Lecture 4.1: DNA Structure & Replication

Chapter 14

Learning Objectives

- Explain the structure of DNA and how it relates to function
- Describe the complementary base pairing rules
- Explain why DNA replication is semiconservative
- Understand the key enzymes involved in DNA replication and their roles
- Describe the directionality of DNA synthesis (5' to 3')
- Explain how the leading and lagging strands are replicated differently

DNA: The Molecule of Heredity

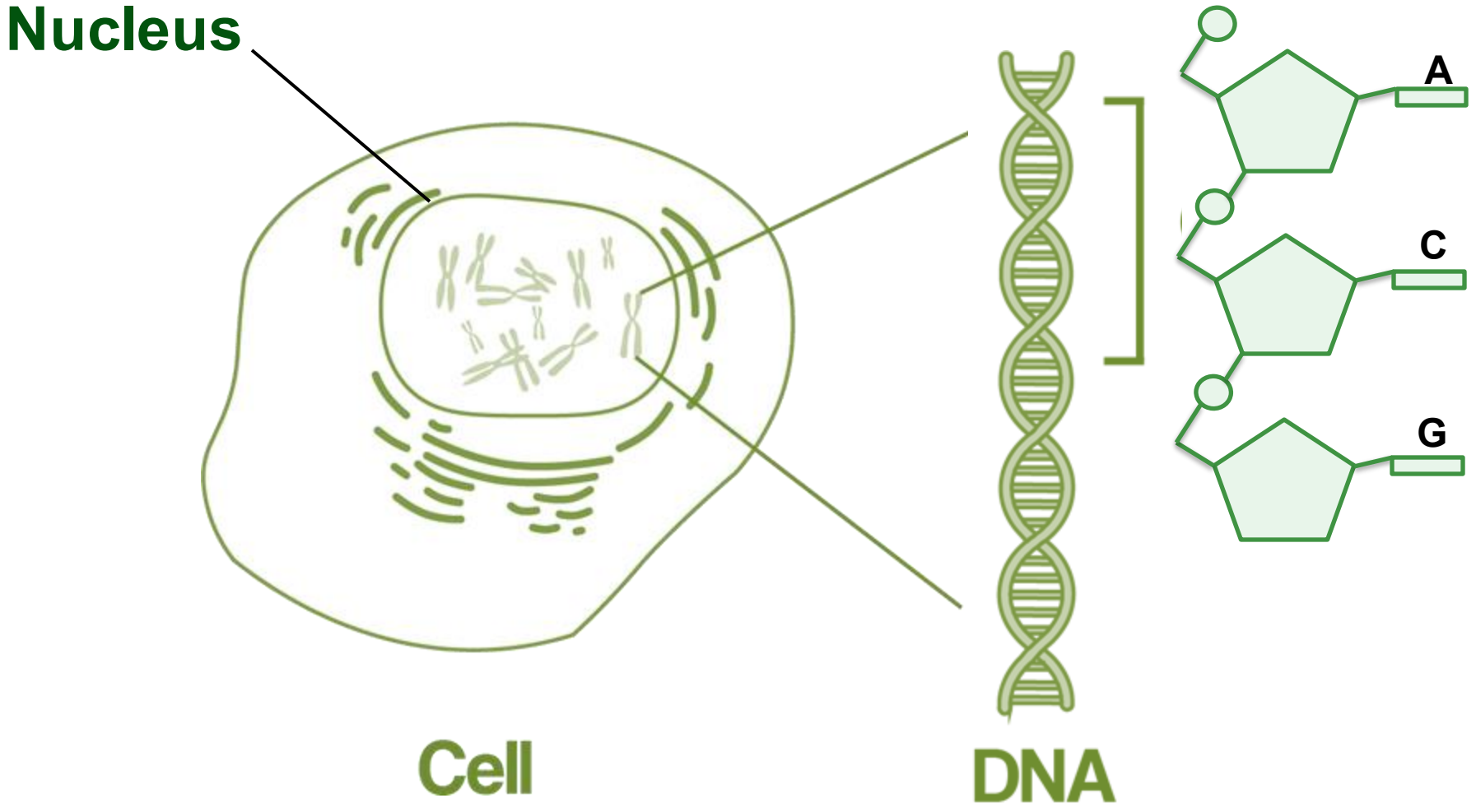
DNA = **D**eoxyribo**n**ucleic **A**cid

- The genetic material in all living organisms (and many viruses)
- Contains the instructions for building and maintaining an organism
- Passed from parents to offspring

Key Questions We'll Answer:

- What does DNA look like?
- How is information stored in DNA?
- How is DNA copied so accurately?

DNA provides every instruction to build and operate a cell via the order and matching of nucleotides

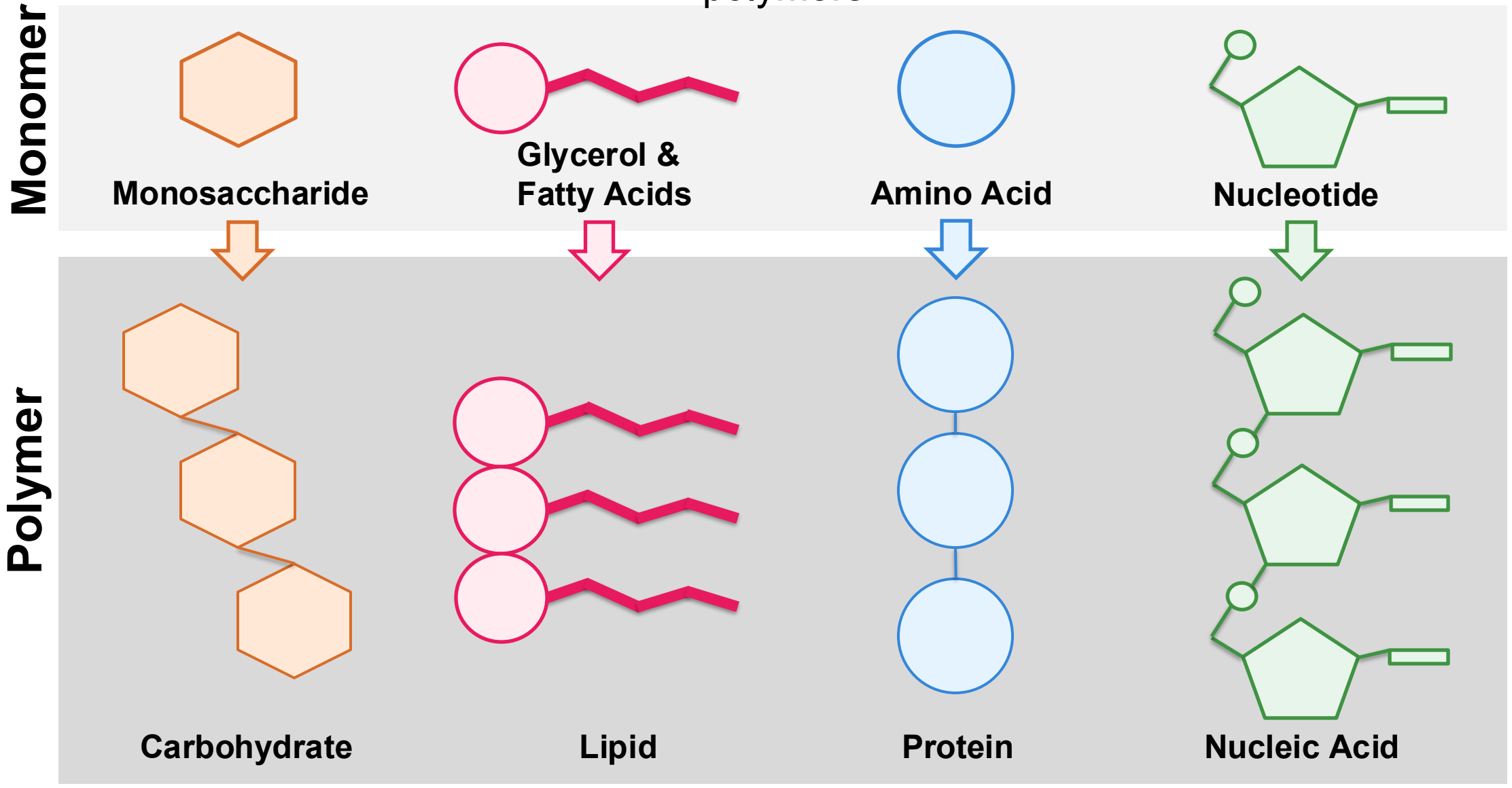


Each nucleotide has only 1 of the 4 bases

The book that contains instructions

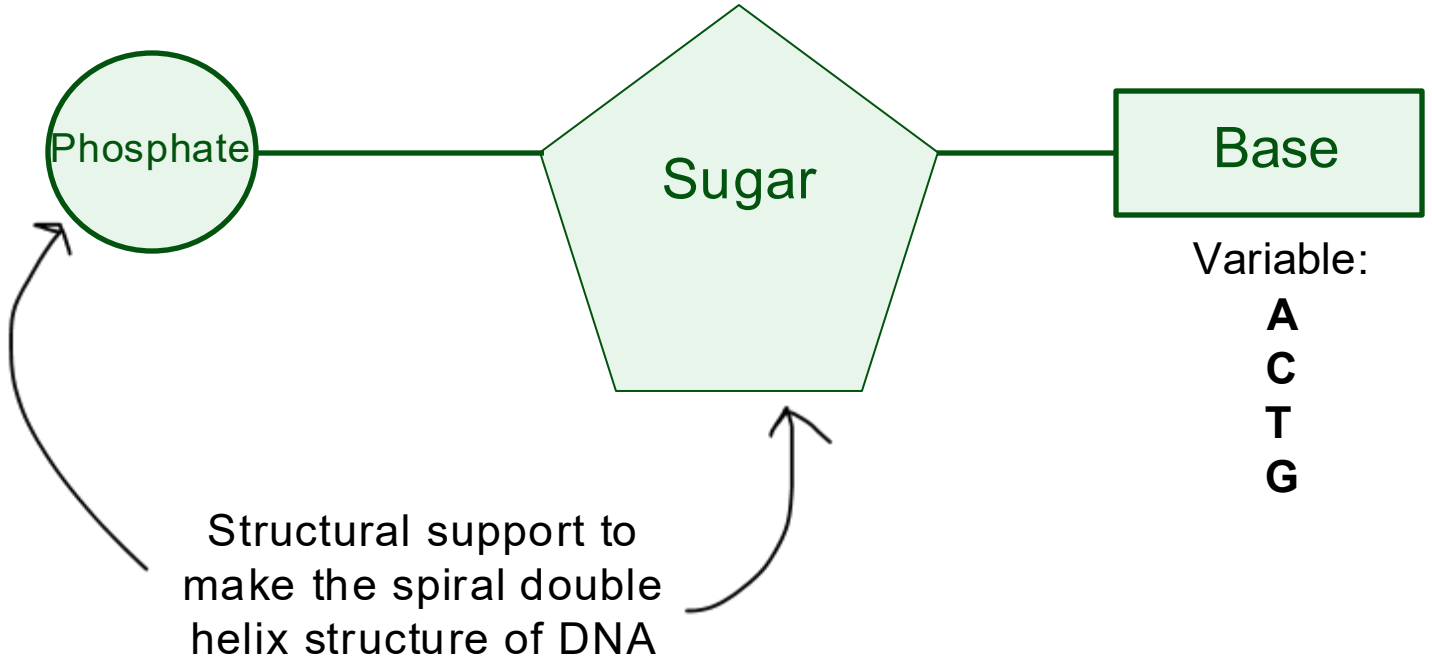
The basic building block of all biomolecules is a monomer

Polymerization: Monomers (repeating subunits) are bound into varying lengths called polymers



DNA = universal code, all of life has the same nucleotides with a structural backbone and bases

The nucleic acid monomer is a nucleotide:



Each nucleotide has **3 parts:**

1. **Phosphate group** (P) - negatively charged
2. **Sugar** (deoxyribose) - 5-carbon sugar
3. **Nitrogenous base** - contains nitrogen

Think of nucleotides like Lego blocks - they connect to form long chains!

The bases are the information. The sequence of bases informs everything!

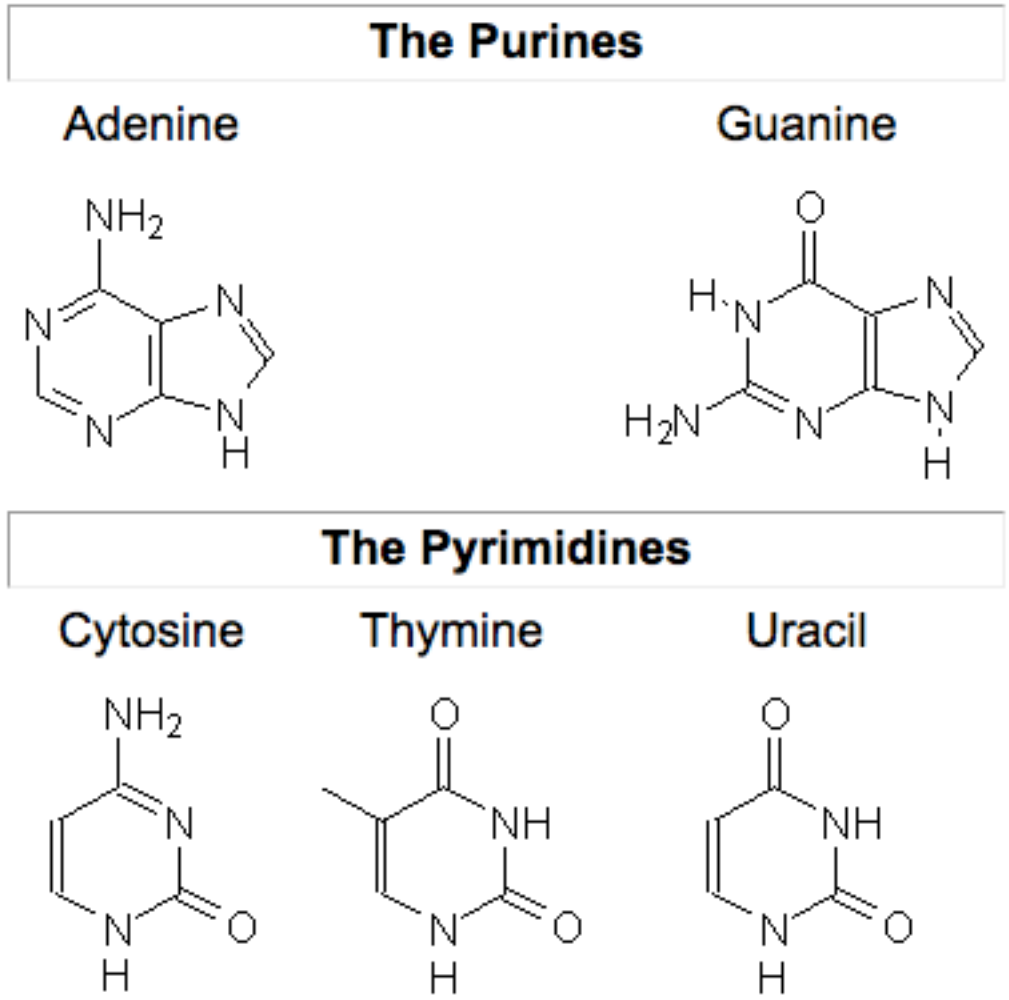
The Four Bases

The Four Nitrogenous Bases

Two categories:

PURINES (larger, double ring):
- **A**denine (A)
- **G**uanine (G)

PYRIMIDINES (smaller, single ring):
- **C**ytosine (C)
- **T**hymine (T)



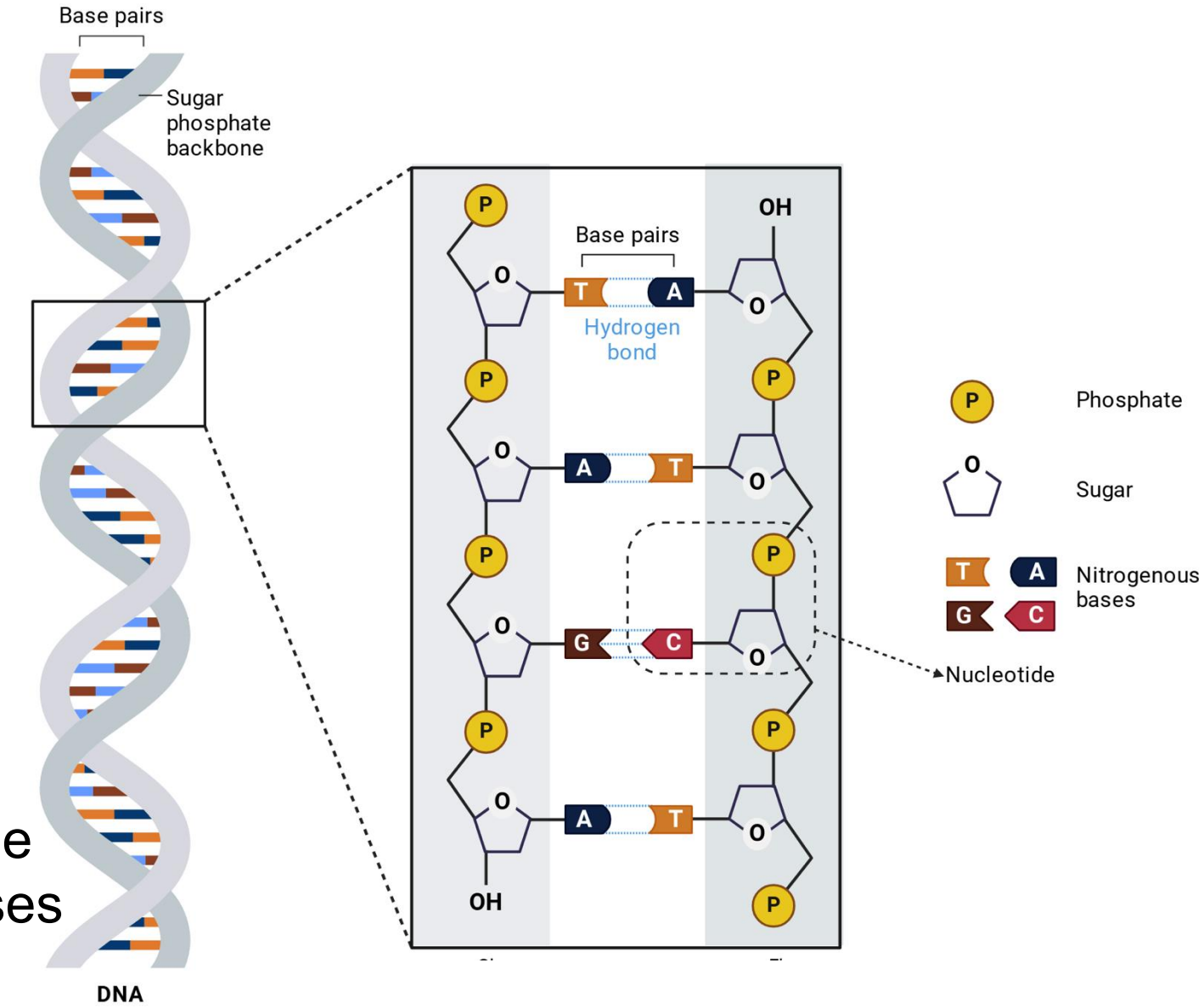
The Sugar-Phosphate Backbone

How Nucleotides Connect

Nucleotides link together through the **sugar-phosphate backbone**:

- The phosphate of one nucleotide bonds to the sugar of the next
- This creates a strong, stable "backbone"
- The bases stick out from the backbone

Important: The backbone is the same in all DNA - only the sequence of bases varies!



DNA Has Directionality

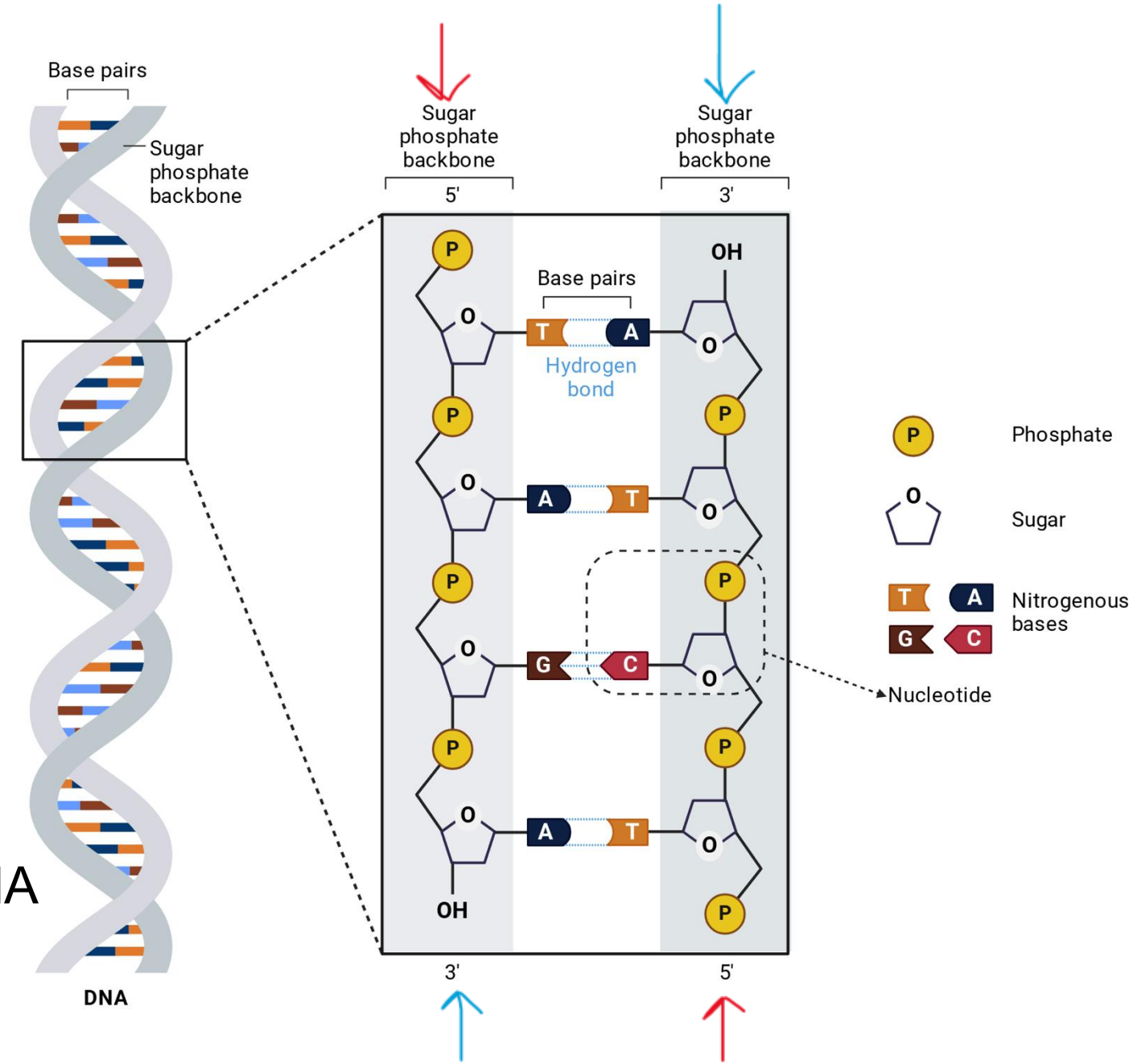
The sugar in DNA is numbered:

- **5' carbon** - has the phosphate group attached
- **3' carbon** - has a hydroxyl (-OH) group

DNA strands have directionality:
One end is the **5' end** (phosphate)
Other end is the **3' end** (hydroxyl)

Analogy: Like a one-way street - it matters which direction you're going!

This directionality is CRUCIAL for DNA replication!



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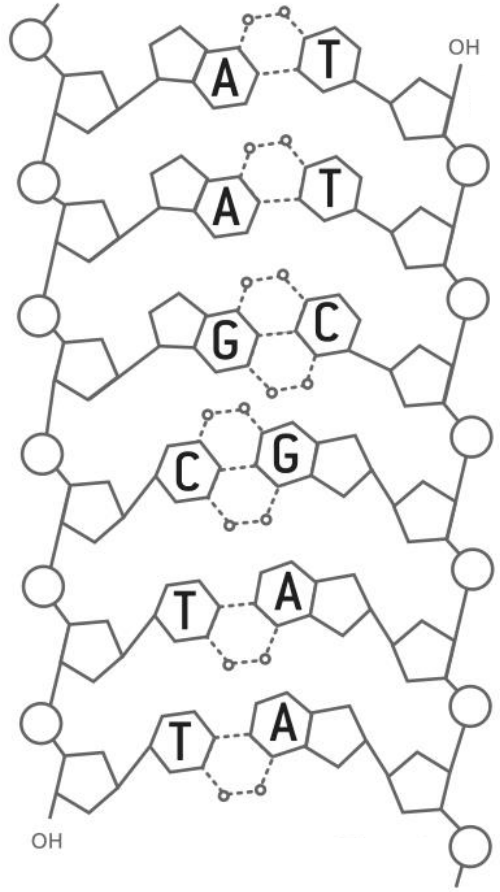

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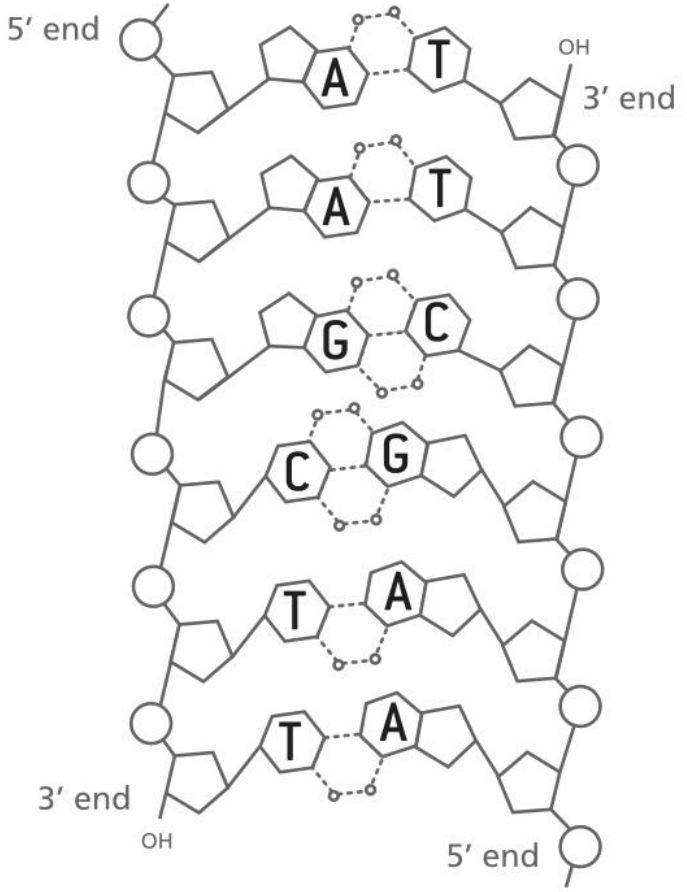


Chargaff's Rules

An Important Pattern: Chargaff's Rules (1950)

Erwin Chargaff analyzed DNA from many organisms and found:

Chargaff's Rules:

1.The amount of **A** always equals the amount of **T**

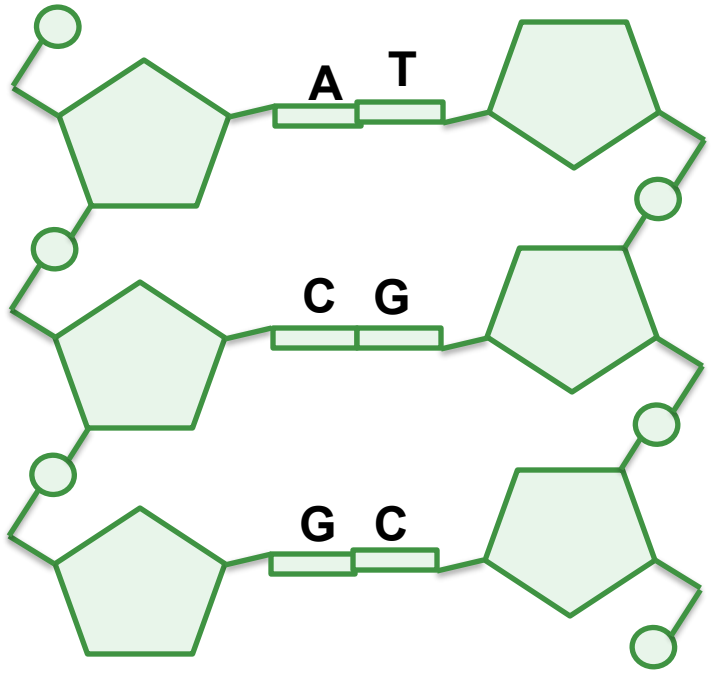
2.The amount of **G** always equals the amount of **C**

This was a MAJOR clue about DNA structure! But why?

ICA Q2: What do you know about DNA that makes this true?

Organism	**%A**	**%T**	**%G**	**%C**
Human	30.3	30.3	19.5	19.9
E. coli	24.7	23.6	26.0	25.7

In DNA There are PAIRING RULES:



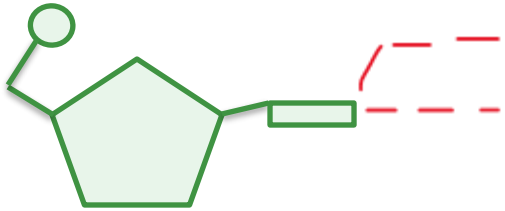
DNA

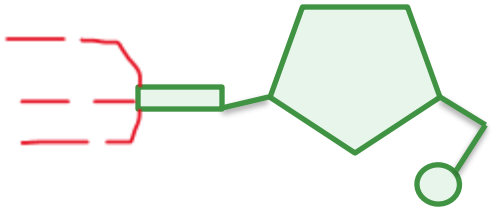
A pairs with T
C pairs with G

ALWAYS

In DNA pairing rules are dictated by hydrogen bonds

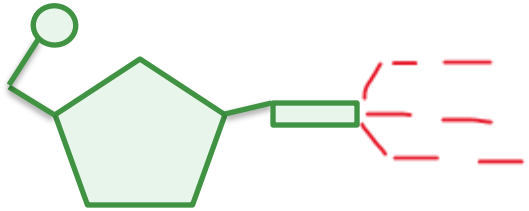
A

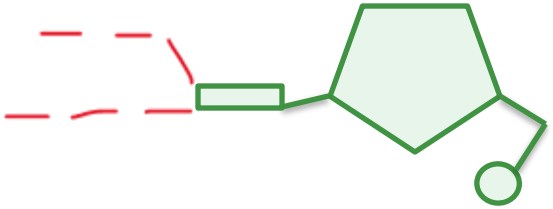




B

C



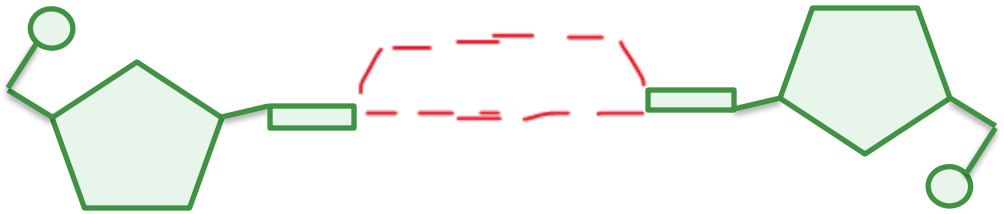


D

ICA Q3: Hydrogen bonds are the red dotted lines. Predict which nucleotides should pair together (example: A with C). Your answer should have two pairs.

In DNA pairing rules are dictated by hydrogen bonds

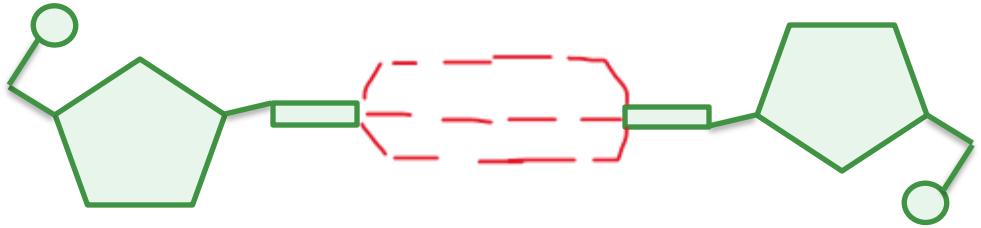
A



D

2 hydrogen bonds match up

C



B

3 hydrogen bonds match up

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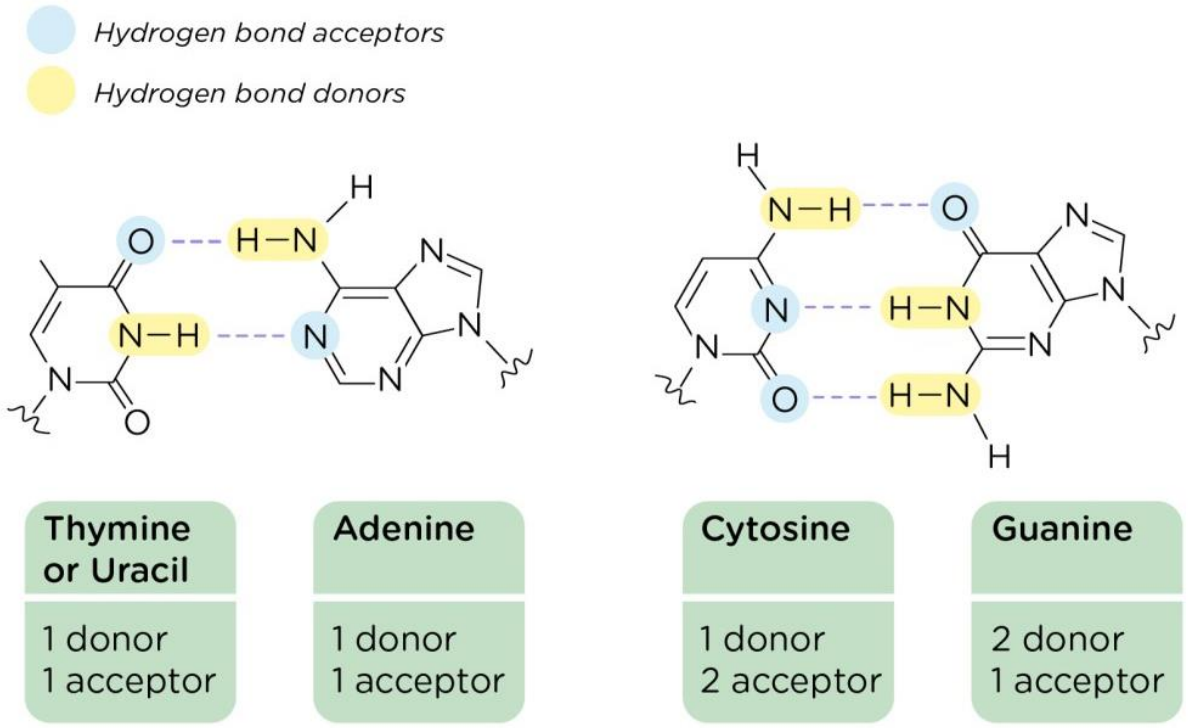
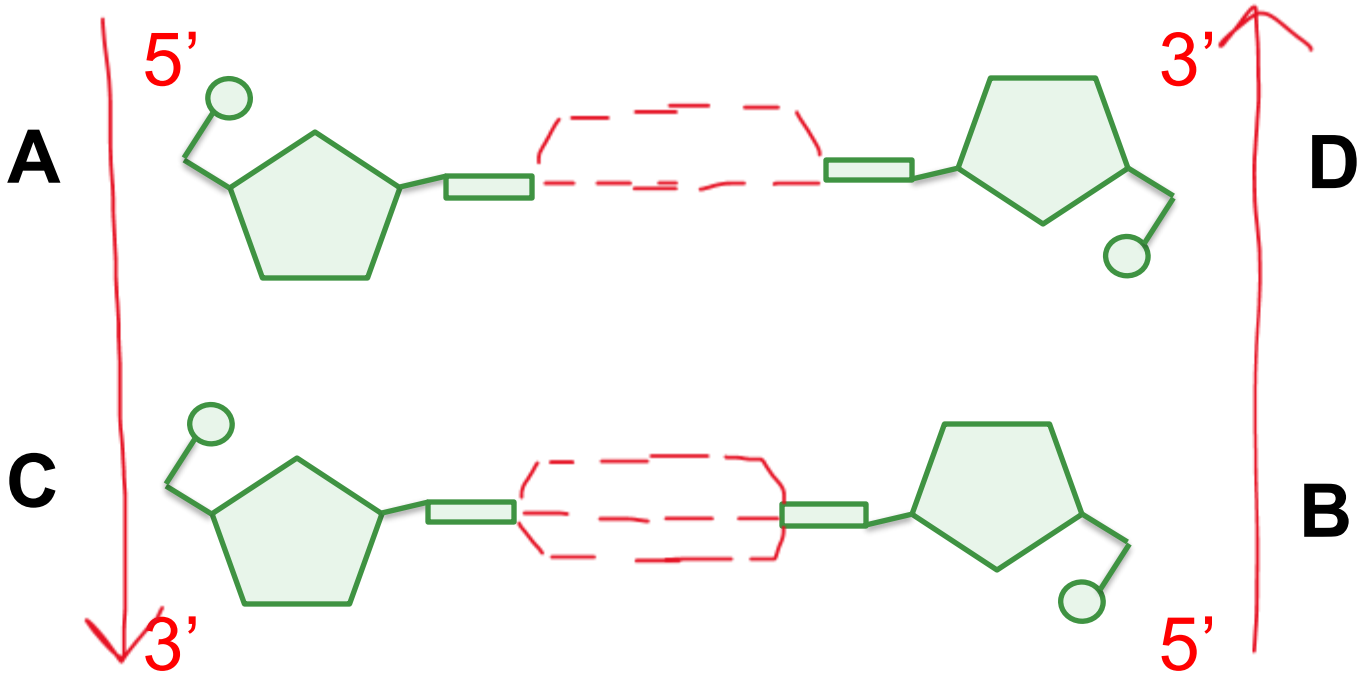


The Secret: Complementary Base Pairing
The two strands are held together by **hydrogen bonds** between bases
Base Pairing Rules:
•**A** pairs with **T** (2 hydrogen bonds)
•**G** pairs with **C** (3 hydrogen bonds)

This explains Chargaff's Rules! If A always pairs with T, their amounts must be equal!

Why this pairing?
•Shape: Purines (large) pair with pyrimidines (small) → uniform width
•Hydrogen bonding: A-T and G-C form stable hydrogen bonds
•A-G or C-T wouldn't fit properly!

DNA also has MUST run antiparallel!



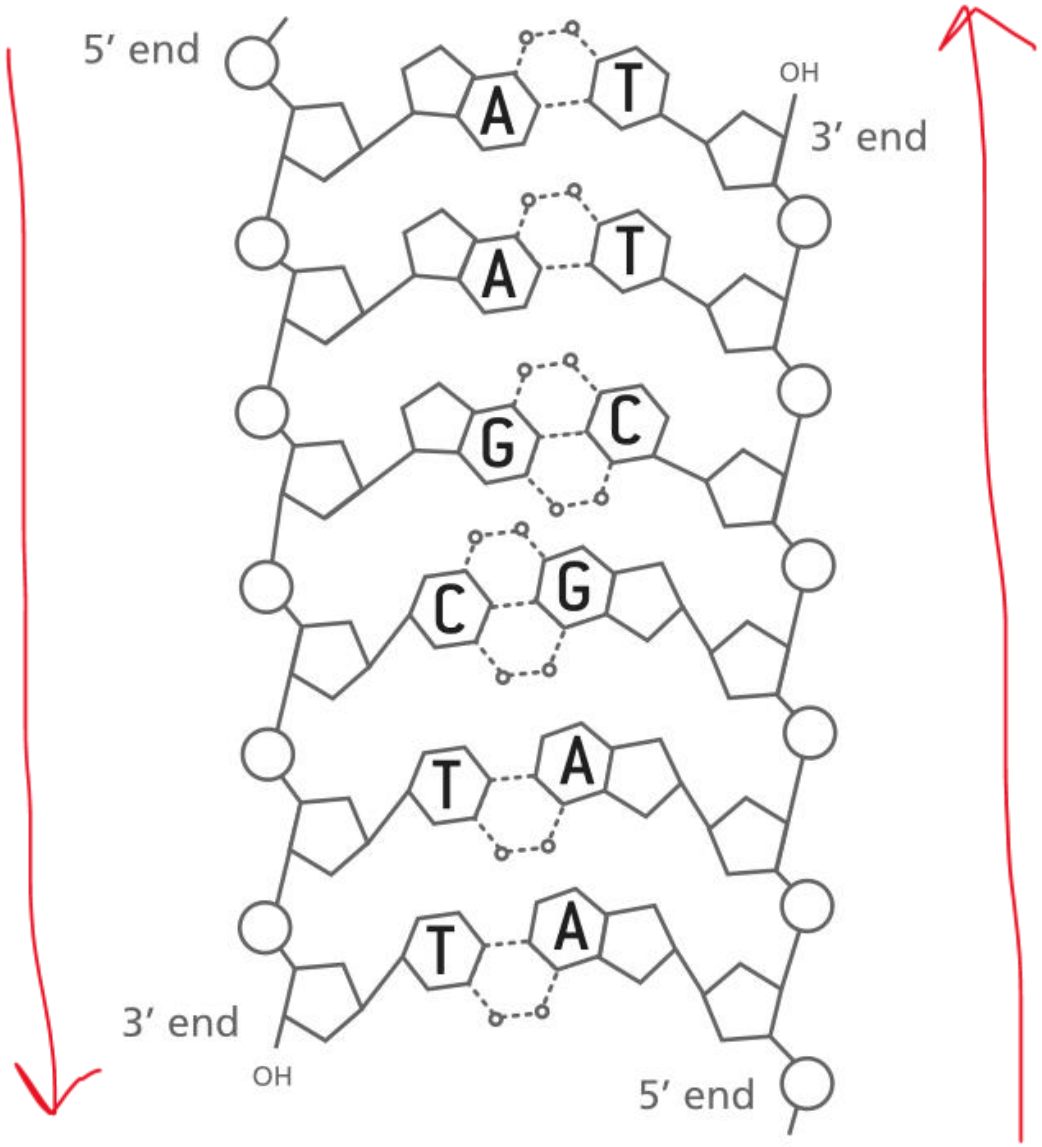
You could not have paired A with A in the previous ICA question

DNA also has MUST run antiparallel!

Antiparallel means:

- One strand runs 5' → 3' going down
- Other strand runs 3' → 5' going down (or 5' → 3' going up!)

Analogy: Like a two-way street or a zipper where the teeth face opposite directions



ICA Q4: If one strand of DNA has the sequence 5'-ATCG-3', what is the sequence of the complementary strand? Include the directionality labels!

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Antiparallel means:

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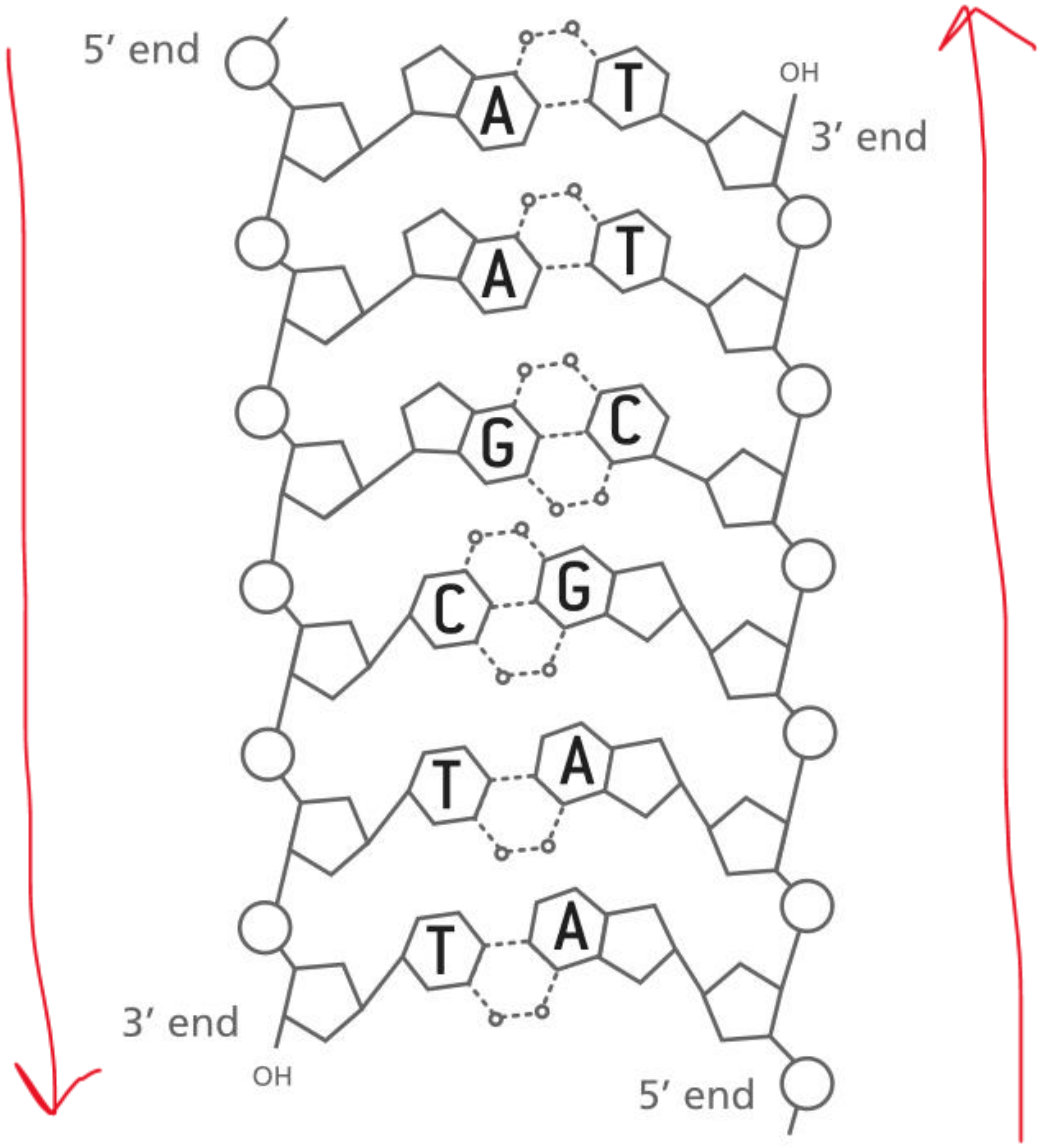


ICA Q4:

5'-ATCG-3',
3'-TAGC-5'

remember antiparallel! If the original is 5'→3', the complement must be 3'→5'

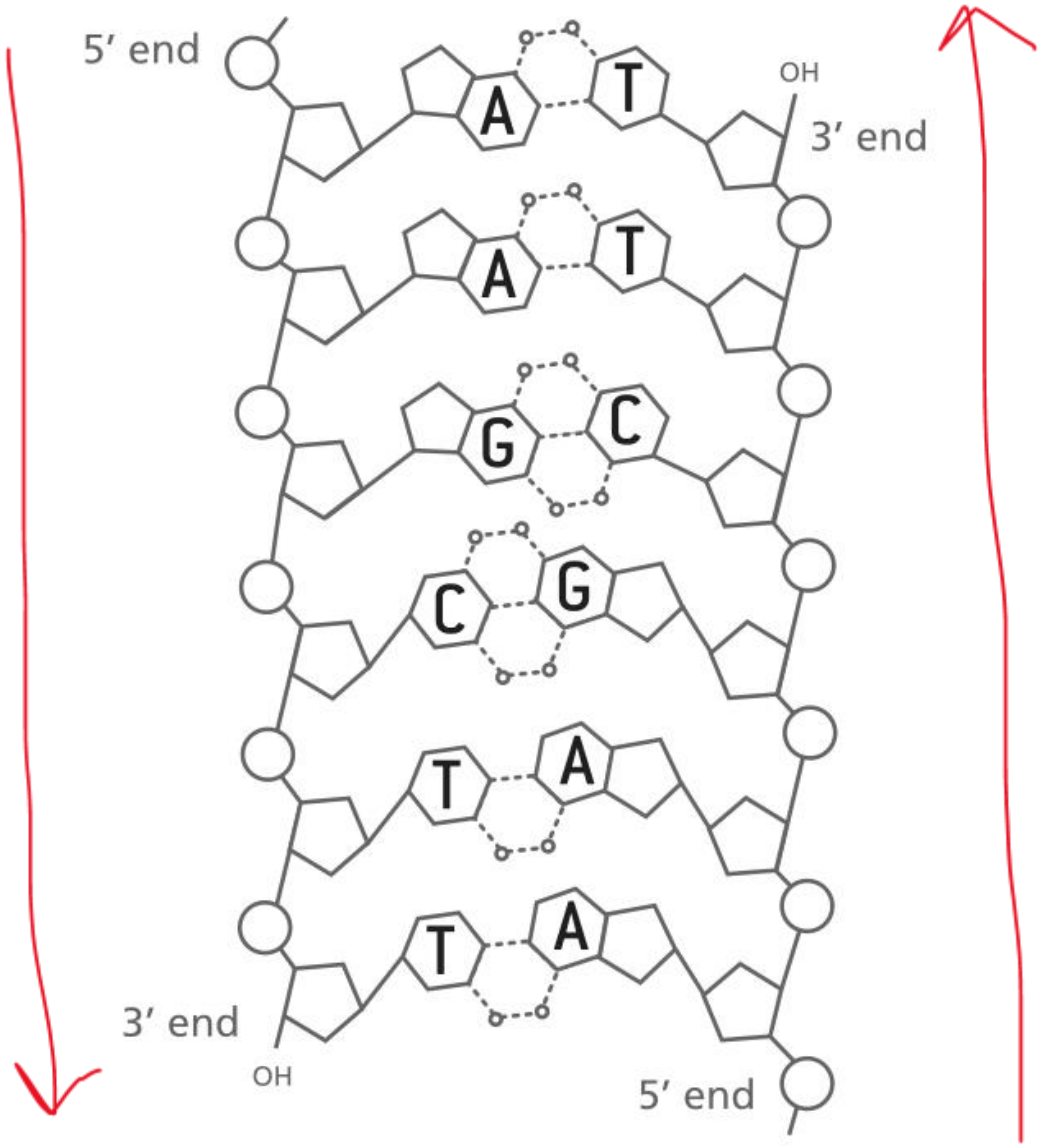
DNA Structure Summary

The "Ladder" Analogy:

- **Sides of ladder** = sugar-phosphate backbone
- **Rungs of ladder** = complementary base pairs (A-T, G-C)
- **Twisted ladder** = double helix

Critical features:

✓ Two antiparallel strands
✓ Complementary base pairing (A-T, G-C)
✓ Sugar-phosphate backbone on outside
✓ Bases on inside
✓ Strands held together by hydrogen bonds



Why Does Structure Matter?

Structure Relates to Function

DNA's structure is perfectly designed for its functions:

1. Information Storage

- Sequence of bases = genetic code
- Four bases can create millions of different sequences

2. Stability

- Double helix protects bases inside
- Multiple hydrogen bonds provide stability
- Backbone provides structural support

3. Replication (coming up!)

- Complementary base pairing allows accurate copying
- Each strand can serve as a template

The Big Question: How is DNA Copied?

Why does DNA need to be copied?

- Every time a cell divides, it needs to pass on genetic information
- Each daughter cell needs a complete copy of DNA (meiosis)
- Your body makes ~2 trillion cell divisions per day! (mitosis)

Requirements for accurate copying:

- Must copy the entire genome (all 3 billion base pairs in humans!)
- Must be very accurate (< 1 error per billion bases)
- Must happen relatively quickly

How does the cell accomplish this?

equipment, and to Dr. G. E. R. Deacon and the captain and officers of R.R.S. *Discovery II* for their part in making the observations.

[1] Young, F. B., Gerrard, H., and Jevons, W., *Phil. Mag.*, **40**, 149 (1920).
[2] Longuet-Higgins, M. S., *Mon. Not. Roy. Astro. Soc., Geophys. Supp.*, **5**, 285 (1949).
[3] Von Arx, W. S., Woods Hole Papers in Phys. Oceanog. Meteor., **11** (3) (1950).
[4] Ekman, V. W., *Arkiv. Mat. Astron. Fysik.* (*Stockholm*), **2** (11) (1905).

MOLECULAR STRUCTURE OF NUCLEIC ACIDS

A Structure for Deoxyribose Nucleic Acid

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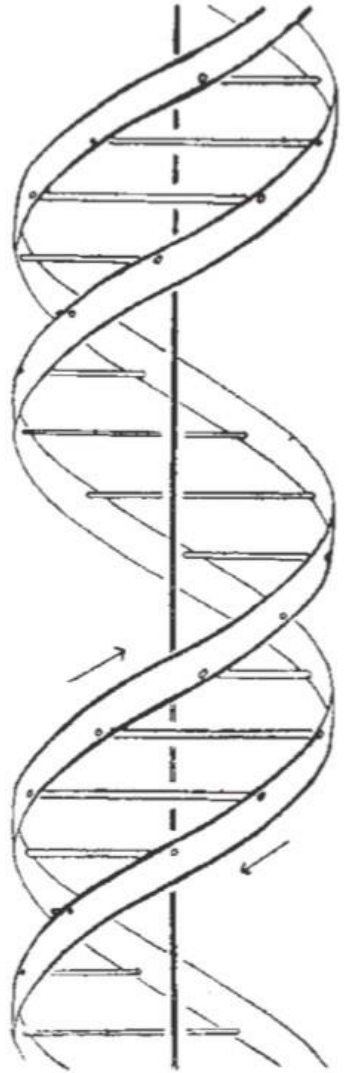
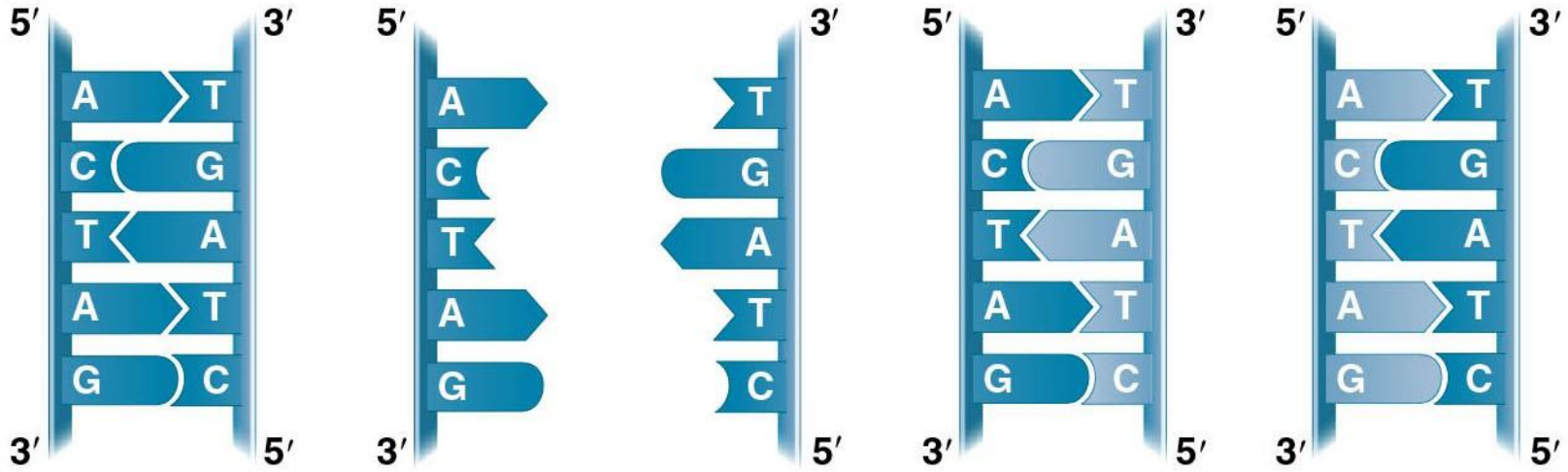


It has not escaped our notice that the specific pairing we have postulated immediately suggests a possible copying mechanism for the genetic material.

Full details of the structure, including the conditions assumed in building it, together with a set of co-ordinates for the atoms, will be published elsewhere.



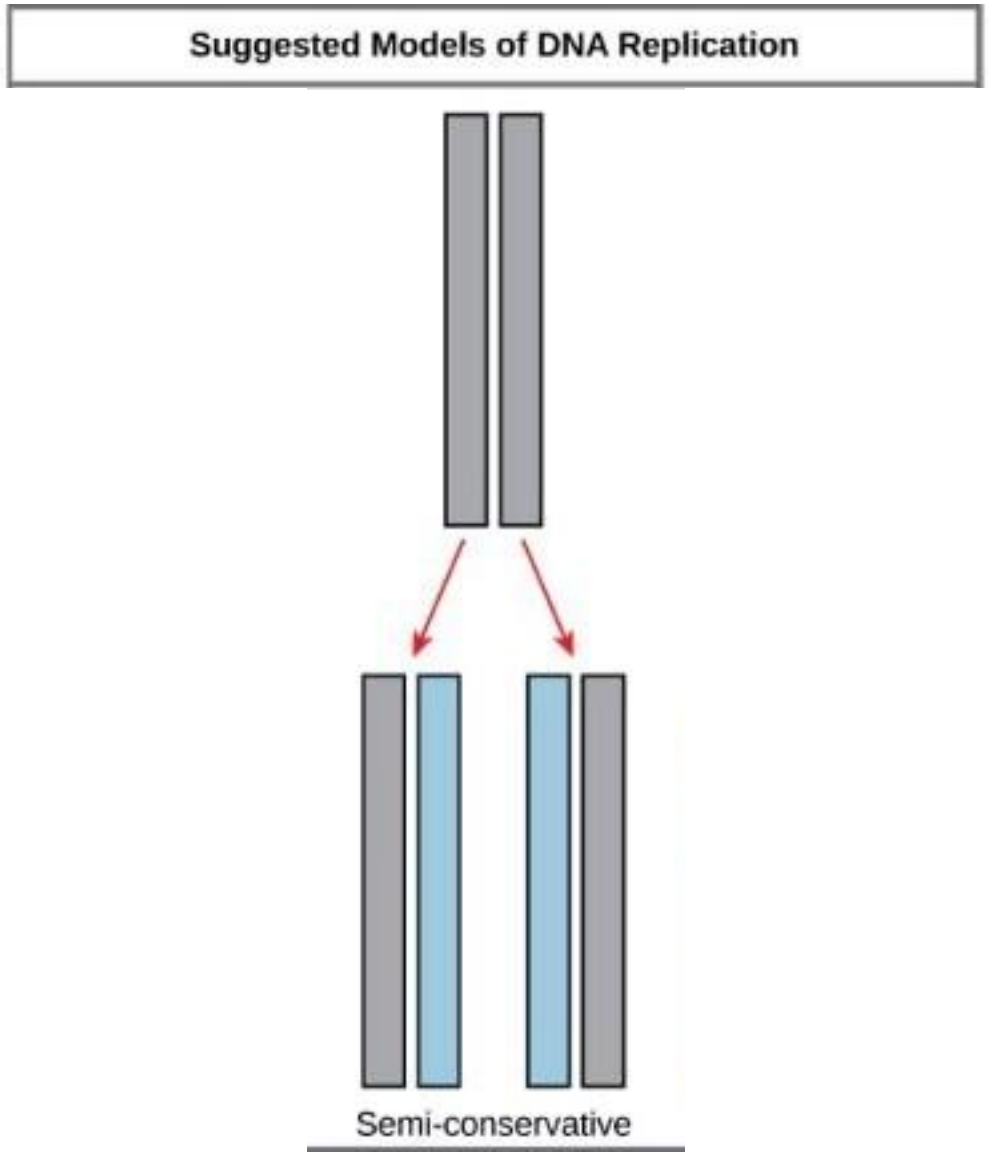
(a) Parental molecule

(b) Separation of parental strands into templates

(c) Nucleotides complementary to the parental (dark blue) strand are connected to form the sugar-phosphate backbones of the new "daughter" (light blue) strands.

"Now our model for DNA, is in effect, a pair of templates, each of which is complementary to the other. We imagine that prior to duplication the hydrogen bonds are broken, and the two chains unwind and separate. ***Each chain then acts as a template for the formation on to itself of a new companion chain, so that eventually we shall have two pairs of chains, where we only had one before.*** *Moreover, the sequence of the pairs of bases will have been duplicated exactly."*

The three suggested possible models by which DNA replication might occur.



Semi-conservative replication– the two strands come apart – each acts as a template for synthesis of a new complementary strand.

Gray indicates the original DNA strands, and blue indicates newly synthesized DNA.

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Conservative replication– original parent double strands remain intact and two completely new double helix strands are synthesized

Semi-conservative replication– the two strands come apart – each acts as a template for synthesis of a new complementary strand.

Dispersive replication– both original parent strands are broken up into small pieces and incorporated into newly synthesized strands

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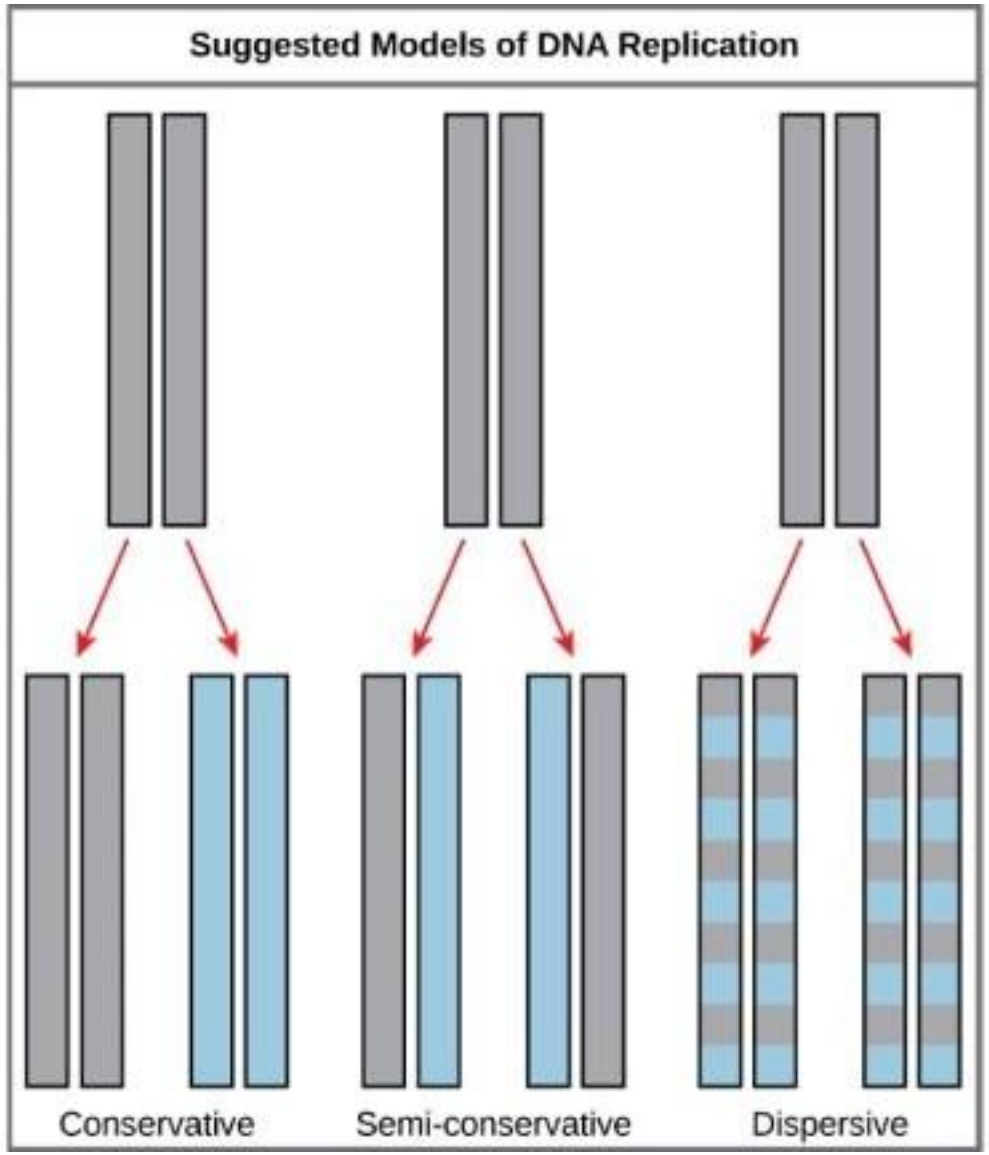
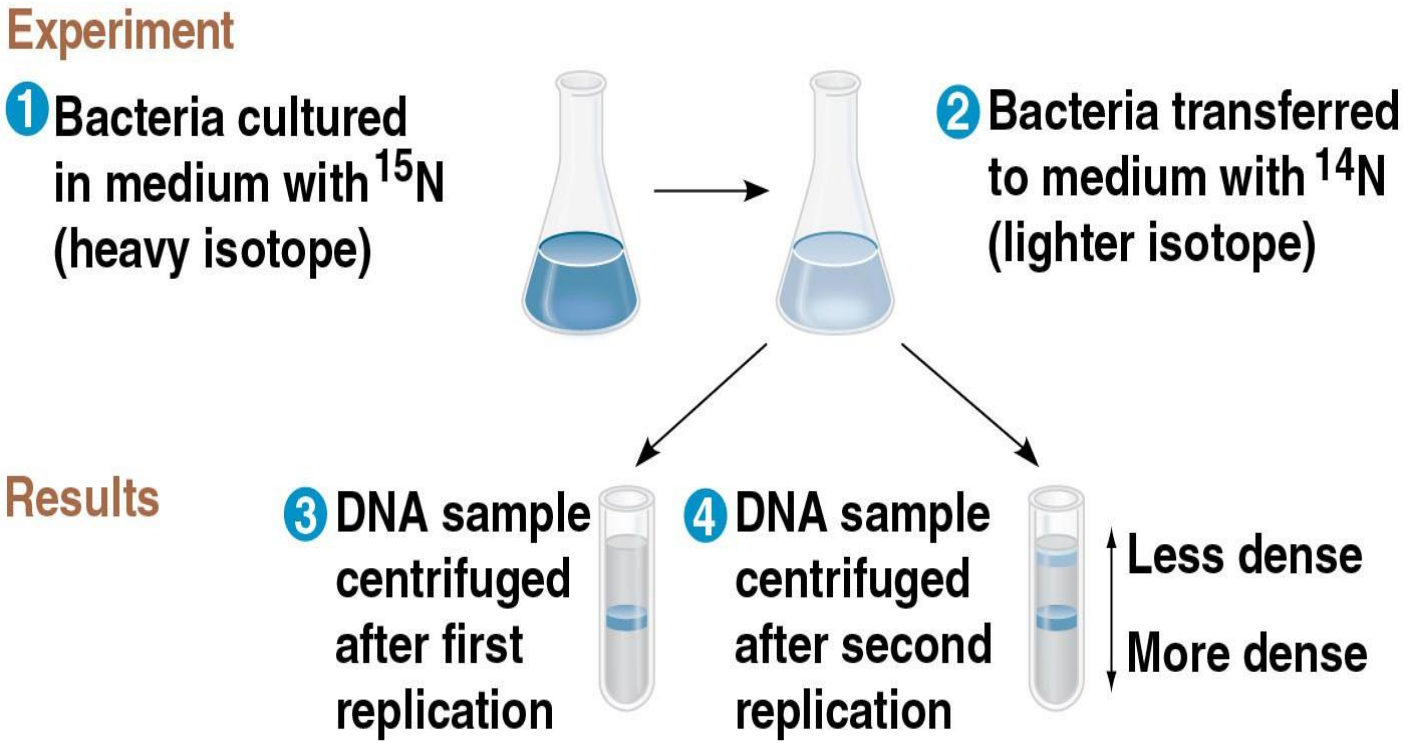
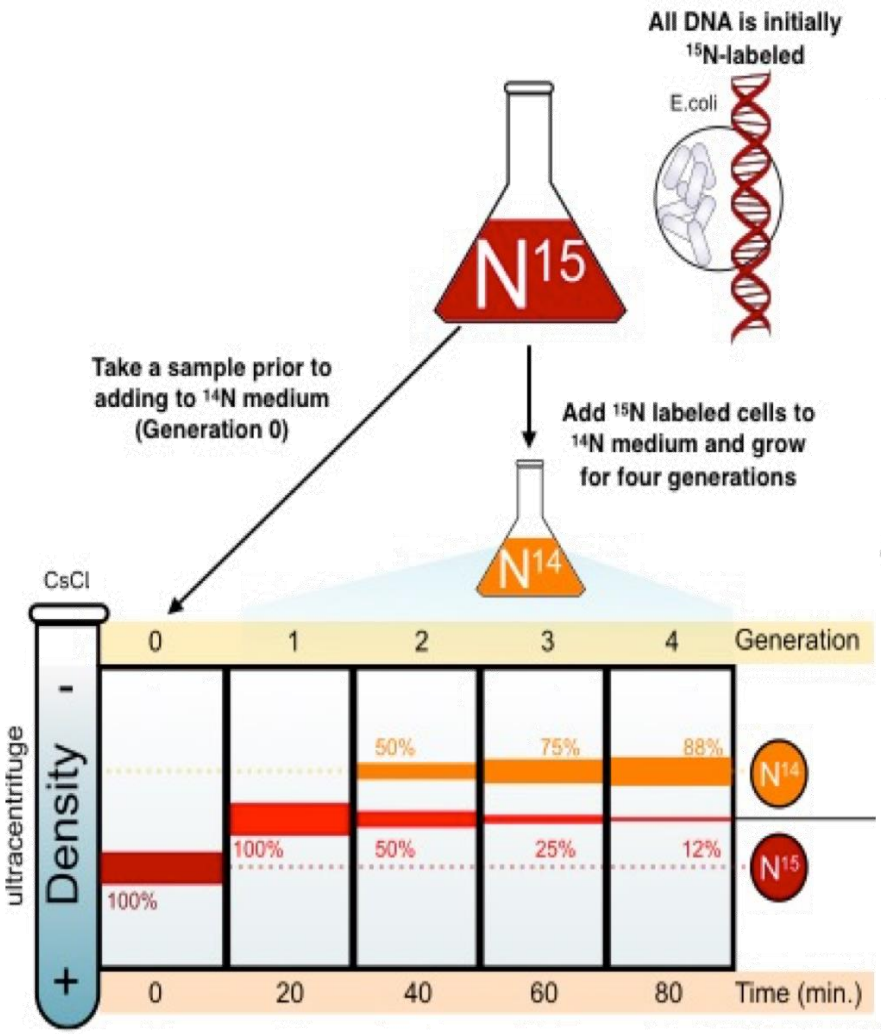


The Meselson-Stahl Experiment



Clever experimental design using isotopes:

- Grew bacteria in medium with heavy nitrogen (^{15}N)
- DNA incorporated heavy nitrogen → "heavy DNA"
- Then switched bacteria to normal nitrogen (^{14}N)
- After one replication, used centrifugation to separate DNA by weight



Results after one replication:

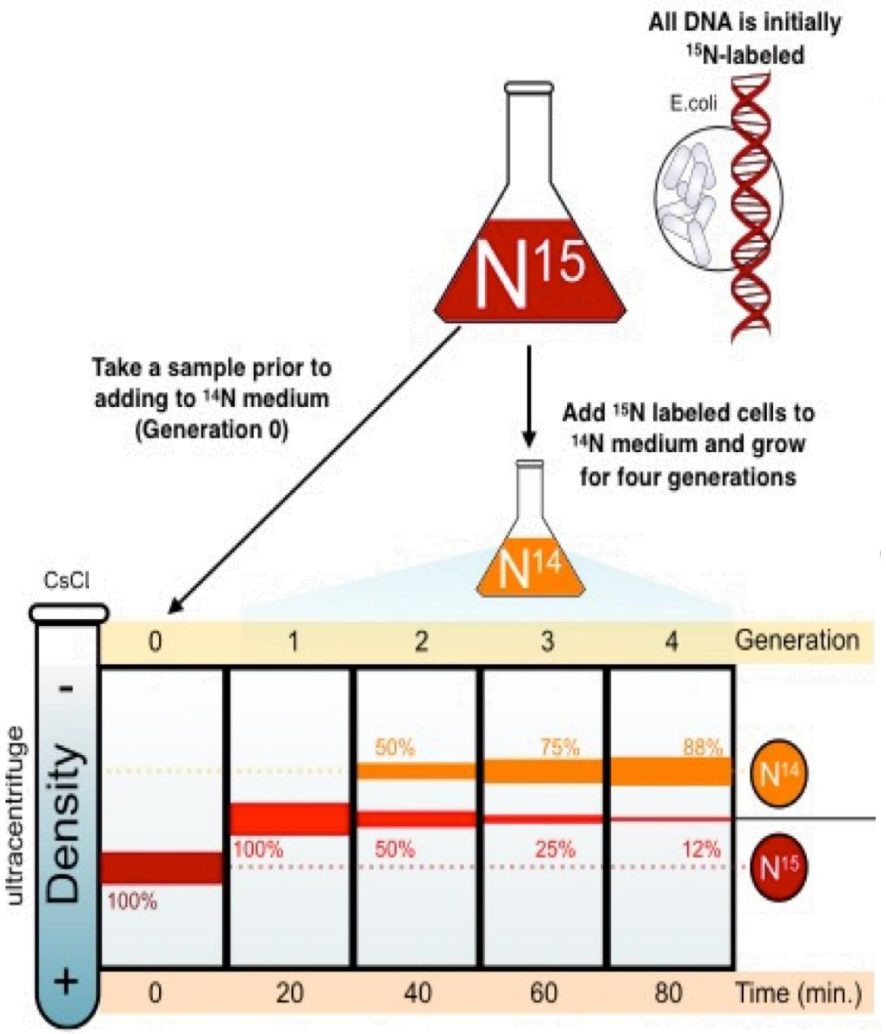
•ALL DNA was intermediate weight (hybrid – orangish red)

•ICA Q5A: Which hypothesis did this rule out?

Conservative: one old DNA molecule, one new DNA molecule

Semiconservative: two molecules, each with one old and one new strand

Dispersive: two molecules with mixture of old and new throughout



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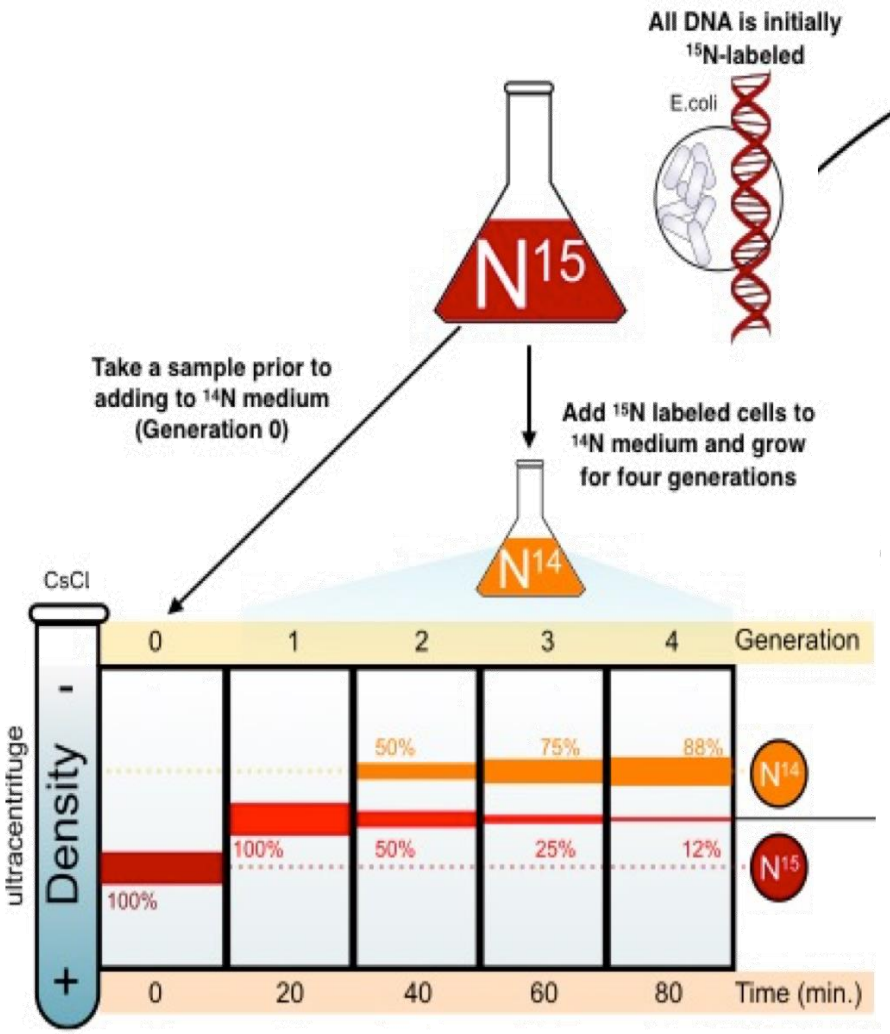
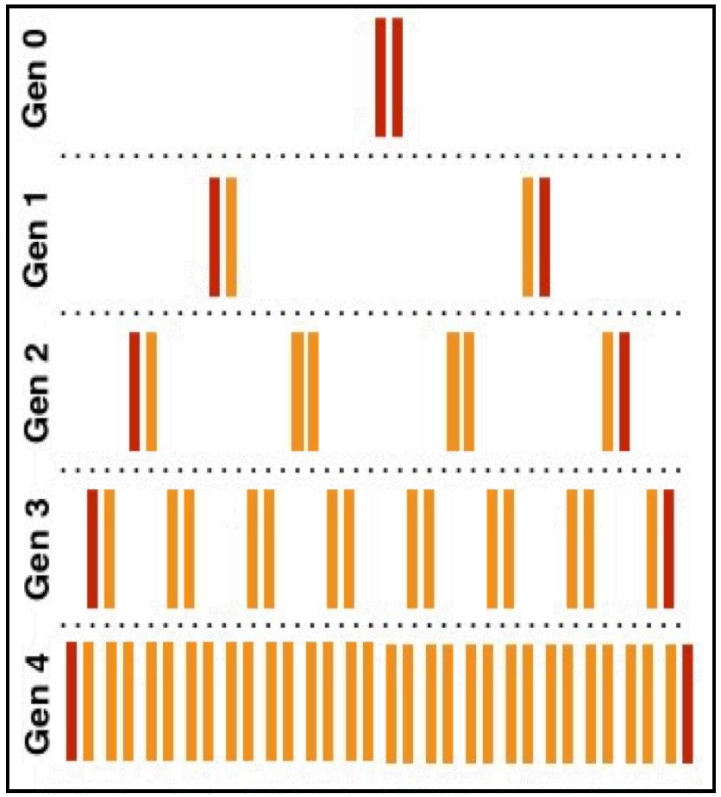
Results after two replications:

•50% intermediate weight (hybrid – orangish red), 50% light weight (orange)

•ICA Q5B: Which hypothesis did this prove?





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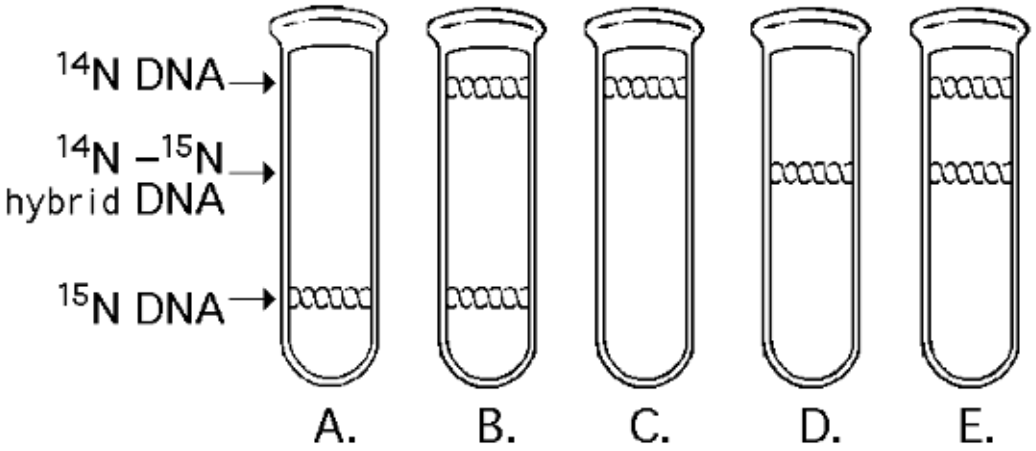
•ICA Q5B: Which hypothesis did this prove?

Semiconservative! If it were dispersive, it would keep looking like gen 1

ICA Q5C:

Imagine the Meselson and Stahl experiments had supported conservative replication instead of semi-conservative replication. What results would you predict to observe after <u>two rounds</u> of replication?



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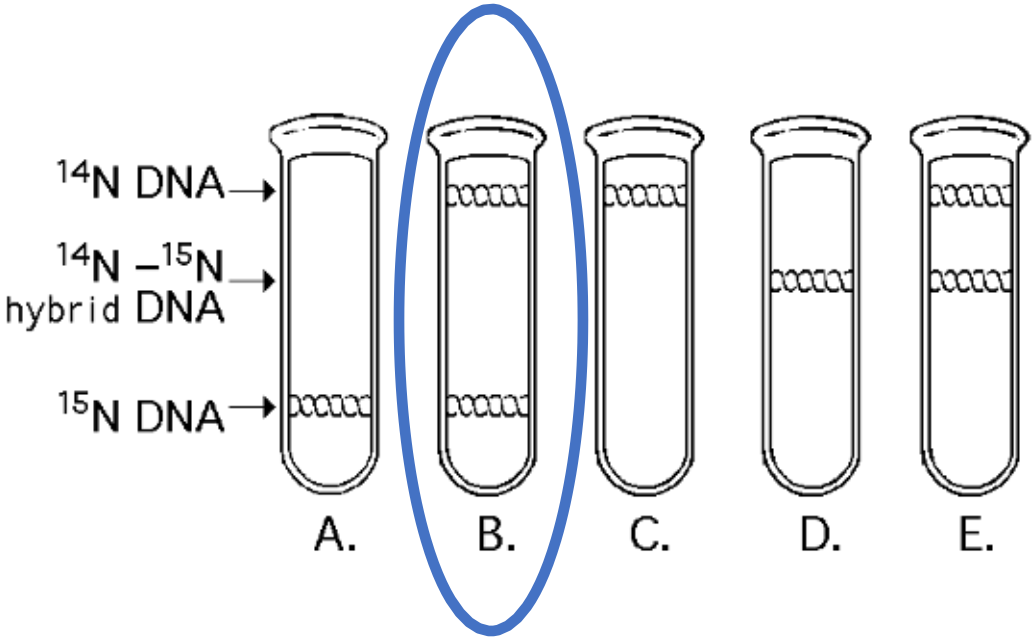
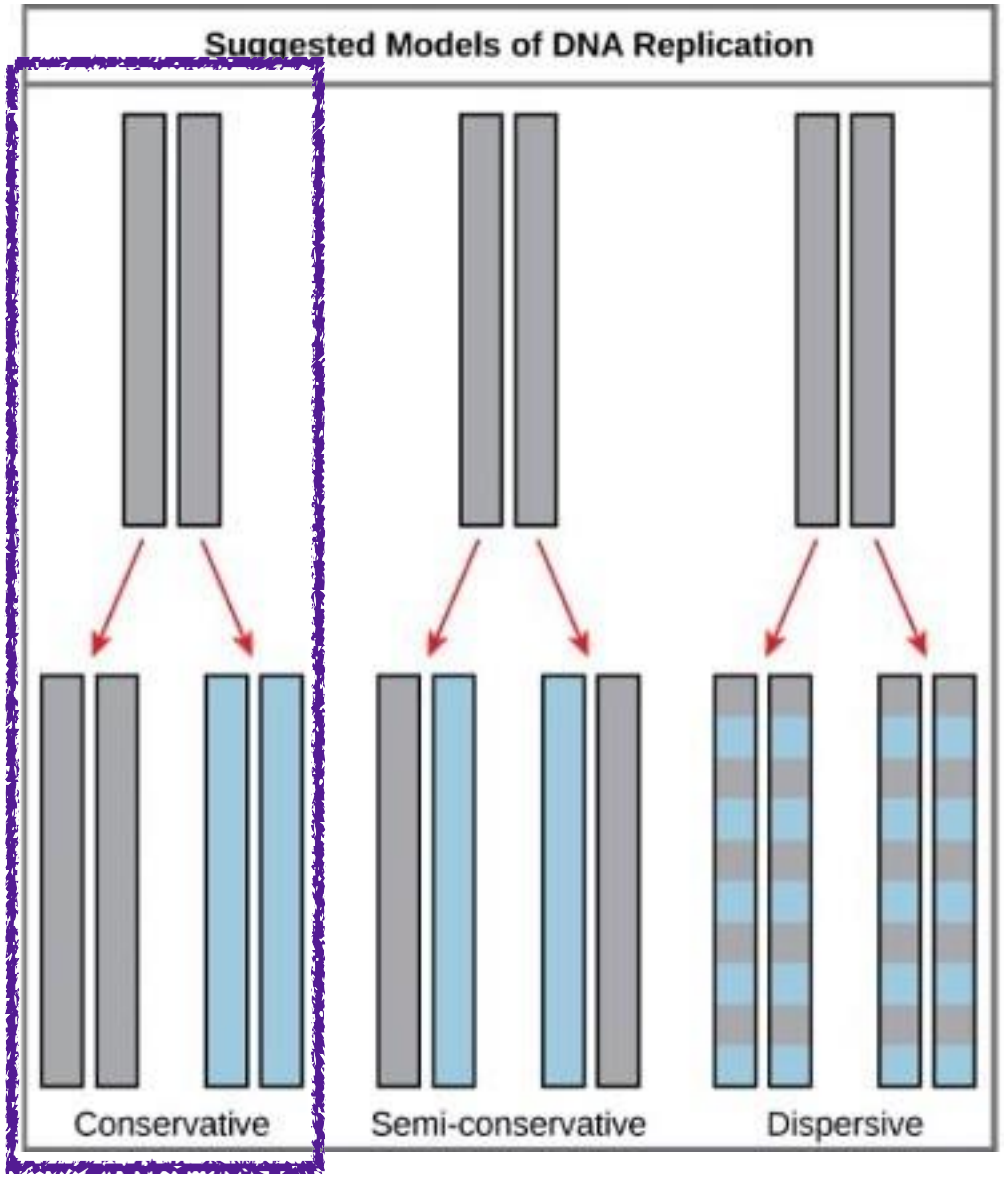


You would always have an original DNA molecule intact (the heavy 15N) and a entirely new copy, (14N) NO hybrids between the two.

The three suggested possible models by which DNA replication might occur.

Conservative replication– original parent double strands remain intact and two completely new double helix strands are synthesized



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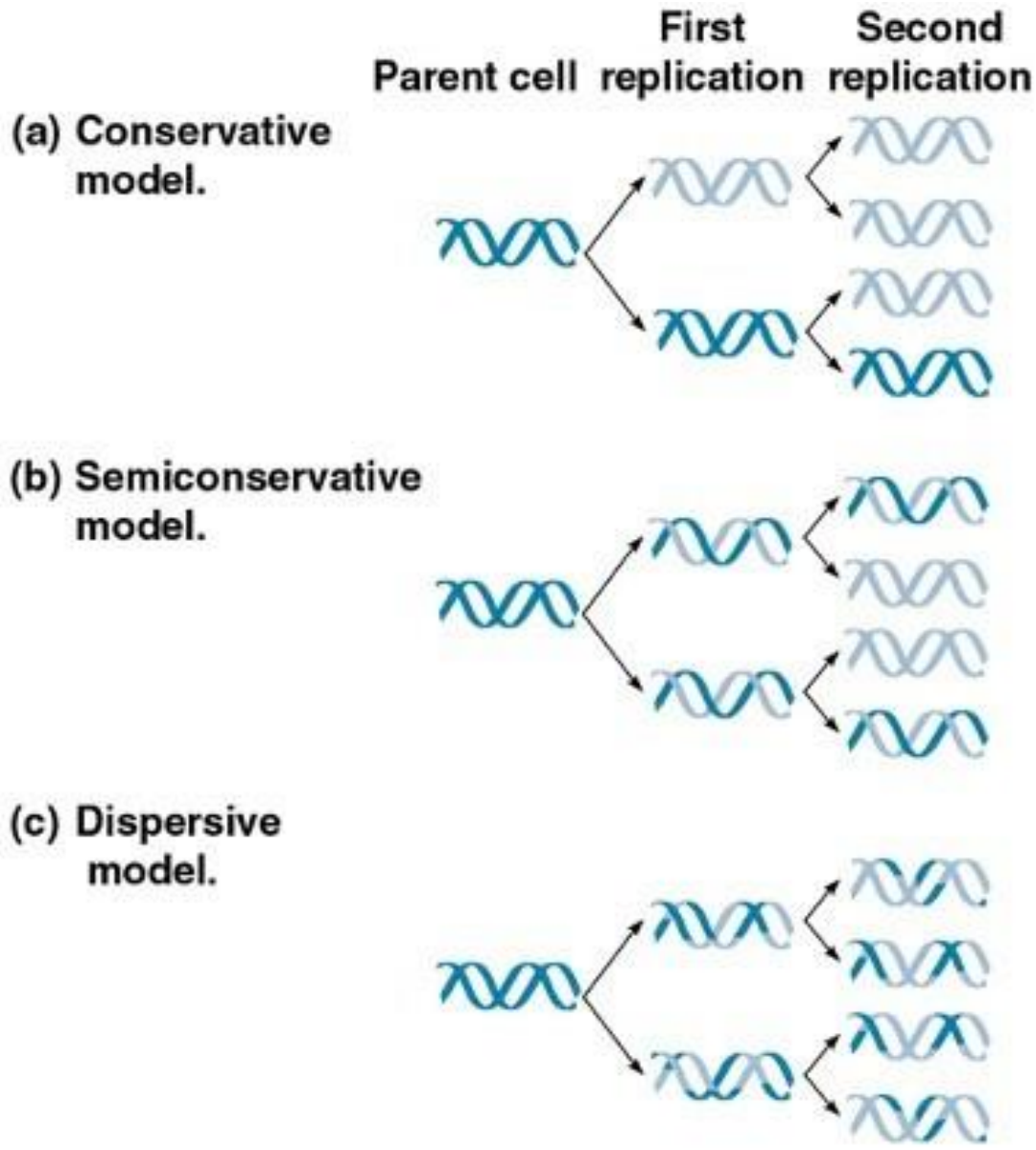
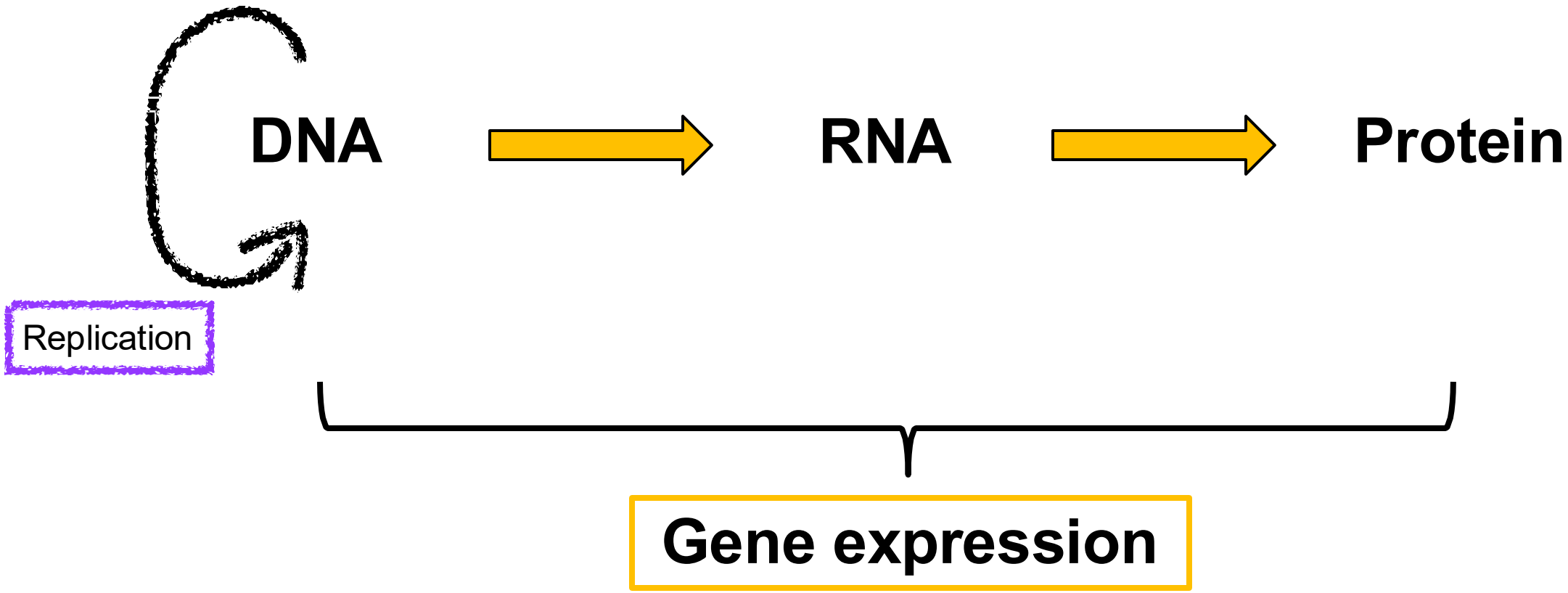



DNA
RNA
Protein
Replication
Gene expression

The Replication Process: Overview

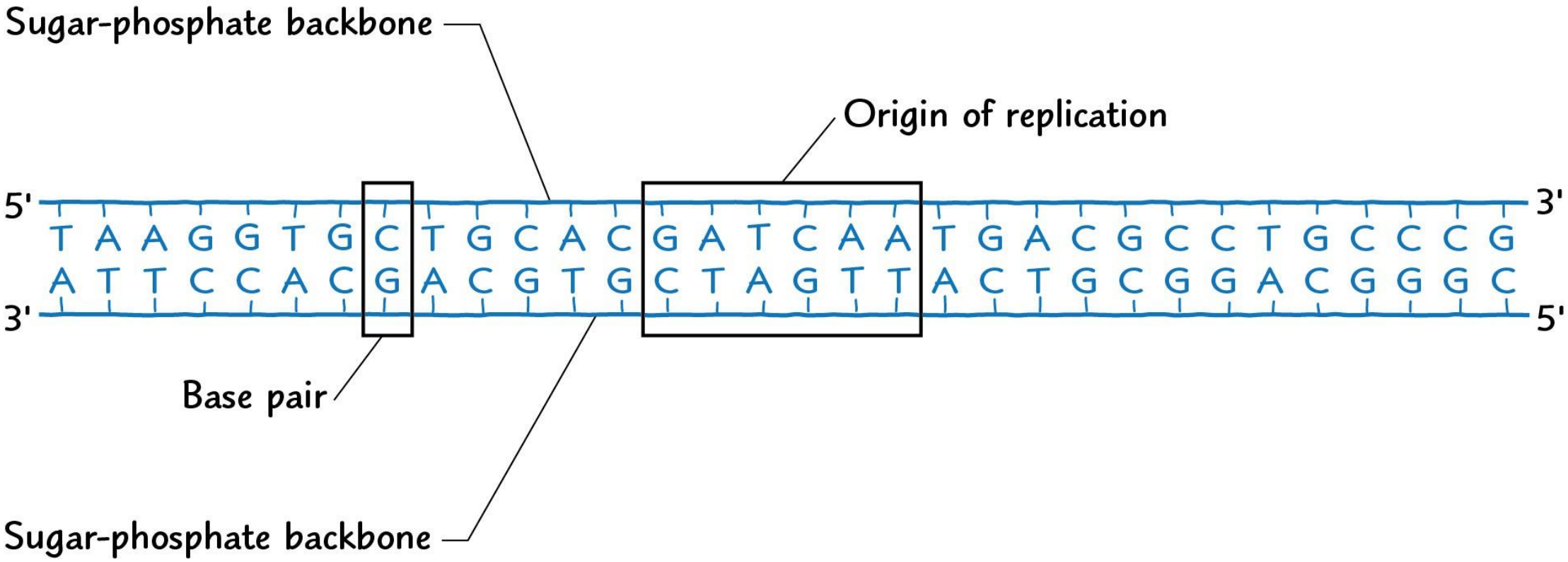
Key steps:

1. **Initiation:** DNA unwinds and separates at origin
2. **Elongation:** New nucleotides added to growing strands
3. **Termination:** Process completes, two DNA molecules form

Key players (enzymes):

- Helicase
- Primase
- DNA Polymerase
- Ligase

DNA replication begins when double-stranded DNA is separated, beginning in the middle of the **origin of replication**, a short stretch of DNA.



Step 1: Finding Where to Start

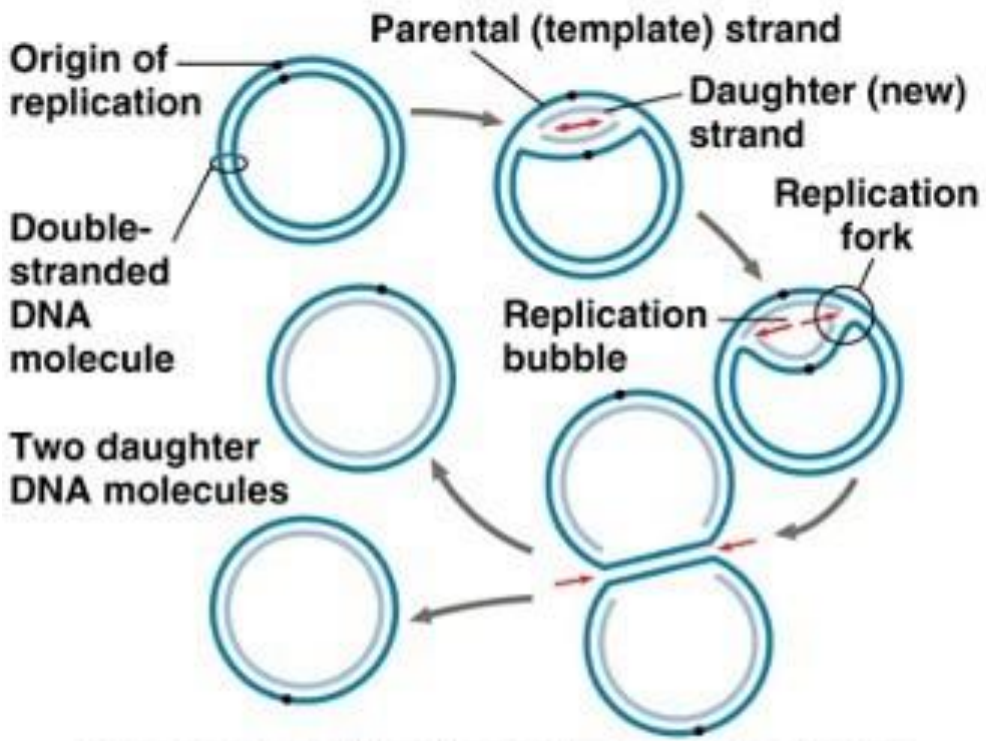
Origin of replication: Specific sequence where replication begins

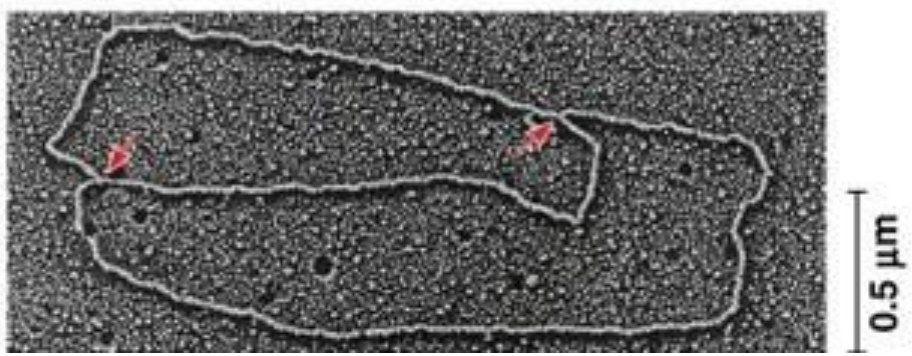
- **Prokaryotes (bacteria):** Single circular chromosome, ONE origin
- **Eukaryotes (humans):** Linear chromosomes, MULTIPLE origins

Why multiple origins in eukaryotes?

- Human genome = 3 billion base pairs
- DNA polymerase adds ~50 nucleotides/second
- With one origin, would take ~23 days to replicate!
- With multiple origins, replication takes only a few hours

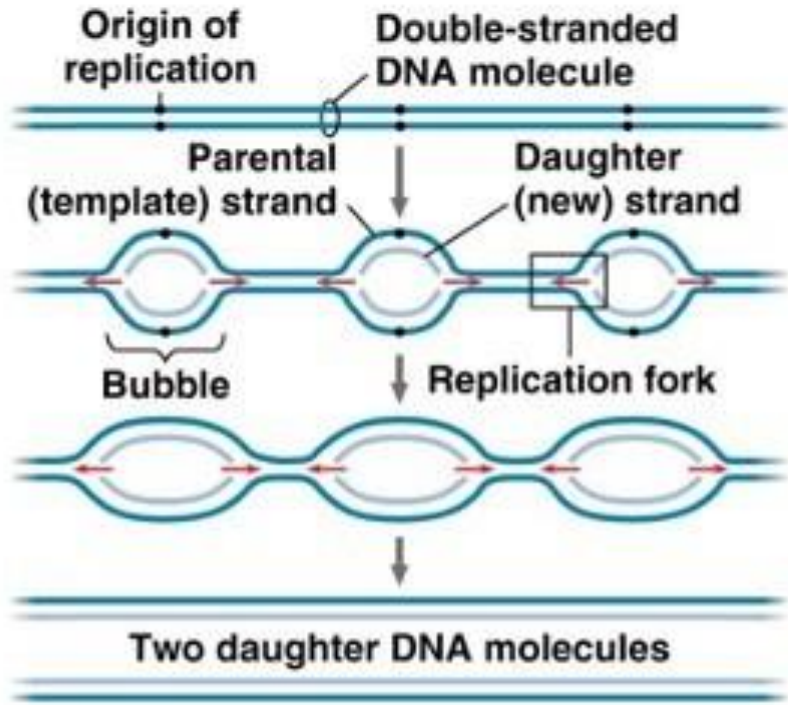
(a) Origin of replication in an *E. coli* cell

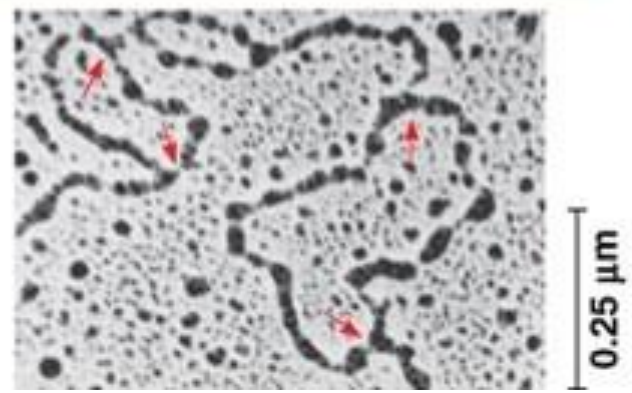




ONE ORIGIN

(b) Origins of replication in a eukaryotic cell





MULTIPLE ORIGINS

Starting Replication

1. The origin must be recognized and parental strands of DNA must be unwound to begin replication

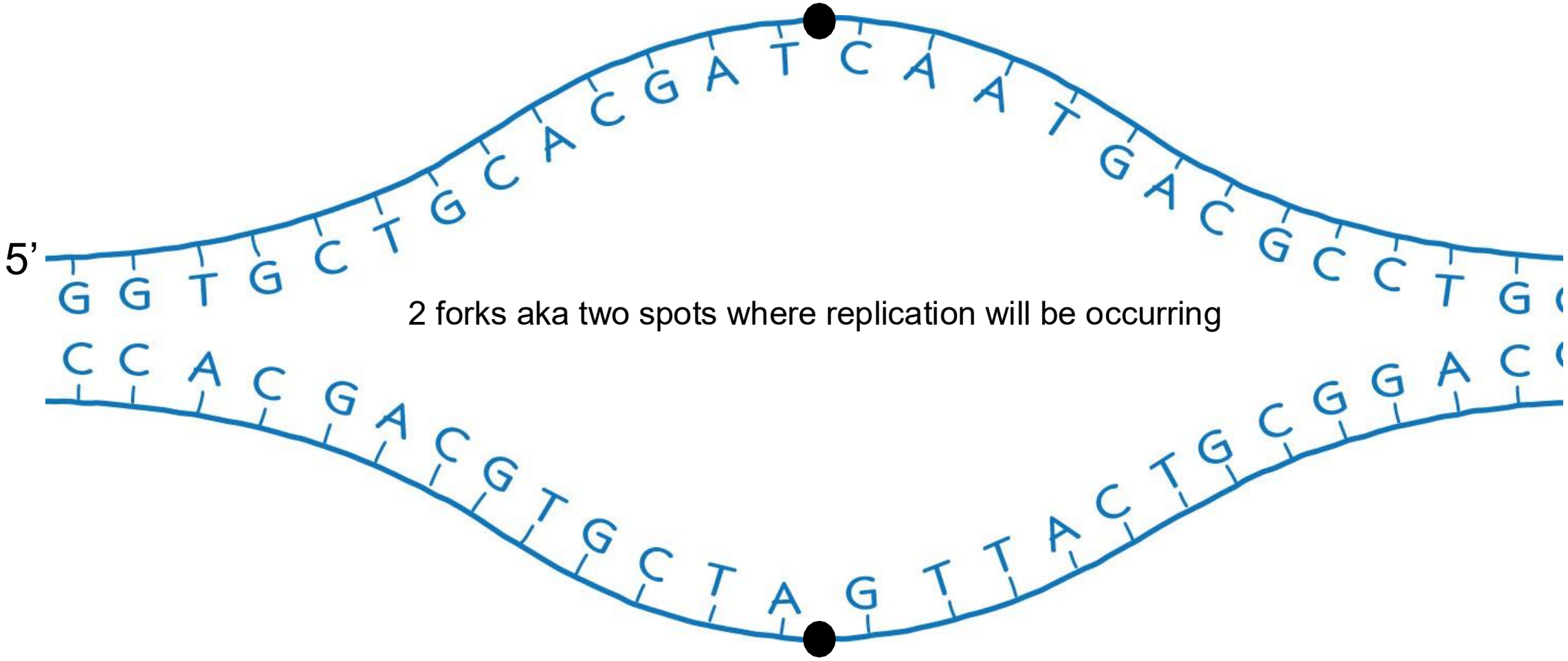
At the end of each replication bubble is a **replication fork**, a Y-shaped region where parental DNA strands are being unwound

Helicases are enzymes that untwist the double helix at the replication forks, separating the two strands and creating the replication fork

Single-strand binding proteins bind to and stabilize single-stranded DNA

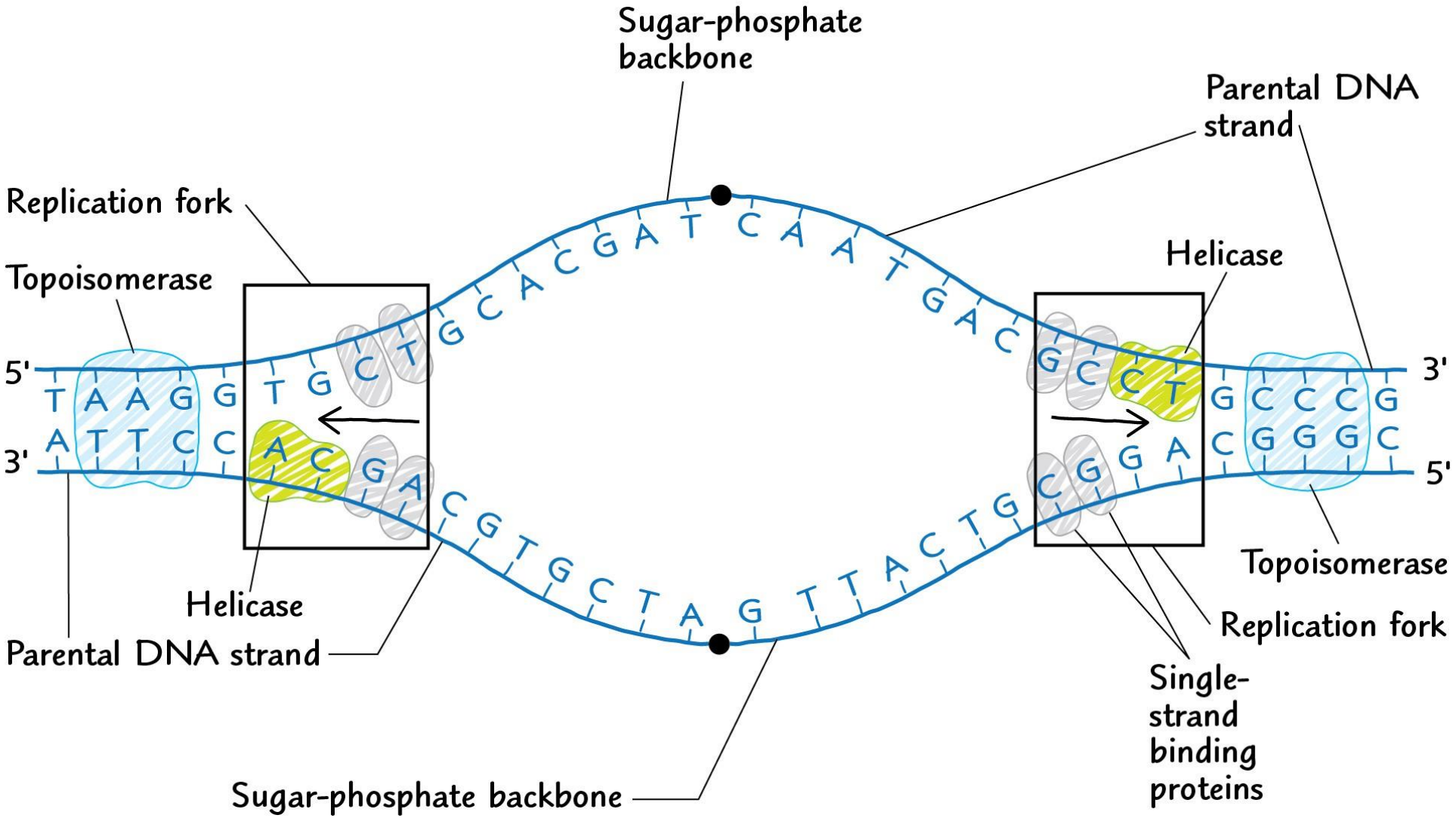
Topoisomerase relieves the strain of twisting of the double helix by breaking, swiveling, and rejoining DNA strands

ICA q6: Building a Replication Bubble



On your ICA Q6, illustrate the early events of DNA replication using the provided replication bubble:

- The dot (•) lies in the middle of the origin of replication to show where replication will begin.
- Label the Parental DNA strands (x2).
- Draw a box around the Replication forks and label them (x2)
  - **replication fork** = Y-shaped region where parental DNA strands are being opened
  - add arrows indicating the direction each fork is opening --> goal: open more DNA, arrow should go towards the closed DNA
- Finish labeling the 3' and 5' ends to indicate the antiparallel nature of DNA.
- Draw and label the enzymes and other proteins needed to separate and unwind the DNA strands
  - **Topoisomerase:** goal = to relieve strain on closed pieces of DNA so they don't get messed up as helicase works
  - **Helicase:** goal = to unwind the DNA in the direction of the each form
  - **Single-strand binding protein:** goal = stabilize SINGLE strands


Sugar-phosphate backbone
Parental DNA strand
Replication fork
Topoisomerase
Helicase
5'
3'
T A A G G T G C T
A T T C C A C G A
G C A C G A T C A A T G A C
C G T G C T A G T T A C T G
G C C T
C G G G C
G A
C G
Helicase
Topoisomerase
Replication fork
Parental DNA strand
Single-strand binding proteins
Sugar-phosphate backbone

DNA polymerase adds nucleotides to the growing chain of DNA complementary to the template strand

DNA pol has TWO important restrictions:

1. Requires a free 3'-OH group to add nucleotides by forming a phosphodiester bond between the 3'-OH end and the 5' phosphate of the next nucleotide

2. Can only add nucleotides in the 5'→ 3' direction

DNA polymerase adds nucleotides to the growing chain of DNA complementary to the template strand

DNA pol has TWO important restrictions:

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DNA pol requires a short RNA primer to serve as the initial nucleotide chain so it can add nucleotides- this primer is five to ten nucleotides long and is synthesized by the enzyme **primase**

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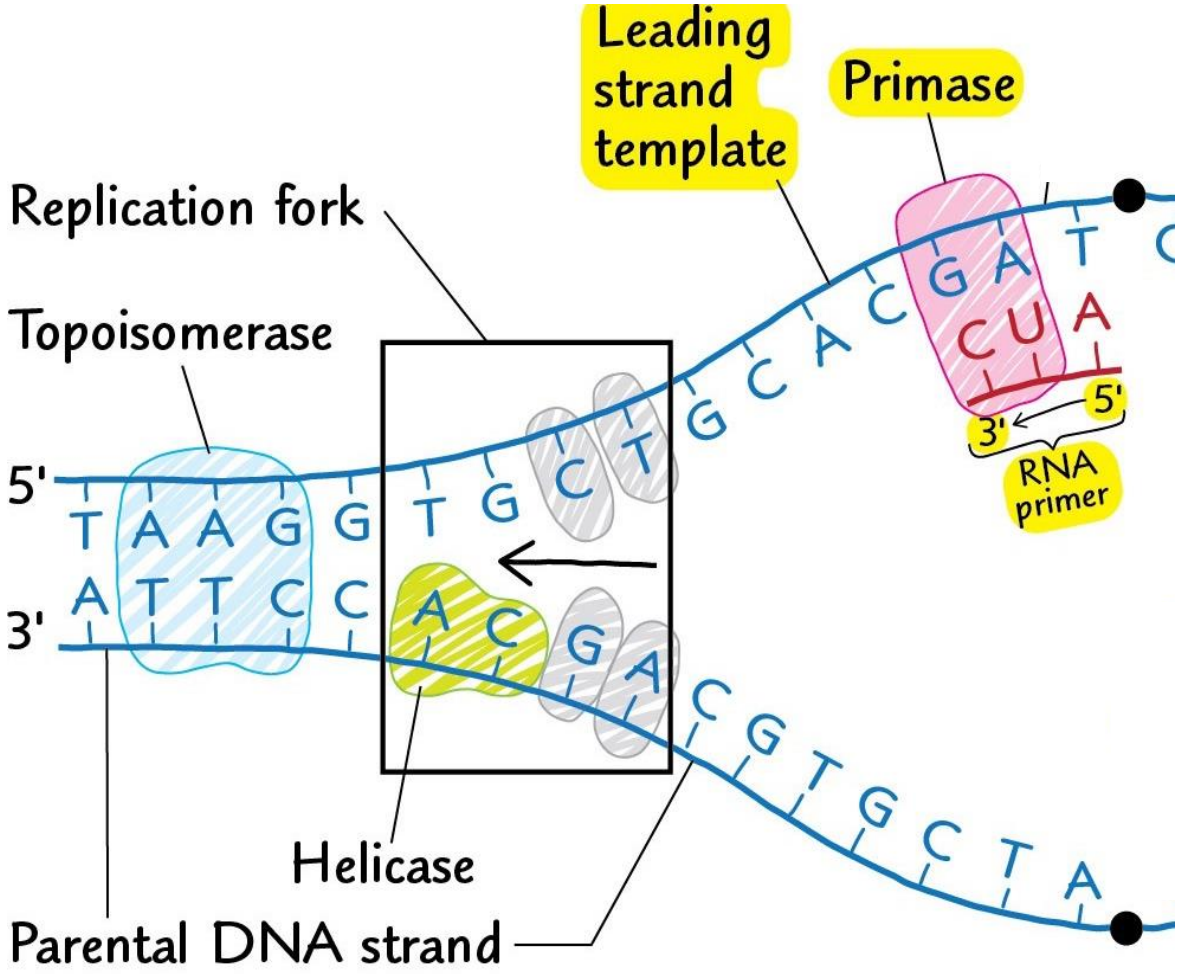
DNA pol requires a short RNA primer to serve as the initial nucleotide chain so it can add nucleotides- this primer is five to ten nucleotides long and is synthesized by the enzyme **primase**

Along one template strand of DNA, the DNA polymerase synthesizes a **leading strand** continuously, moving toward the replication fork

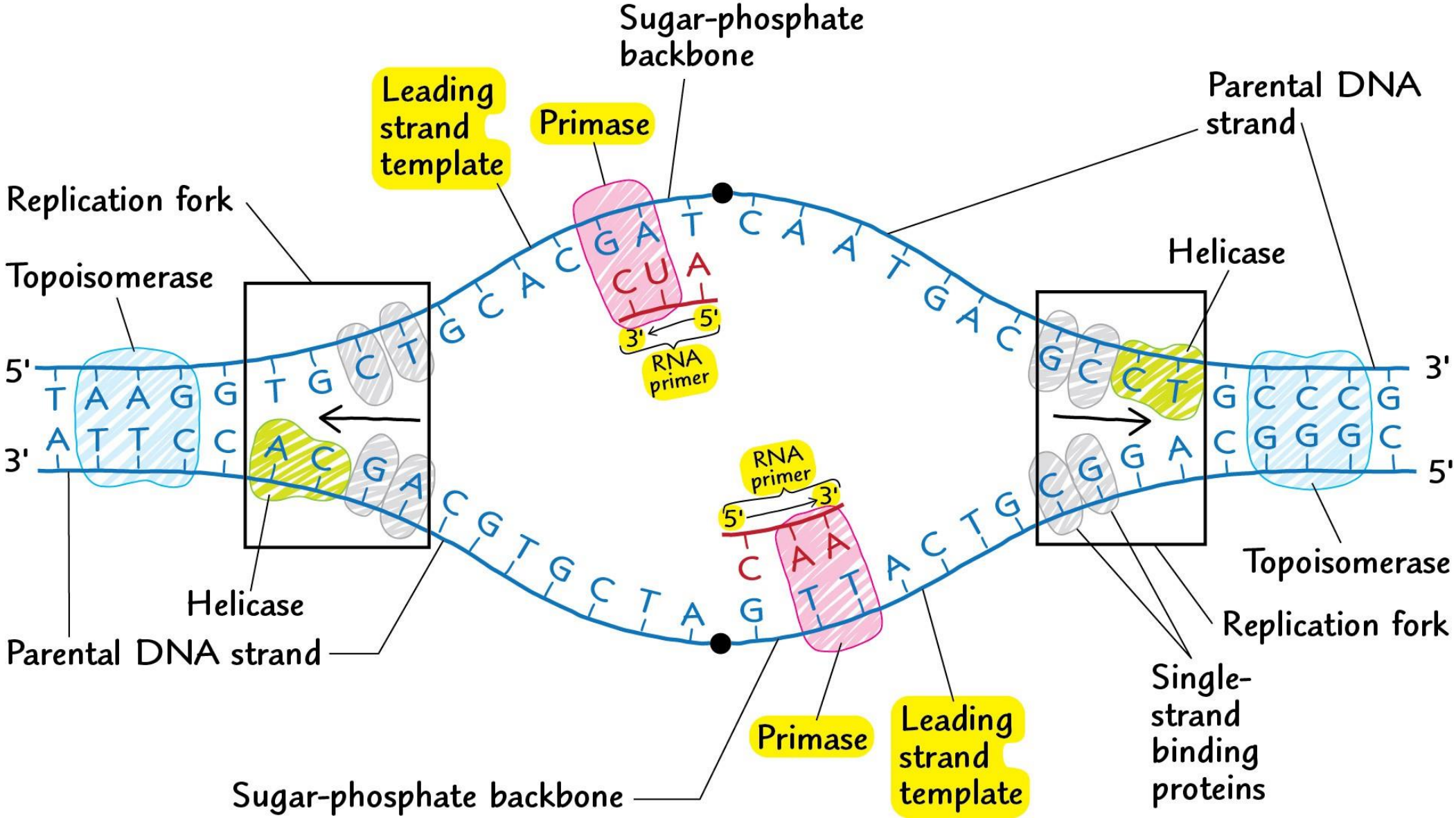
Part B- Draw RNA Primers for the Leading Strands

On your replication bubble starting at the middle of the origin of replication on your *top* strand, draw and label an RNA primer for the leading strand with three bases complementary to the DNA template strand.

- Make RNA nucleotides a different color or use and asterisk or some symbol /label so you know they are RNA not DNA nucleotides.
- Use capital letters for all bases.
- Label the 3' and 5' ends on the primer and draw an arrow indicating the direction of synthesis.
- Draw and label the enzyme primase.
- Label the DNA that serves as the template for this leading strand.



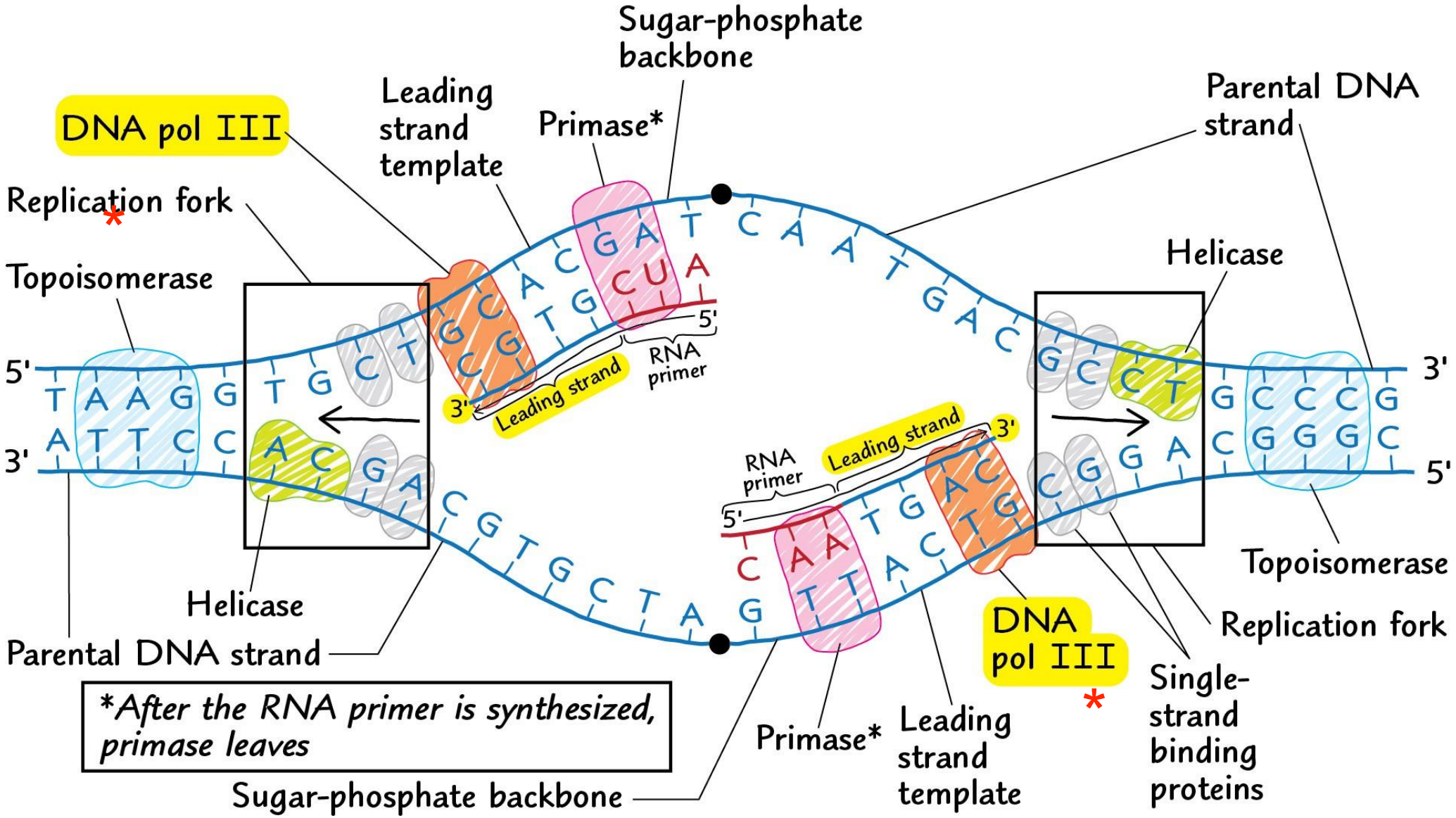
On your own, repeat the above instructions starting in the middle of the *bottom* of the replication bubble.


Sugar-phosphate backbone
Leading strand template
Primase
Parental DNA strand
Replication fork
Topoisomerase
Helicase
5'
3'
RNA primer
Helicase
Topoisomerase
Replication fork
Parental DNA strand
Sugar-phosphate backbone
Primase
Leading strand template
Single-strand binding proteins

Part C- Replicate your DNA!

- Starting from your RNA primer, draw the synthesis of the leading strand on the top and bottom of the replication bubble. Synthesize new DNA until you run into the single-strand binding proteins.

  - Make sure to indicate DNA nucleotides vs. RNA primers for yourself (use a different color, a label, etc)
  - Be sure to label the 5' and 3' ends of your daughter DNA strands. *Hint: they are STILL antiparallel*
  - Use an arrow to indicate the direction of synthesis of each new strand from 5' to 3'.
  - Include and label DNA polymerase. Hint: DNA polymerase should be adding the nucleotides, so will it be right after the primer or right before the single stranded binding protein?


DNA pol III
Replication fork
Topoisomerase
Leading strand template
Primase*
Sugar-phosphate backbone
Parental DNA strand
Helicase
Leading strand
RNA primer
5'
3'
Helicase
Parental DNA strand
Sugar-phosphate backbone
Primase*
Leading strand template
DNA pol III
Single-strand binding proteins
Replication fork
Topoisomerase
Parental DNA strand
*After the RNA primer is synthesized, primase leaves

If there's a leading strand…

… there's also a **lagging strand**, which DNA polymerase must work in the direction away from the replication fork to elongate the gaps you have in your current version of the bubble

Lagging strand is synthesized as a series of segments called **Okazaki fragments**, which are joined together by **DNA ligase**

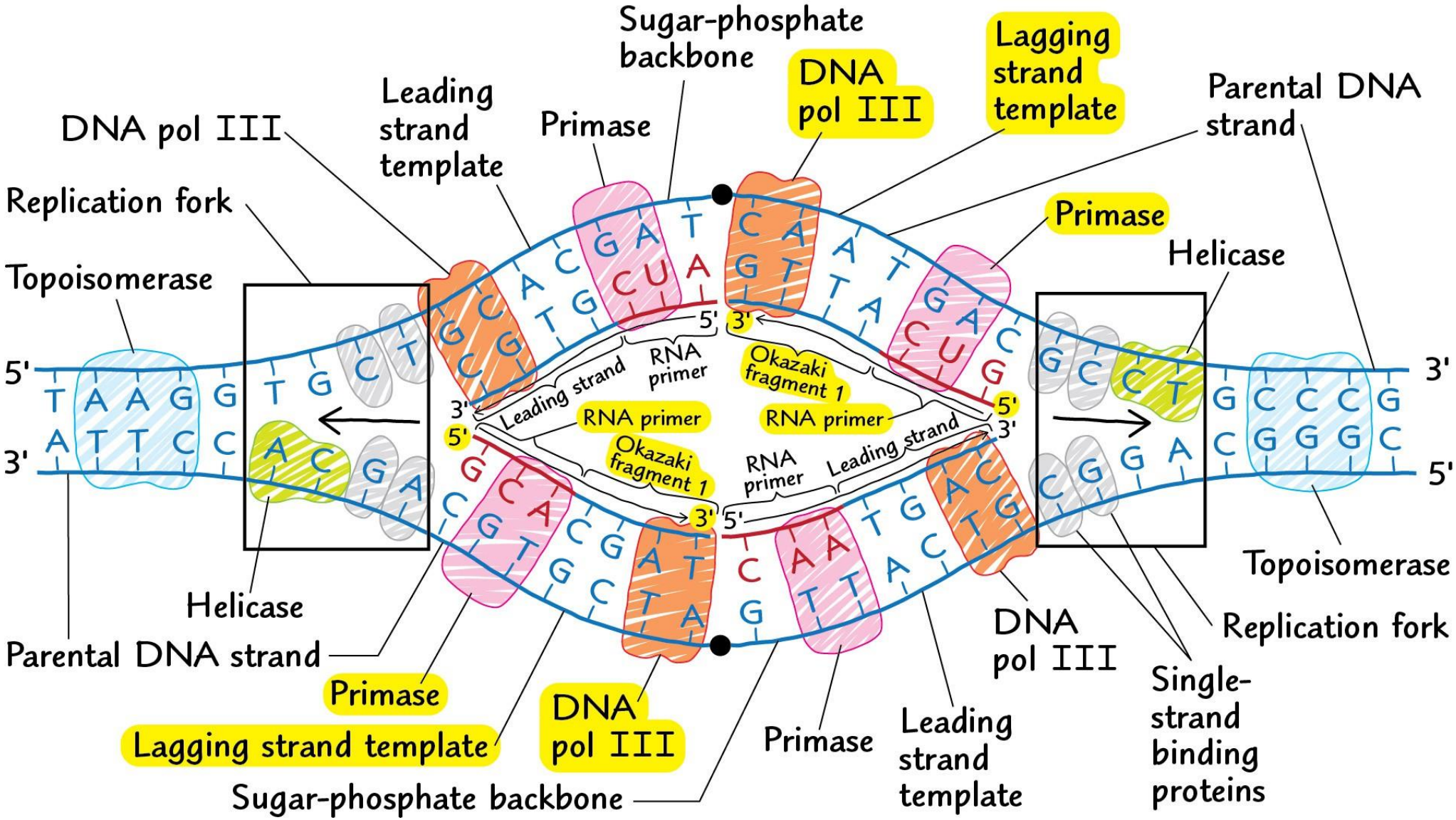
The **lagging strand** is synthesized discontinuously away from the replication fork
Problem: The template runs 5' → 3', but DNA polymerase must synthesize 5' → 3'

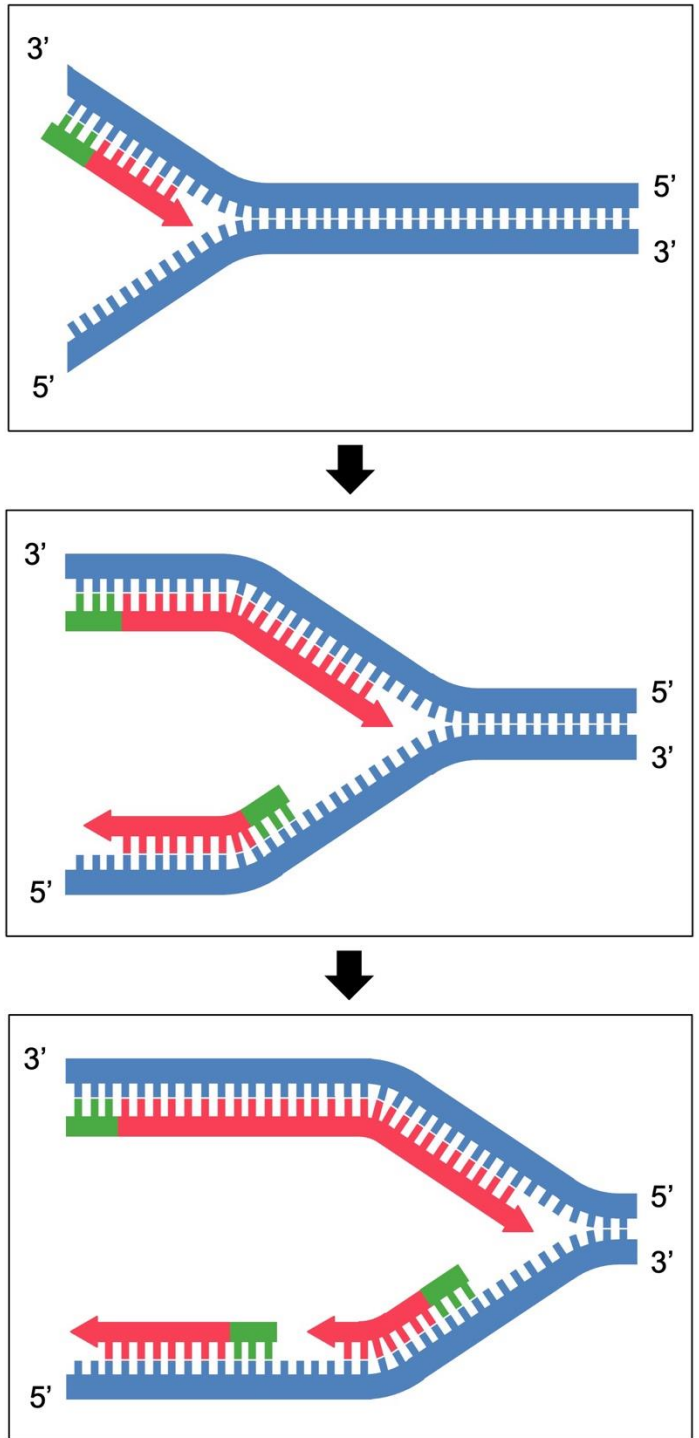
This means synthesis goes AWAY from the fork!
Solution: Made in short segments called **Okazaki fragments**

Part D- Draw Okazaki Fragments

On the top strand, to the right of the origin of replication (•) you should have single stranded DNA. Starting with the nucleotide to the left of the single stranded binding protein (away from the fork) put in the complement for 3 bases as the RNA primer. Label as RNA primer and indicate this is RNA not DNA.

- Label the lagging strand template (the DNA that we are using to create the lagging strand)
- Add and label the enzyme primase. HINT: the enzyme that created the RNA primer
- Add new nucleotides only in the 5' to 3' direction. Use an arrow to indicate the direction of synthesis. This is an Okazaki fragment.
- Label the fragment "Okazaki fragment 1" since this is the first Okazaki fragments to be made on this side of the bubble. As the bubble gets larger there will be more fragments.
- Add and label DNA pol, HINT: DNA pol created the Okazaki fragment. Should it be next to the primase or the origin of replication (•)?


Sugar-phosphate backbone
DNA pol III
Lagging strand template
Leading strand template
Primase
DNA pol III
Parental DNA strand
Replication fork
Primase
Topoisomerase
Helicase
5'
3'
Leading strand
RNA primer
Okazaki fragment 1
RNA primer
RNA primer
Okazaki fragment 1
RNA primer
Leading strand
Helicase
Topoisomerase
Parental DNA strand
Replication fork
Primase
DNA pol III
Lagging strand template
Single-strand binding proteins
Sugar-phosphate backbone
Primase
Leading strand template



In this example – leading stand is on top of the right side of the bubble.

All strands are being BUILT in the 5'→ 3' direction

The bottom strand is the lagging strand – it is lagging because it is started AFTER the leading strand and works in response to the bubble being opened

As the bubble is opened more, there is more room for another Okazaki fragment

Part E- Finish the DNA Strands

What two processes still need to happen to end up with two **identical copies of the original double-stranded DNA**?

1. HINT: what about this sequence is not the same as the parental strand?

2. HINT: How do we prevent gaps in the DNA?

Part E- Finish the DNA Strands

What two processes still need to happen to end up with two identical copies of the original double-stranded DNA?

1. RNA primers must be removed and replaced with DNA nucleotides so that the daughter strands are comprised of only DNA nucleotides. **DNA polymerase I** carries out this process.

2. All DNA fragments must be joined using **DNA ligase** so that the daughter DNA is one continuous strand of DNA. (Okazaki fragments to each other and to the leading strand)

Summary of factors involved in DNA replication

Protein	Function
Helicase 	Unwinds parental double helix at replication forks
Single-strand binding protein 	Binds to and stabilizes single-stranded DNA until it is used as a template
Topoisomerase 	Relieves overwinding strain ahead of replication forks by breaking, swiveling, and rejoining DNA strands
Primase 	Synthesizes an RNA primer at 5′ end of leading strand and at 5′ end of each Okazaki fragment of lagging strand
DNA pol III 	Using parental DNA as a template, synthesizes new DNA strand by adding nucleotides to an RNA primer or a pre-existing DNA strand
DNA pol I 	Removes RNA nucleotides of primer from 5′ end and replaces them with DNA nucleotides added to 3′ end of adjacent fragment
DNA ligase 	Joins Okazaki fragments of lagging strand; on leading strand, joins 3′ end of DNA that replaces primer to rest of leading strand DNA

Prokaryotic vs. Eukaryotic Replication

Prokaryotic Replication

- Smaller genome- replication initiates at a single origin
- Replication proceeds at a faster rate than eukaryotes
- Replication is continuous

Eukaryotic Replication

- Larger and more complex genome- replication initiated at multiple origins along a linear chromosome
- Replication proceeds at a slower rate than prokaryotes
- Replication is coordinated with the cell cycle

Eukaryotes have MANY more DNA polymerases and contain their DNA in structures called nucleosomes that must be removed before and replaced after replication

Remember the S-Phase checkpoint?

DNA Polymerase has proofreading ability:

DNA polymerase adds nucleotides

If WRONG nucleotide is added (doesn't match template):

- DNA polymerase detects the mistake
- **Exonuclease activity** removes the incorrect nucleotide
- Correct nucleotide is inserted

Analogy: Like spell-check that catches typos as you type!

This reduces errors by 1,000-fold!

Backup System: Mismatch Repair
Even with proofreading, some errors slip through

Mismatch repair system:

- Specialized proteins scan newly replicated DNA
- Detect mismatched base pairs (like A-C or G-T)
- Cut out incorrect nucleotide
- DNA polymerase fills in with correct nucleotide
- Ligase seals the gap

Announcements

- **I have updated the schedule on Canvas – we will NOT be having class on 11/26**
- **Problem set 4A will be available today**
- **Lab 12 AND Lab 13 assignments due on SUNDAY at 11:59pm**
- **Exam 4 is during finals week!! There is not a final exam in this class.**
  - 9am class – Monday 12/8 at 8am (follow the MWF 9am on finals schedule)***
  - 12pm class – Wednesday 12/10 at 10:30am (follow the MWF 12pm on finals schedule)***

****If you happen to need to switch days, I will allow it on first-come-first-serve basis. There will be two different exams, so if you take the exam on Wednesday, you will NOT be able to ask the Monday class what was on the exam. If you need to switch, please EMAIL me for my records, do not tell me in person.*