.5	24.6
Fruit fly (*Drosophila melanogaster*)	27.3	27.6	22.5	22.5
Bacterium (*Escherichia coli*)	26.1	23.9	24.9	25.1

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The Structure of DNA

James Watson & Francis Crick proposed:

1. DNA is a double-stranded helix
2. with antiparallel strands, and
3. with bases linked by hydrogen bonding.

****

❖ ***Their model accounts for:***

1) Storage of genetic <u>information</u>,

2) Possibility of <u>mutation</u>, and

3) How <u>replication</u> functions with DNA.

❖ ***** All are required functions of the Hereditary Material!!***

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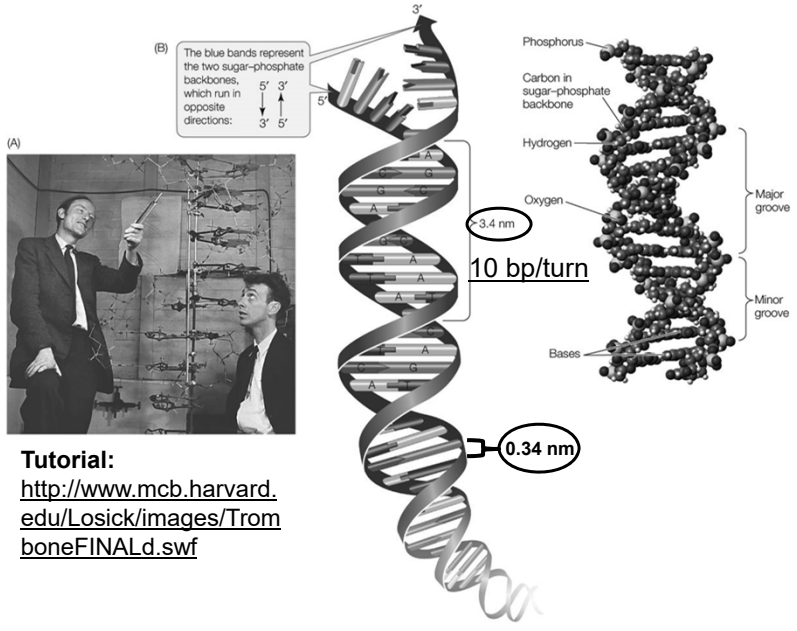
Fig. 13.8 DNA Is a Double Helix



Tutorial:
http://www.mcb.harvard.edu/Losick/images/TromboneFINALd.swf

...e, Figure 13.8 © 2011 Sinauer Ass

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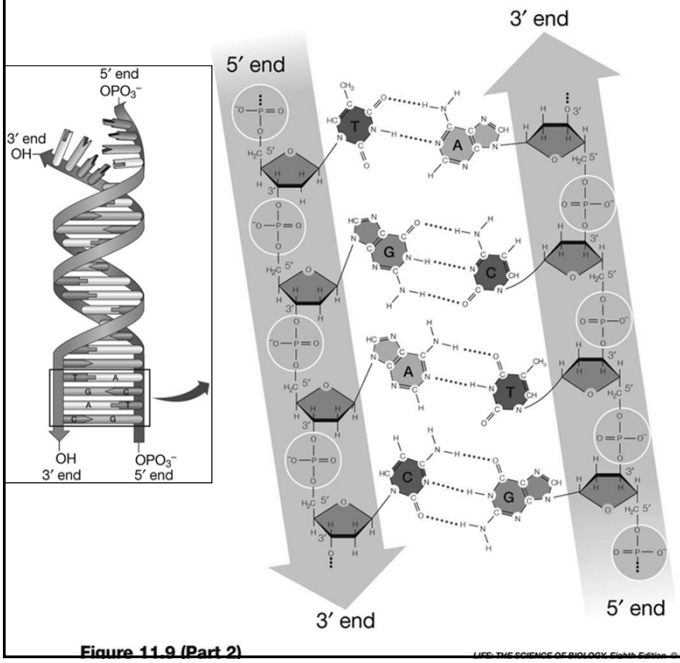
Fig. 13.9 Base Pairing in DNA Is Complementary



1. **2 strands (duplex)**
2. **Right-handed helix**
3. **Antiparallel**
4. **Pur-Pyr (20Å)**
5. **Regular diameter (20Å)**
6. **G≡C (3H)**
7. **A=T (2H)**

The STAPLES RULES!! ☺ ….
http://www.imb-jena.de/ImgLibDoc/bp/pu_py.html

Figure 11.9 (Part 2)

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13.3) DNA Replication

"It has not escaped our notice that the specific pairing we have postulated immediately suggests a possible copying mechanism for the genetic material."

~ James Watson & Francis Crick, *Nature*, 1953

- Semiconservative, conservative, and dispersive models for DNA replication were hypothesized.

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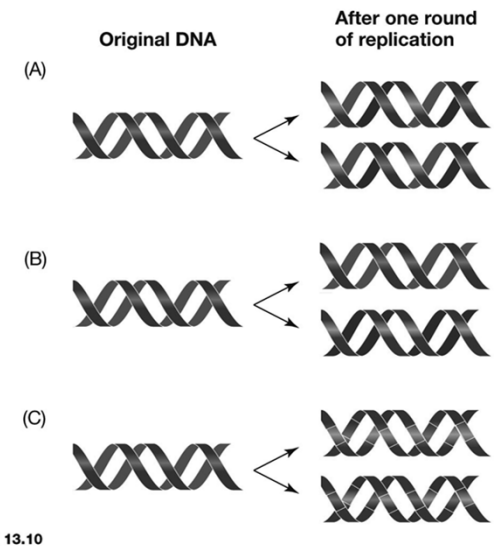
Possible Modes of DNA Replication



1. **Semiconservative** = each daughter duplex has 1 old & 1 new strand (W & C predict.)
2. **Conservative** = each daughter duplex is all old or all new
3. **Dispersive** = each daughter duplex has fragments of old and new DNA

Tutorial: http://www.wiley.com/legacy/college/boyer/0470003790/animations/replication/replication.htm - basics
http://www.wiley.com/college/pratt/0471393878/student/animations/dna_replication/index.html

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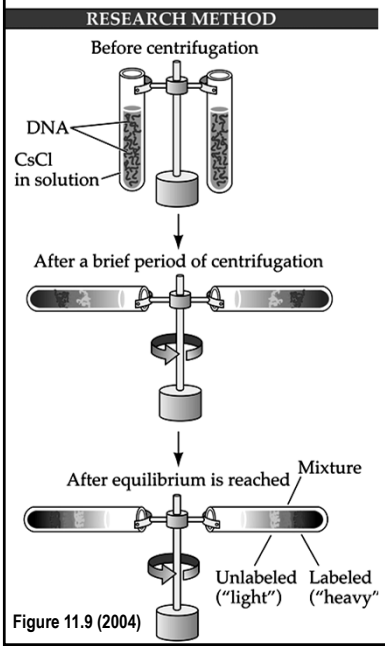
Equilibrium Density Gradient Centrifugation



- **CsCl Density Gradient Centrifugation**
  - Separate molecules based on density/molecular weight
    - 100K x g
  - Even slightly different weights of isotopes of the same atoms may be distinguished
- **Molecules of same density as CsCl in region of tube will settle/reach equilibrium there**
  - **Denser/heavier nearer to bottom**

http://highered.mcgraw-hill.com/olc/dl/120076/bio22.swf

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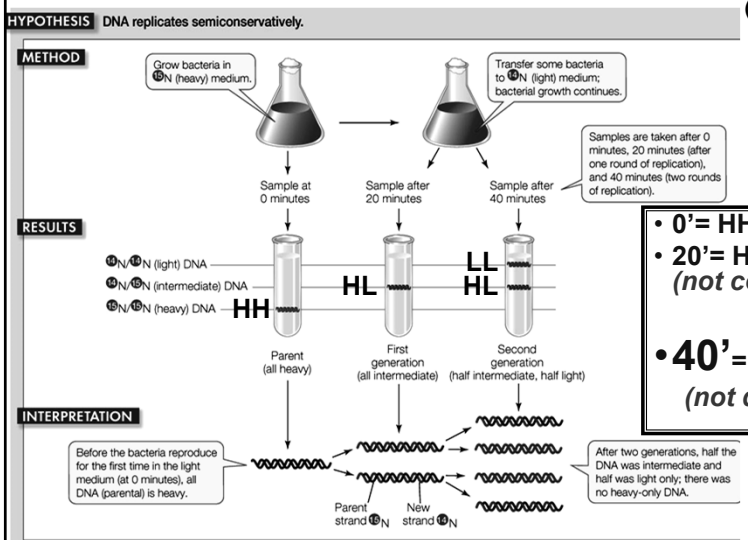
Meselson and Stahl's Experiment

(Matthew & Franklin)



- 0'= HH
- 20'= HL *(not conservative)*
- **40'= HL + LL** *(not dispersive)*

http://www.dnaftb.org/dnaftb/20/concept/index.html

e, Figure 13.11

Tutorial: http://www.sumanasinc.com/webcontent/anisamples/majorsbiology/meselson.html

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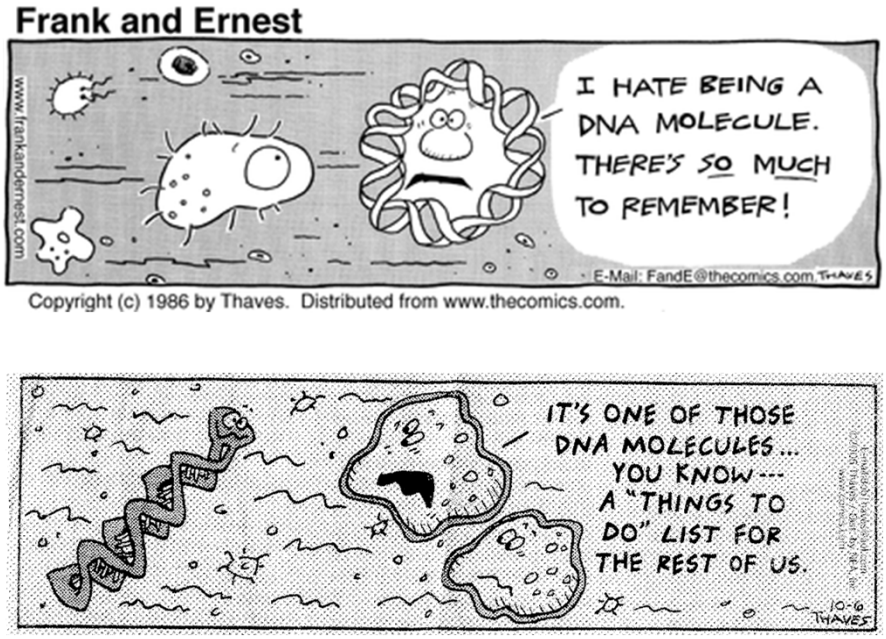

10/6/2005

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13.4) Molecular Mechanism of DNA Replication

- **Arthur Kornberg** (1956):
  1. **DNA polymerase** catalyzes addition of nucleotides to the 3′ end.
  2. NT's are added by *complementary base pairing* with the *template strand*.
  3. Substrates = deoxyribonucleoside triphosphates (***dNTPs***)

http://bioteach.ubc.ca/TeachingResources/MolecularBiology/DNAReplication.swf

http://highered.mcgraw-hill.com/sites/0072943696/student_view0/chapter3/animation__dna_replication__quiz_1_.html

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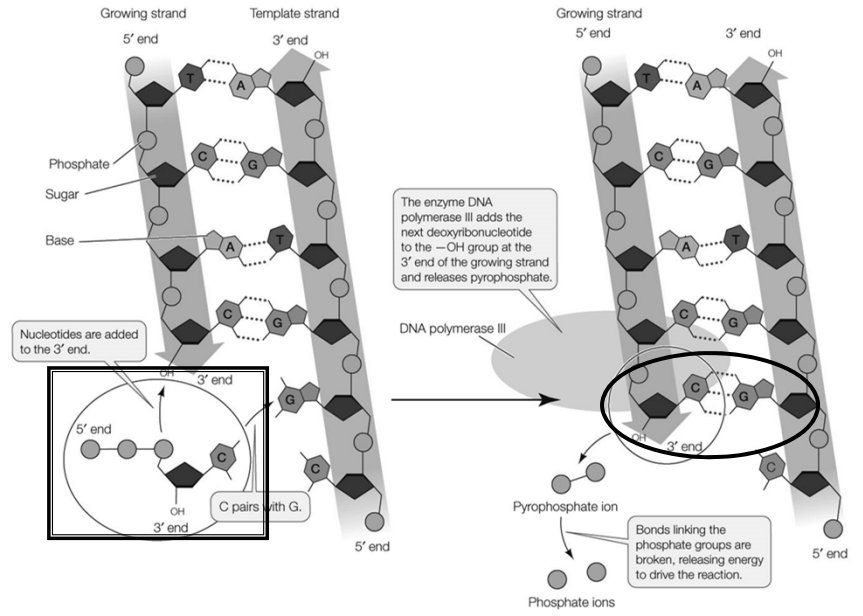
DNA Polymerization: 5'→ 3'!!!



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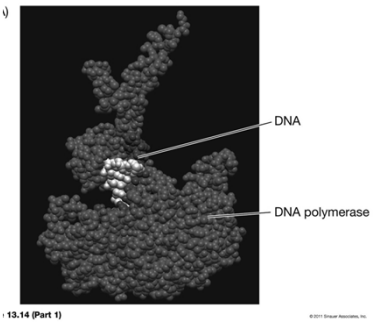
Mechanism of DNA Replication

- Kornberg showed that DNA can replicate in a test tube (***in vitro = "in glass"***)
  - with only a specific enzyme (***DNA polymerase***)
  - and a mixture of four precursors: dATP, dCTP, dGTP, and dTTP ("**dNTPs**").



- According to newer evidence: *DNA replication complex (**Replisome**!)* is in a "fixed" location and DNA is threaded through it for replication.
- DNA Synthesis begins with a small stretch of RNA!!!
  - An "RNA Primer" for DNA synth. to begin.

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A. Initiation of DNA Replication

❖ Many proteins assist in DNA replication.

- **DNA helicases** unwind the double helix at the ***Origin***,
- the template strands are stabilized (ss) by other proteins (**single-strand binding proteins, SSB**).

1. **Dna-A** – (protein) attach to bact. PM and melt ***Ori*** apart
2. **DNA Helicase** – unwind double helix (not initial melting)
3. **SSB Proteins** – keep template DNA strands apart/open
4. **RNA Primase** – lays down ***RNA primer*** to initiate DNA polym'n
5. **DNA Polymerase III** – synthesizes DNA from dNTP's
6. **DNA Polymerase I** – removes RNA primers and fills in gaps w/ DNA
7. **DNA Ligase** – seals last phosphodiester bond between DNA segments on the same strand.

http://www.stolaf.edu/people/giannini/flashanimat/molgenetics/dna-rna2.swf

Dna-A -- http://highered.mcgraw-hill.com/sites/dl/free/0072835125/126997/animation17.html

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1. Origins of Replication (*Ori*)

- Prokaryotes have a ***single Origin*** of replication;
- Eukaryotes have ***many (hundreds!!) Origins***.

- Replication for each proceeds in both directions from an origin of replication.
  - ***BIDIRECTIONAL REPLICATION!!***

http://highered.mcgraw-hill.com/sites/0072943696/student_view0/chapter3/animation__dna_replication__quiz_1_.html

http://www.courses.fas.harvard.edu/~biotext/animations/replication1.swf

http://bioteach.ubc.ca/TeachingResources/MolecularBiology/DNAReplication.swf
http://www.johnkyrk.com/DNAreplication.html

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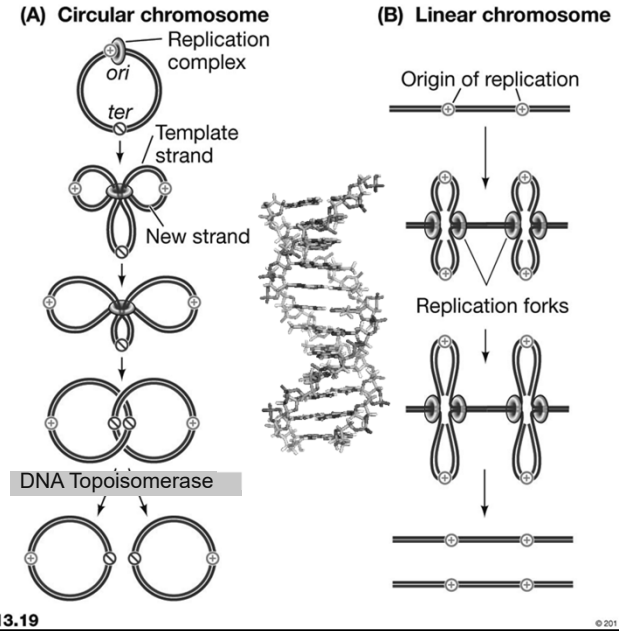
2. Bidirectional Replication



- Origins of replication
  - ***Ori***
- Termination sites
  - ***Ter***
- ***DNA Topo-isomerase***
  - ***eg: DNA Gyrase***

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3. Replication Initiation Enzymes

a) **DNA Helicase -** opens the double helix at ***Ori*** and ahead of the replication complex

b) **RNA Primase** (an RNA Polymerase)
- catalyzes the synthesis of short RNA primers
- to which deoxy nucleotides are later added.

c) ***DNA Polymerase III*** **– most of DNA polymerization** (highly ***processive*** NZ)

Dna-A: http://highered.mcgraw-hill.com/sites/dl/free/0072835125/126997/animation17.html
http://highered.mcgraw-hill.com/sites/0072835125/student_view0/animations.html# -- DnaA, Telomerase

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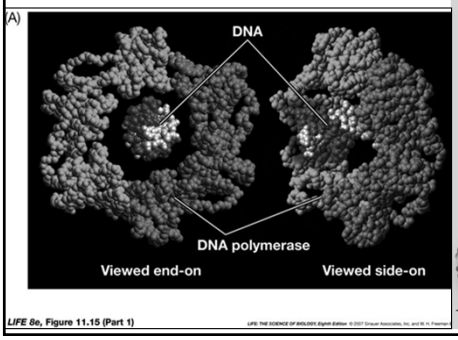
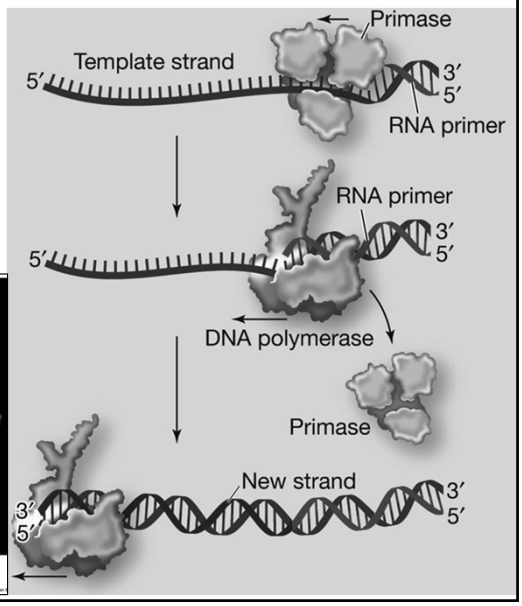
4. DNA Synthesis Requires a Primer

- ***RNA Primase***
  - Dpol needs free 3'-OH
- ***DNA Polymerase III***





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B. Elongation of DNA – (1.) Leading Strand

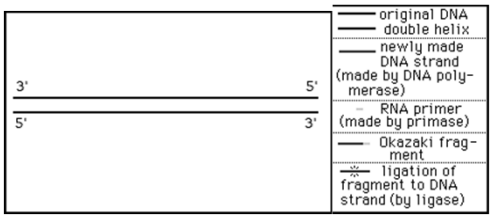
- *DNA polymerase* action causes the ***Leading Strand*** to grow in the 5′-to-3′ direction

a) until replication of that section of DNA is complete (***continuous synthesis***)

b) SSB keep the template duplex open until the replication fork passes

c) RNA primer is degraded and DNA replaces it.
   - By ***Dpol I, & Ligase***

Continuous vs. Discontinuous DNA Synthesis



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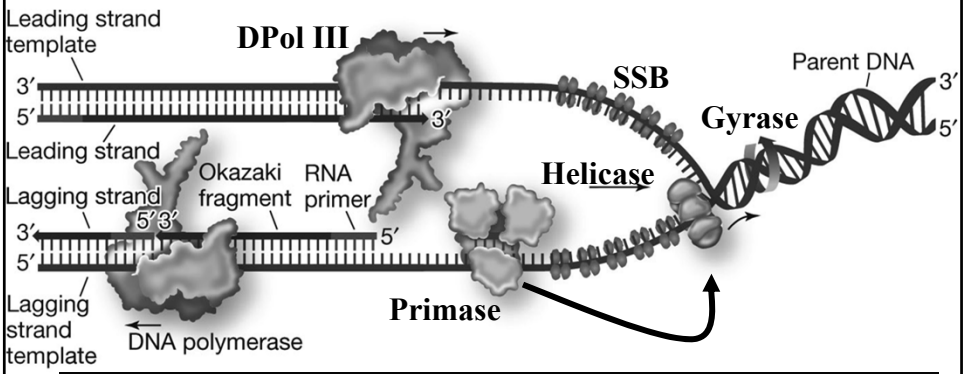
Many Proteins work at the Replication Fork



- ***Replication FORK*** = ½ of a ***replication BUBBLE***
- Each Fork has a ***Leading Strand (continuous synthesis)***
- And a ***Lagging Strand (discontinuous synthesis)*** →
  - Okazaki Fragments = evidence of discont. synthesis.

***LIFE 9e*, Figure 13.15**

http://www.courses.fas.harvard.edu/~biotext/animations/replication1.swf

http://highered.mcgraw-hill.com/sites/0072943696/student_view0/chapter3/animation__dna_replication__quiz_1_.html

http://www.dnalc.org/resources/3d/DNAReplicationBasic_w_FX.html

http://www.johnkyrk.com/DNAreplication.html

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Two Daughter Strands form Differently

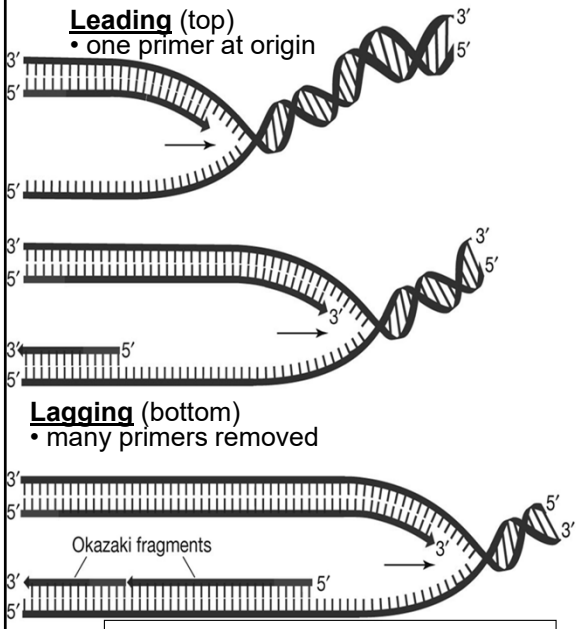

Figure 13.16

http://www.hhmi.org/biointeractive/dna/animations.html

- ***Leading*** → ***Continuous***
- ***Lagging*** → ***Discontinuous***
  - Okazaki Fragments.
  - Several Primers/ Priming sites.

http://www.dnalc.org/resources/3d/DNAReplicationBasic_w_FX.html

http://www.wiley.com/college/boyer/0470003790/animations/replication/replication.htm

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(2.) DNA Elongation – Lagging Strand

- On the ***lagging strand***, growing in the other direction, DNA is made in the 5′-to-3′ direction but ***synthesis*** is ***discontinuous***:
  a) DNA is added as short fragments to primers,
  b) then the polymerase skips past the 5′ end to make the next fragment.
     - Each fragment = ***OKAZAKI FRAGMENT***

http://www.dnalc.org/resources/3d/DNAReplicationBasic_w_FX.html

http://nobelprize.org/educational_games/medicine/dna/a/replication/lagging_ani.html

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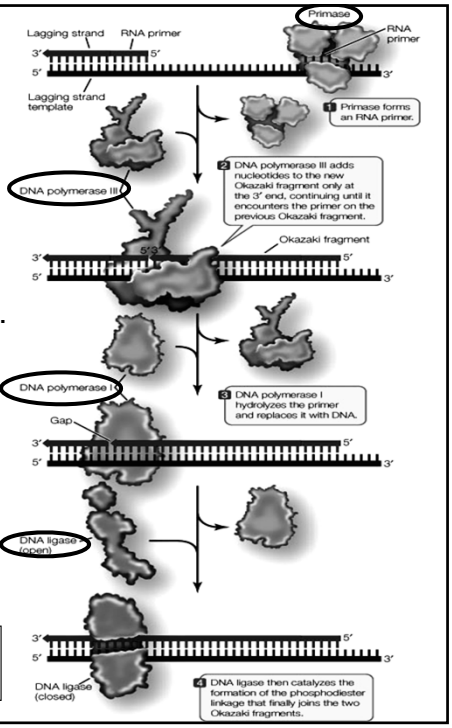
Lagging Strand Synthesis

Fig. 13.17



1. **DPol III** is continually removed and "reloaded" onto template.
   - Stabilized on template by ***"Sliding Clamp" protein***…..
2. ***DPol I*** – exonuclease & polymerase, **5'→3'.**
   - Removes RNA primer.
   - Fills-in DNA gap.
3. ***Ligase*** seals last Phosphodiester bond.

http://www.courses.fas.harvard.edu/~biotext/animations/replication1.swf

http://www.wwnorton.com/college/biology/mbio/animations/dna_replication.asp

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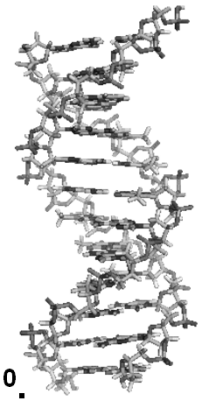
13.5) DNA Proofreading & Repair

- There is about about **one error in 10^6 nucleotide** bases added in DNA replication,
  - Often harmful or fatal!!



- **Repaired by:**
  1. proofreading,
  2. mismatch repair, and
  3. excision repair.
- DNA repair mechanisms lower the error rate to about **one base in 10^9 - 10^{10}.**

❖ ***Although energetically costly and redundant, DNA repair is crucial to cell survival, preventing potentially damaging/lethal mutations!!***

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DNA Methylation "tag" for parental DNA

- The **mismatch repair** mechanism scans new DNA for mismatched base pairs.
  - mismatch repair operates before new DNA strand is ***Methylated***.
    - distinguishes between the ***methylated template strand*** and the unmethylated new strand.
    - determines which base is "correct" (the base on the template strand) and which base needs to be replaced.

- **Excision repair** proteins operate over the life of a cell
  - Enzymes ("Seeker" proteins & Repair NZs) inspect DNA for damage by chemicals, radiation, & random spontaneous chemical reactions.
  - **UvrA(2)/UvrB complex** = seekers; **UvrC/D complex** = endonuclease & helicase

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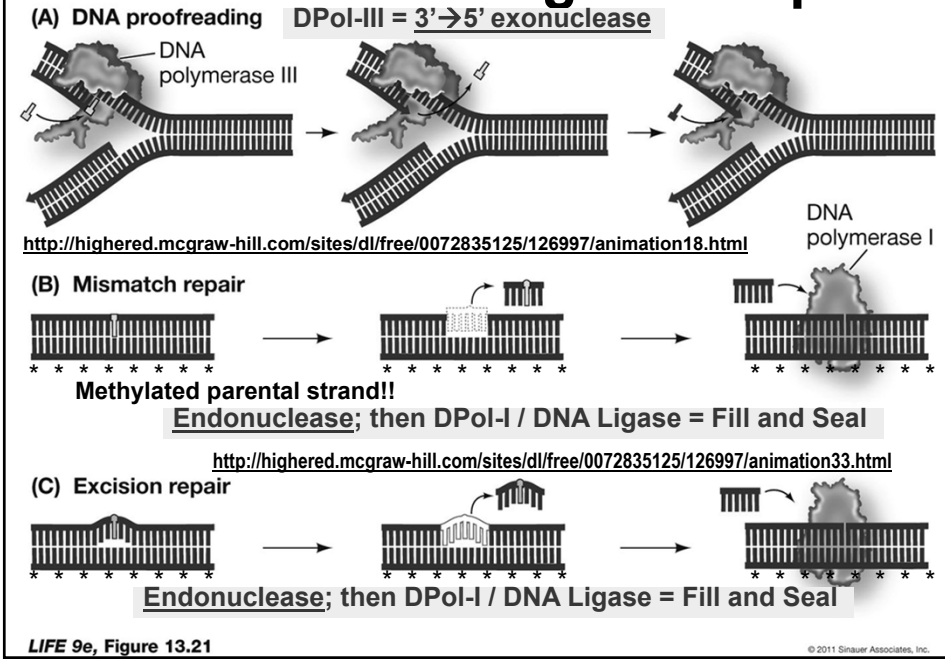
DNA Proofreading and Repair



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13.6) TELOMERES

1. Recall: replication of the lagging strand occurs by the addition of Okazaki fragments to RNA primers.

2. Beyond the very end of a **linear DNA molecule (eukaryotic)**, there is no place for a primer to bind.
   - New chromosomes formed after DNA replication have single-stranded DNA at each 5' end.
   - This single-stranded region is cut off, slightly shortening the chromosome after each cell division.

http://highered.mcgraw-hill.com/sites/dl/free/0072835125/126997/animation19.html

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Telomeres/ Telomerase

1. **Telomeres** = repetitive sequences at the ends of eukaryotic chromosomes that shorten after each round of cell division.
   - ***prevent degradation of linear chromomosomes from loss of 5' ends. (Vertebrates = TTAGGG)***
2. After a number of cell divisions, the telomeres are too short to stabilize chrom. ends
   - no cell division can occur.
   - results in cell death
   - explains in part why cells do not last the entire lifetime of the organism.
3. ***Telomerase*** = enzyme that catalyzes the addition of any lost telomeric sequences. = a ***Reverse Transcriptase!!***
   - = in constantly dividing cells (bone marrow, germ line, & > 90% of cancer cells).
   - Most somatic cells lack telomerase, and thus have limited life spans.

http://highered.mcgraw-hill.com/sites/0072835125/student_view0/animations.html# .....
http://bcs.whfreeman.com/lodish5e/pages/bcs-main.asp?s=10000&n=00010&i=10010.03&v=chapter&o=|00PRS|&ns=0&t=&uid=0&rau=0

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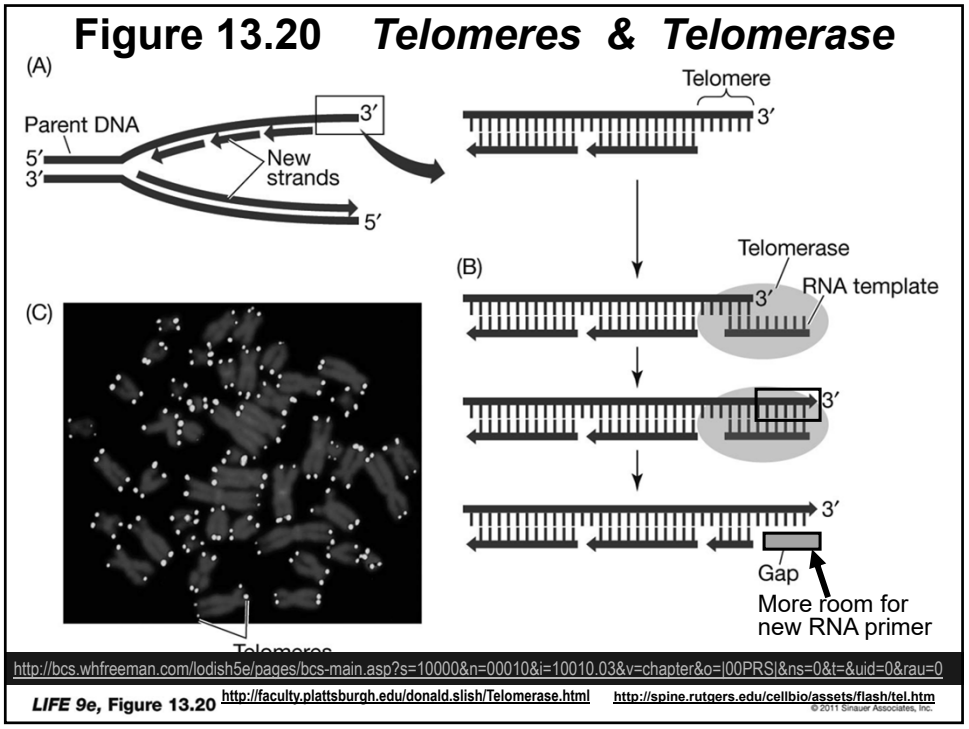
Figure 13.20 Telomeres & Telomerase
(A)
Parent DNA
5′
3′
New strands
3′
5′
Telomere
3′
(B)
Telomerase
RNA template
3′
3′
3′
Gap
More room for new RNA primer
(C)
Telomeres
http://bcs.whfreeman.com/lodish5e/pages/bcs-main.asp?s=10000&n=00010&i=10010.03&v=chapter&o=|00PRS|&ns=0&t=&uid=0&rau=0
LIFE 9e, Figure 13.20
http://faculty.plattsburgh.edu/donald.slish/Telomerase.html
http://spine.rutgers.edu/cellbio/assets/flash/tel.htm
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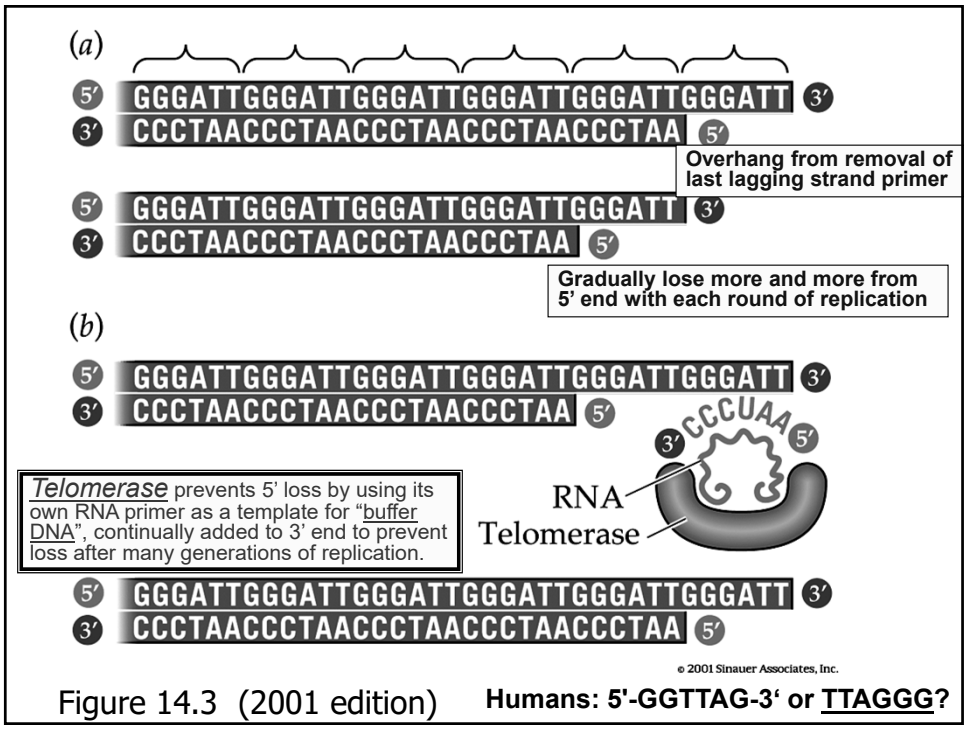
(a)
5′ GGGATTGGGATTGGGATTGGGATTGGGATTGGGATT 3′
3′ CCCTAACCCTAACCCTAACCCTAACCCTAA 5′
Overhang from removal of last lagging strand primer
5′ GGGATTGGGATTGGGATTGGGATTGGGATT 3′
3′ CCCTAACCCTAACCCTAACCCTAA 5′
Gradually lose more and more from 5' end with each round of replication
(b)
5′ GGGATTGGGATTGGGATTGGGATTGGGATTGGGATT 3′
3′ CCCTAACCCTAACCCTAACCCTAA 5′
3′ CCCUAA 5′
RNA
Telomerase
Telomerase prevents 5' loss by using its own RNA primer as a template for "buffer DNA", continually added to 3' end to prevent loss after many generations of replication.
5′ GGGATTGGGATTGGGATTGGGATTGGGATTGGGATT 3′
3′ CCCTAACCCTAACCCTAACCCTAACCCTAA 5′
© 2001 Sinauer Associates, Inc.
Figure 14.3 (2001 edition)
Humans: 5'-GGTTAG-3' or TTAGGG?

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BIOL 230, Part II – Major Concepts

1. Metabolic outocomes: **Oxidative Phosphorylation** (PMF, **chemiosmosis** -- following GLYC, Pyr Oxdn & TCA).
   a) Energy?
   b) Carbons?
2. Photosynthesis: Light reactions make ATP and NADPH from photons; used for cellular energy and to drive C-Fixation in Calvin-Benson cycle.
3. **DNA** is the Genetic material – ***Griffith, Avery/MacLeod/McCarty, Hershey/Chase***
4. DNA structure dictates function ***(Watson/Crick, Wilkins/Franklin, Chargaff)*** – antiparallel, polar, H-bonds (A-T, G-C), sugar-phosphate backbone
   - "boring structure" – complexity of genetic info must be in the base sequence!!!
5. DNA replicates **semiconservatively** – ***Meselson/Stahl (W&C)***
6. ***Kornberg*** – Dpol-III, Dpol-I, SSB, RNA Primase, *Okazaki* Frags., Dna-A, Helicase, Ligase, Gyrase…
7. Proofreading, repair
8. Telomeres

GENETICS LINKS: http://highered.mcgraw-hill.com/sites/0072835125/student_view0/animations.html#

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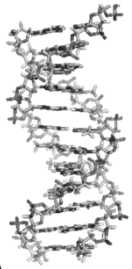
Chapter 14: From DNA to Protein:
Genotype to Phenotype

1. One Gene, One Polypeptide
2. DNA, RNA, and the Flow of Information
3. Transcription: DNA-Directed RNA Synthesis
4. Post-Transcriptional Processing
5. The Genetic Code & Translation
6. Posttranslational Events

(15.) Mutations: Heritable Changes in Genes…..



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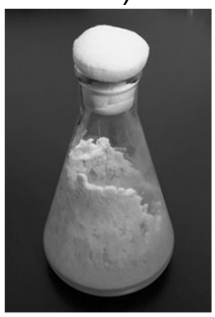
14.1) One Gene, One Polypeptide

❖ ***Genes:***

- made up of DNA; = units of hereditary information.
- *= segments of continuous DNA sequence that encode a functional product (usually a protein or an active RNA).*
- ***expressed*** in the ***phenotype*** (physical characteristics) as polypeptides.



- **Beadle and Tatum's experiments:**
  - with the bread mold ***Neurospora crassa –*** haploid!
  - exposure to X-rays resulted in mutant strains lacking a specific enzyme in a biochemical pathway.
  - *Specific **Gene** expression → Specific **protein** activity!!*

- These results led to the ***One-Gene, One-Polypeptide Hypothesis***.

https://www.dnalc.org/resources/nobel/beadle_tatum.html

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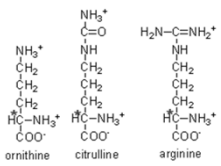
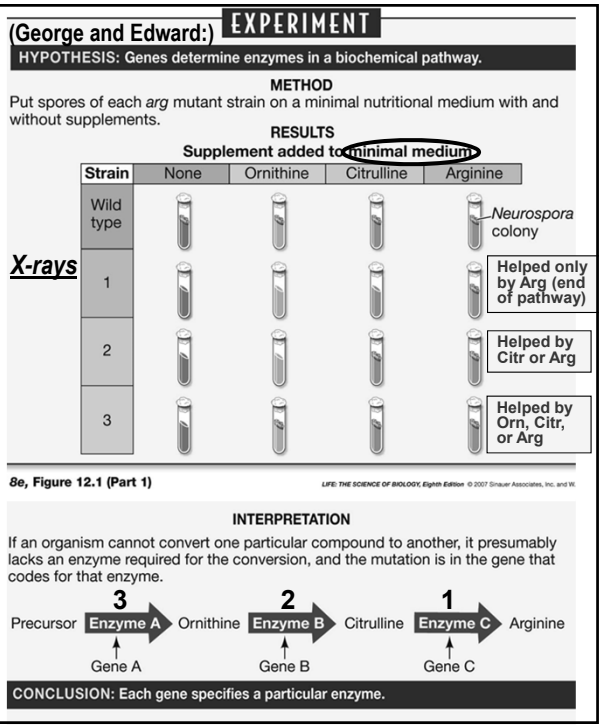
Beadle & Tatum, 1940s

- Mutants (***auxotrophic***) that cannot synthesize Arginine for themselves
  - *Wild Type* = ***Prototrophs***
- Some *arg-* mutants can use some molecular precursors, but not others, to make Arg.
  - ***The MORE supplements that help the mutant, the EARLIER in the pathway is the mutated gene/enz.***



- ***Each mutated unit of heredity (gene) controlled one enzyme in ARG biosynthesis***



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