LECTURE PRESENTATIONS

For CAMPBELL BIOLOGY, NINTH EDITION

Jane B. Reece, Lisa A. Urry, Michael L. Cain, Steven A. Wasserman, Peter V. Minorsky, Robert B. Jackson

Chapter 16

The Molecular Basis of Inheritance

Lectures by
Erin Barley
Kathleen Fitzpatrick

Overview: Life's Operating Instructions

- In 1953, James Watson and Francis Crick introduced an elegant double-helical model for the structure of deoxyribonucleic acid, or DNA
- DNA, the substance of inheritance, is the most celebrated molecule of our time
- Hereditary information is encoded in DNA and reproduced in all cells of the body
- This DNA program directs the development of biochemical, anatomical, physiological, and (to some extent) behavioral traits

Figure 16.1

Concept 16.1: DNA is the genetic material

- Early in the 20th century, the identification of the molecules of inheritance loomed as a major challenge to biologists

The Search for the Genetic Material: *Scientific Inquiry*

- When T. H. Morgan’s group showed that genes are located on chromosomes, the two components of chromosomes—DNA and protein—became candidates for the genetic material
- The key factor in determining the genetic material was choosing appropriate experimental organisms
- The role of DNA in heredity was first discovered by studying bacteria and the viruses that infect them

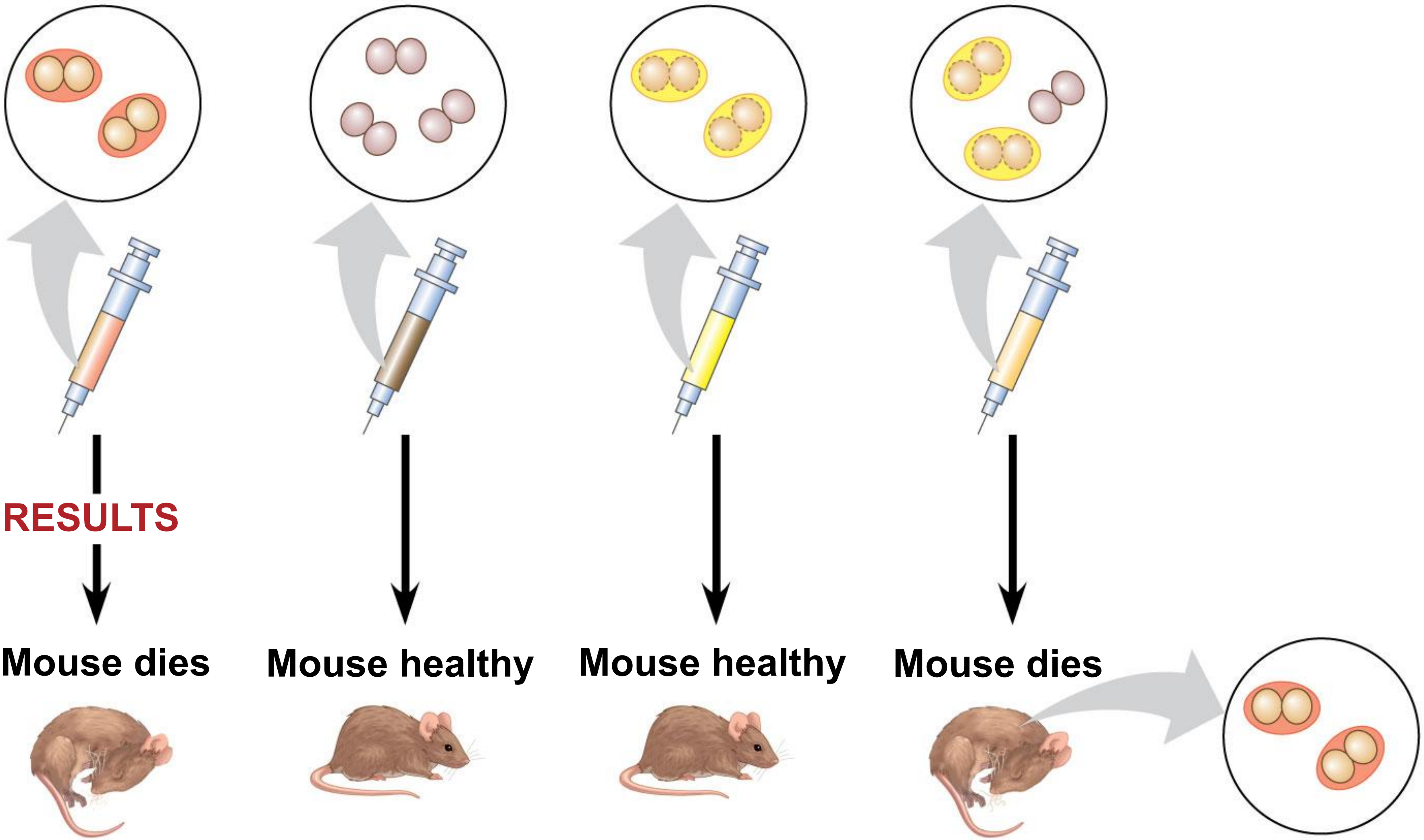
Evidence That DNA Can Transform Bacteria

- The discovery of the genetic role of DNA began with research by Frederick Griffith in 1928
- Griffith worked with two strains of a bacterium, one pathogenic and one harmless

- When he mixed heat-killed remains of the pathogenic strain with living cells of the harmless strain, some living cells became pathogenic
- He called this phenomenon **transformation**, now defined as a change in genotype and phenotype due to assimilation of foreign DNA

Figure 16.2

EXPERIMENT



Living S cells (control)

Living R cells (control)

Heat-killed S cells (control)

Mixture of heat-killed S cells and living R cells

RESULTS

Mouse dies

Mouse healthy

Mouse healthy

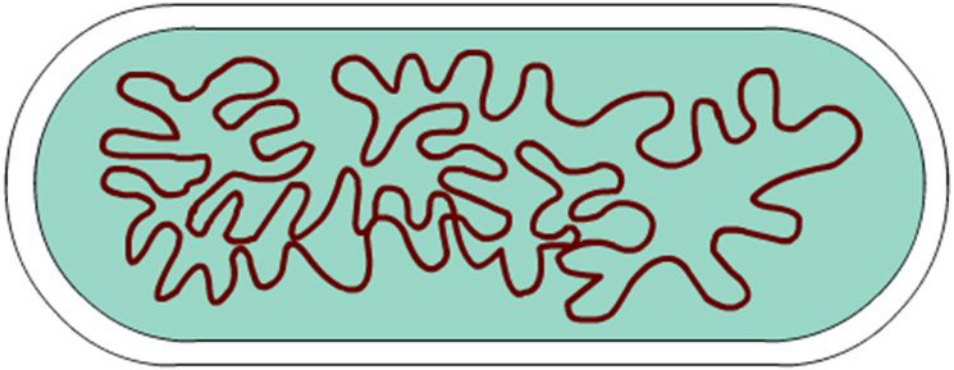
Mouse dies

Living S cells

- In 1944, Oswald Avery, Maclyn McCarty, and Colin MacLeod announced that the transforming substance was DNA
- Their conclusion was based on experimental evidence that only DNA worked in transforming harmless bacteria into pathogenic bacteria
- Many biologists remained skeptical, mainly because little was known about DNA

Evidence That Viral DNA Can Program Cells

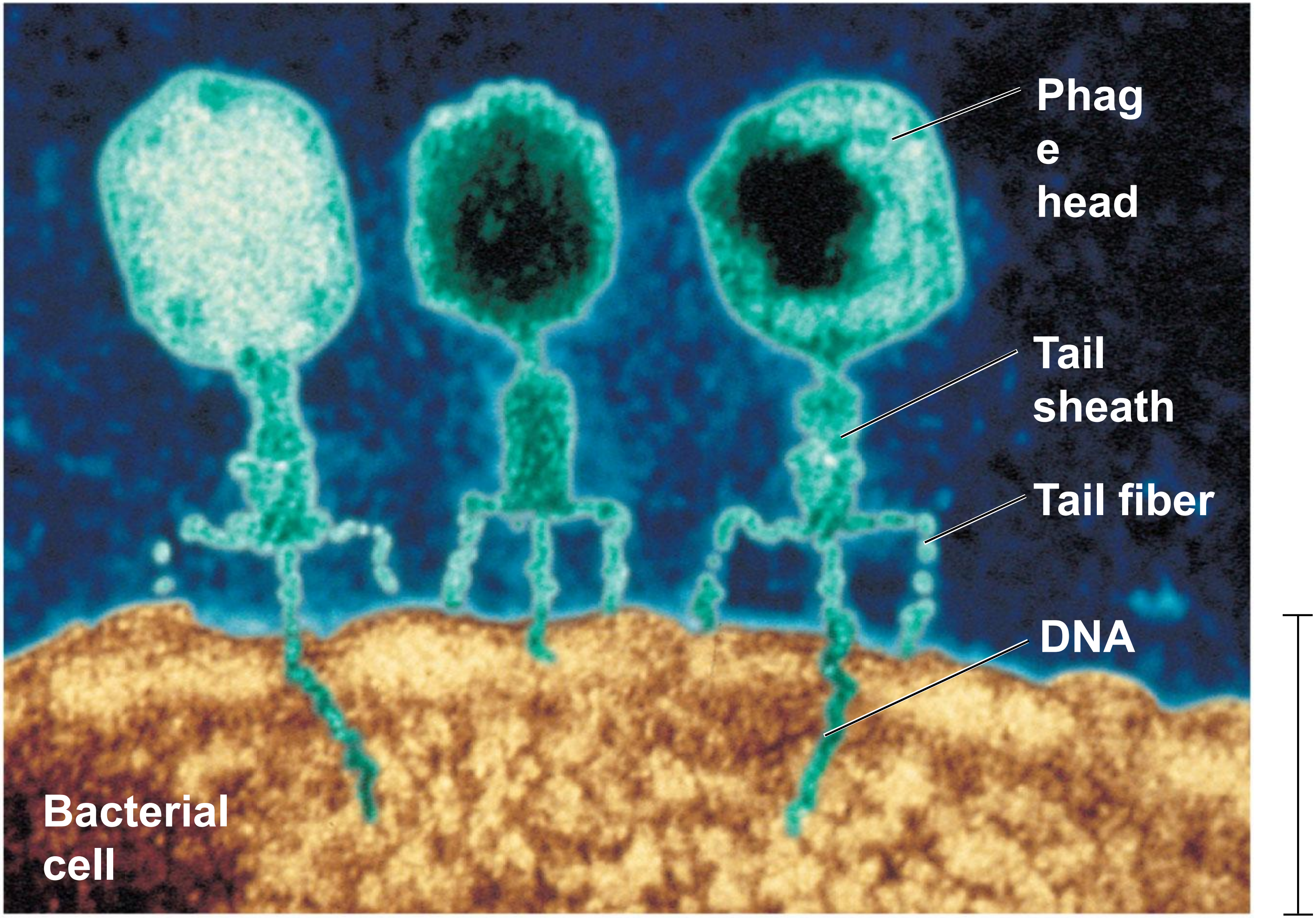
- More evidence for DNA as the genetic material came from studies of viruses that infect bacteria
- Such viruses, called **bacteriophages** (or **phages**), are widely used in molecular genetics research



Animation: Phage T2 Reproductive Cycle

Right-click slide / select “Play”

Figure 16.3



- In 1952, Alfred Hershey and Martha Chase performed experiments showing that DNA is the genetic material of a phage known as T2
- To determine this, they designed an experiment showing that only one of the two components of T2 (DNA or protein) enters an *E. coli* cell during infection
- They concluded that the injected DNA of the phage provides the genetic information

Animation: Hershey-Chase Experiment

Right-click slide / select “Play”

Figure 16.4-1

EXPERIMENT

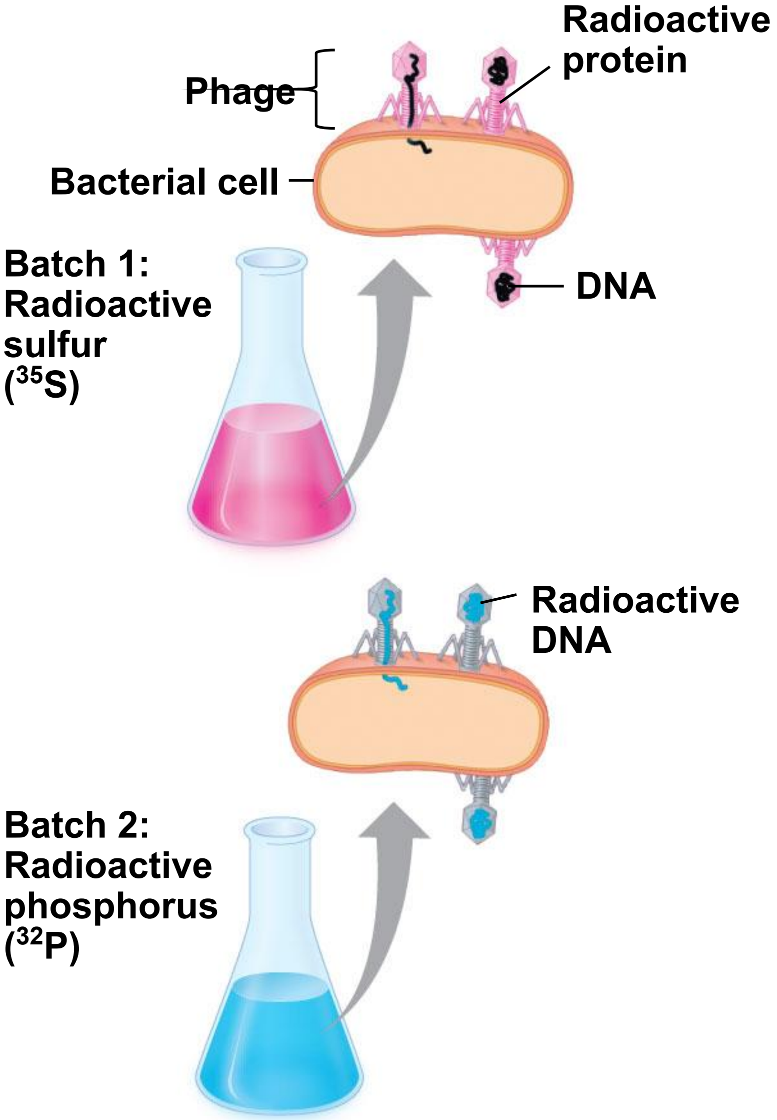


Figure 16.4-2

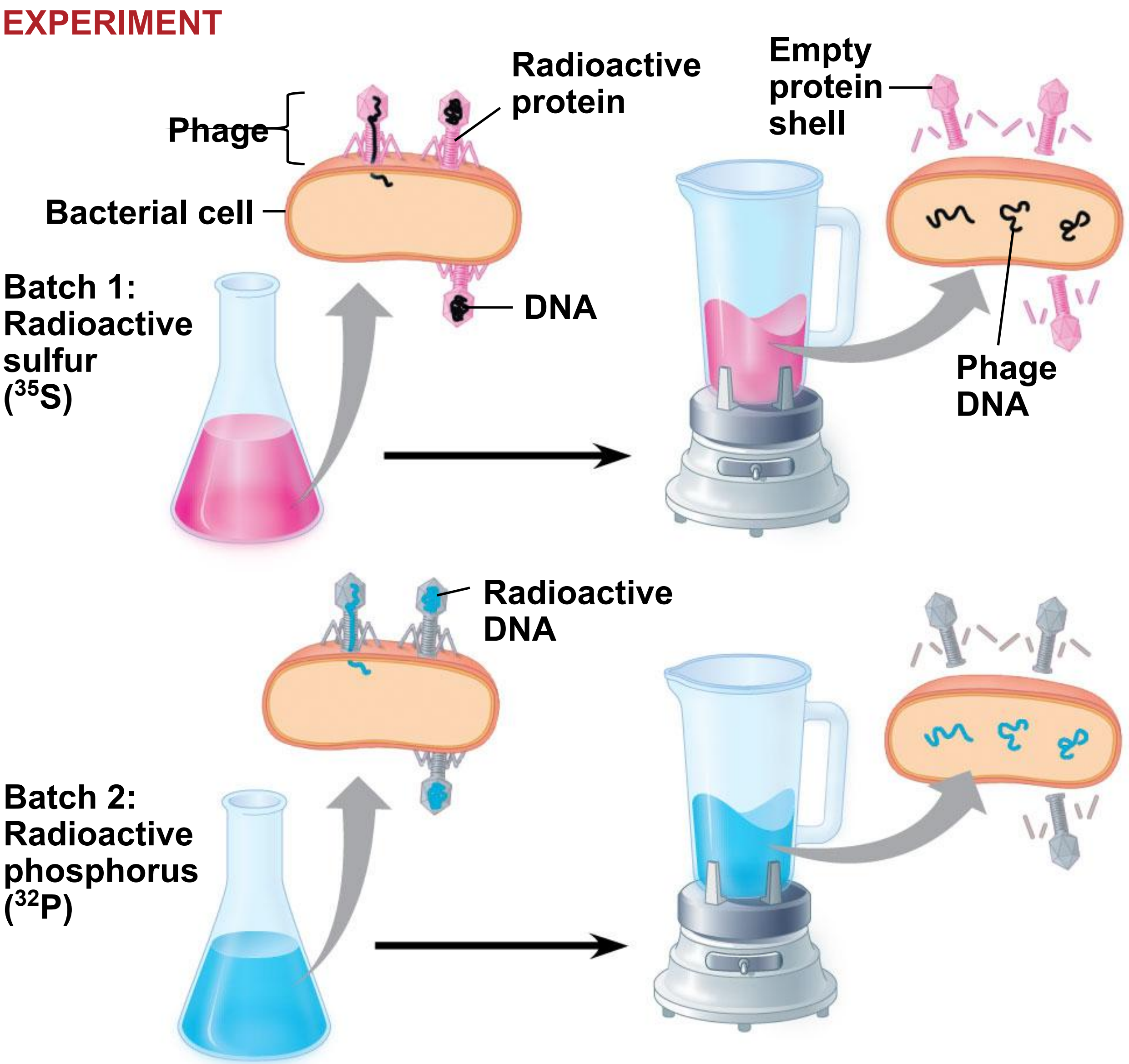
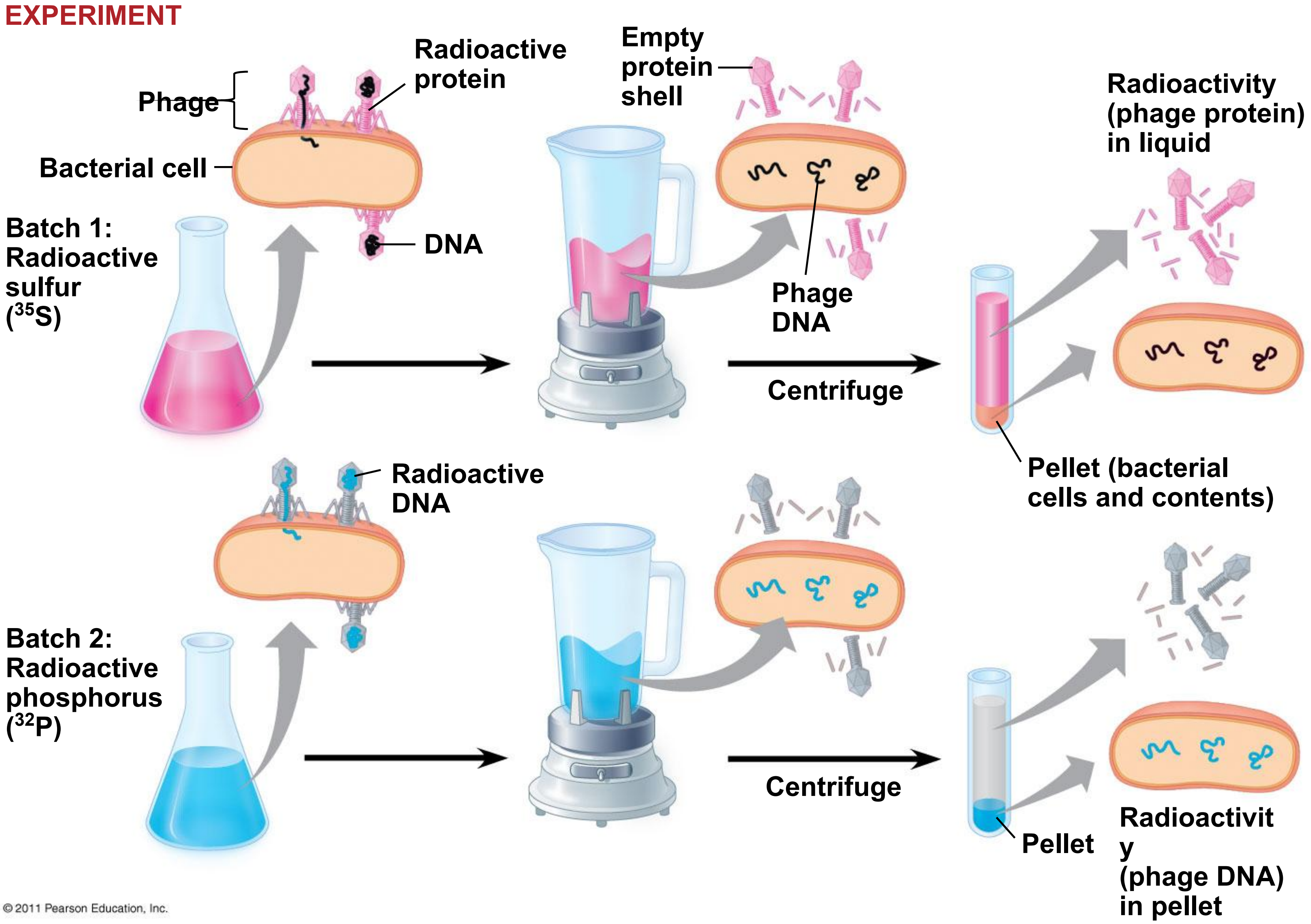
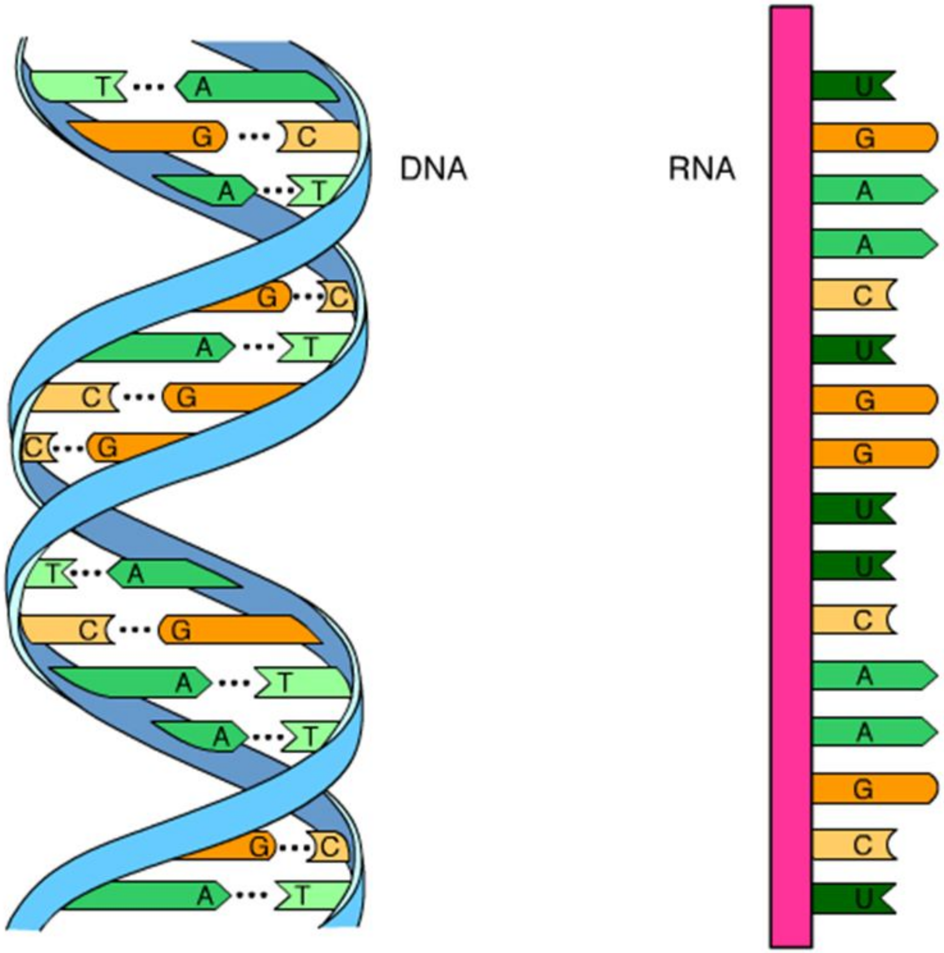

EXPERIMENT
Phage
Radioactive protein
Empty protein shell
Bacterial cell
DNA
Batch 1: Radioactive sulfur (^{35}S)
Phage DNA
Radioactive DNA
Batch 2: Radioactive phosphorus (^{32}P)

Figure 16.4-3


EXPERIMENT
Phage
Bacterial cell
Radioactive protein
DNA
Batch 1: Radioactive sulfur (^{35}S)
Empty protein shell
Phage DNA
Centrifuge
Radioactivity (phage protein) in liquid
Pellet (bacterial cells and contents)
Radioactive DNA
Batch 2: Radioactive phosphorus (^{32}P)
Centrifuge
Pellet
Radioactivit y (phage DNA) in pellet

Additional Evidence That DNA Is the Genetic Material

- It was known that DNA is a polymer of nucleotides, each consisting of a nitrogenous base, a sugar, and a phosphate group
- In 1950, Erwin Chargaff reported that DNA composition varies from one species to the next
- This evidence of diversity made DNA a more credible candidate for the genetic material

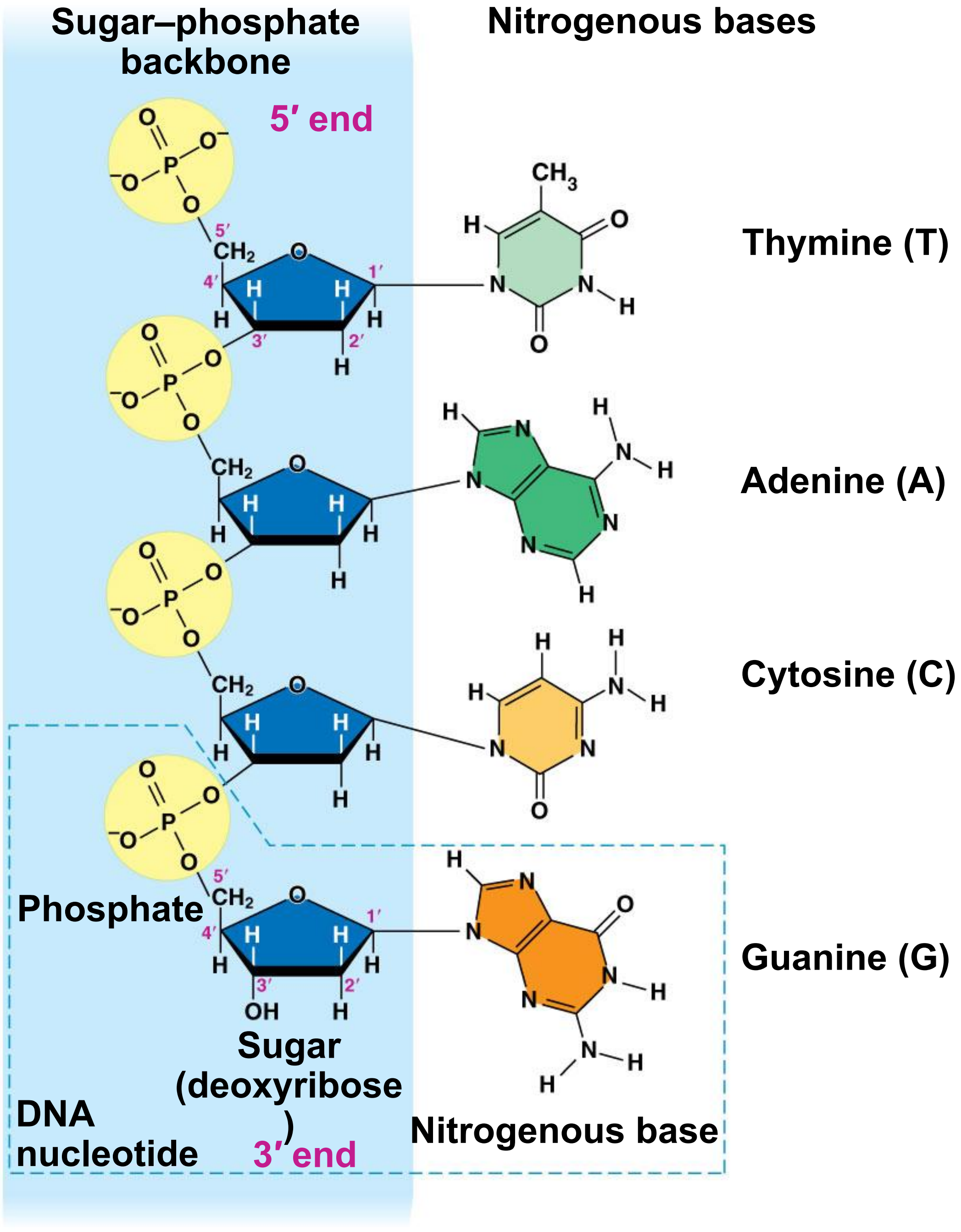


Animation: DNA and RNA Structure

Right-click slide / select "Play"

- Two findings became known as Chargaff’s rules
  - The base composition of DNA varies between species
  - In any species the number of A and T bases are equal and the number of G and C bases are equal
- The basis for these rules was not understood until the discovery of the double helix

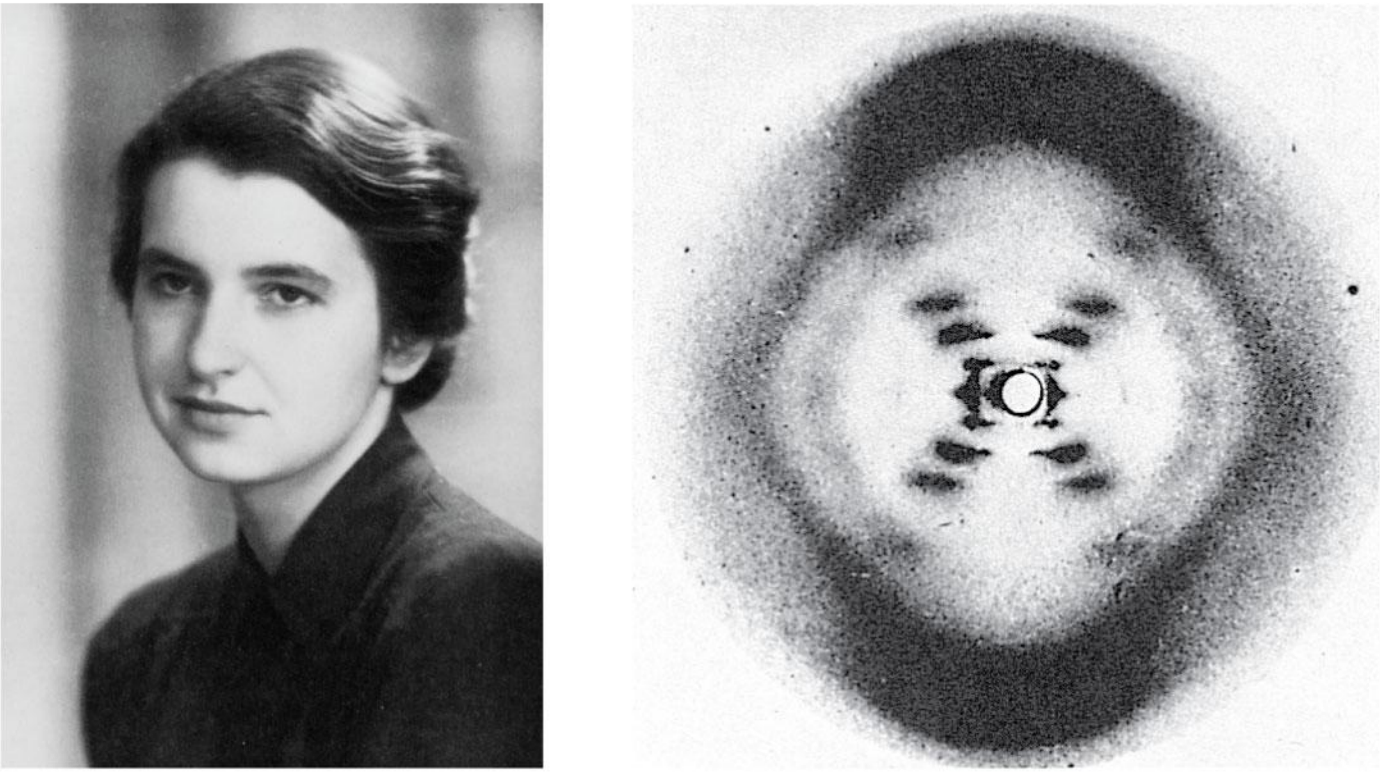
Figure 16.5


Sugar–phosphate backbone
Nitrogenous bases
5′ end
Thymine (T)
Adenine (A)
Cytosine (C)
Guanine (G)
Phosphate
Sugar (deoxyribose)
DNA nucleotide
3′ end
Nitrogenous base
5′
4′
3′
2′
1′
CH₂
OH
CH₃

Building a Structural Model of DNA: *Scientific Inquiry*

- After DNA was accepted as the genetic material, the challenge was to determine how its structure accounts for its role in heredity
- Maurice Wilkins and Rosalind Franklin were using a technique called X-ray crystallography to study molecular structure
- Franklin produced a picture of the DNA molecule using this technique

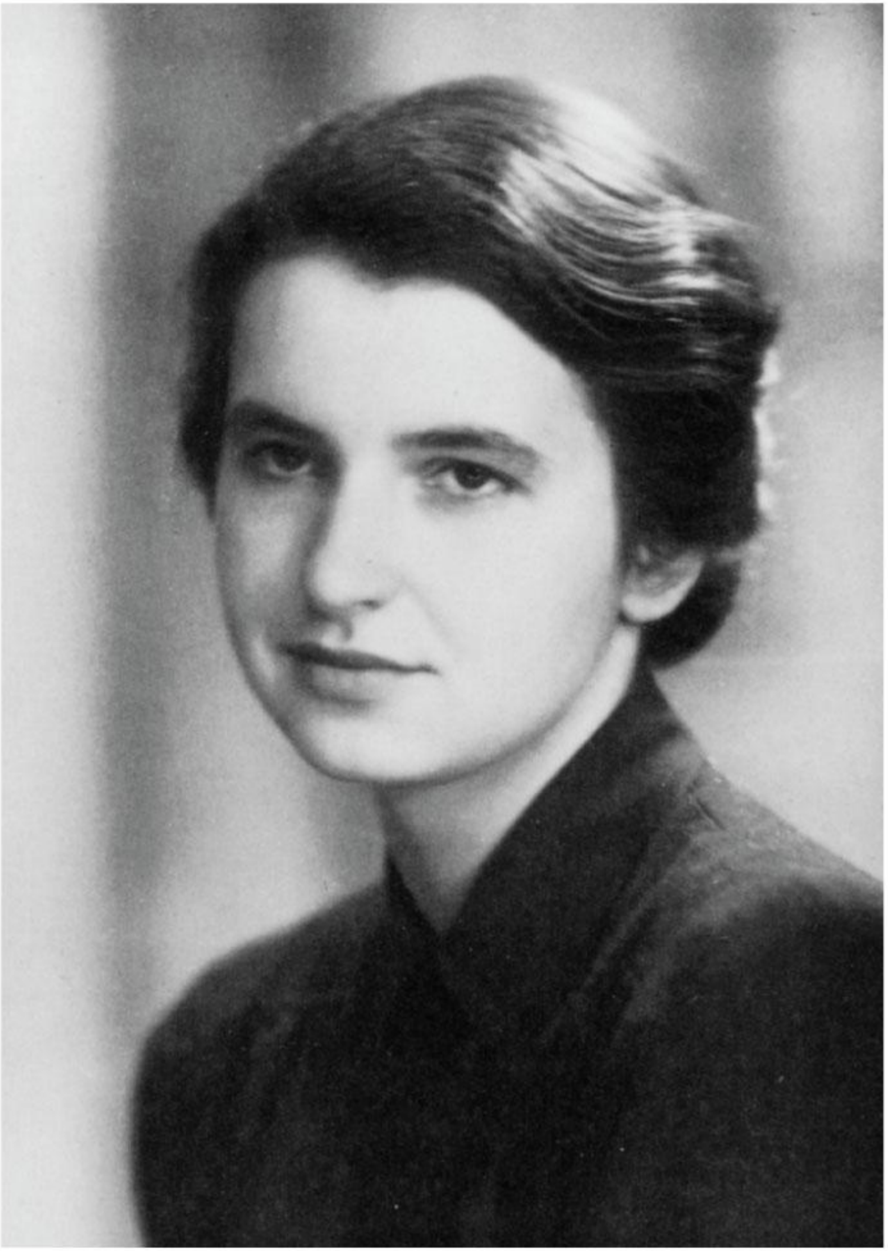
Figure 16.6



(a) Rosalind Franklin

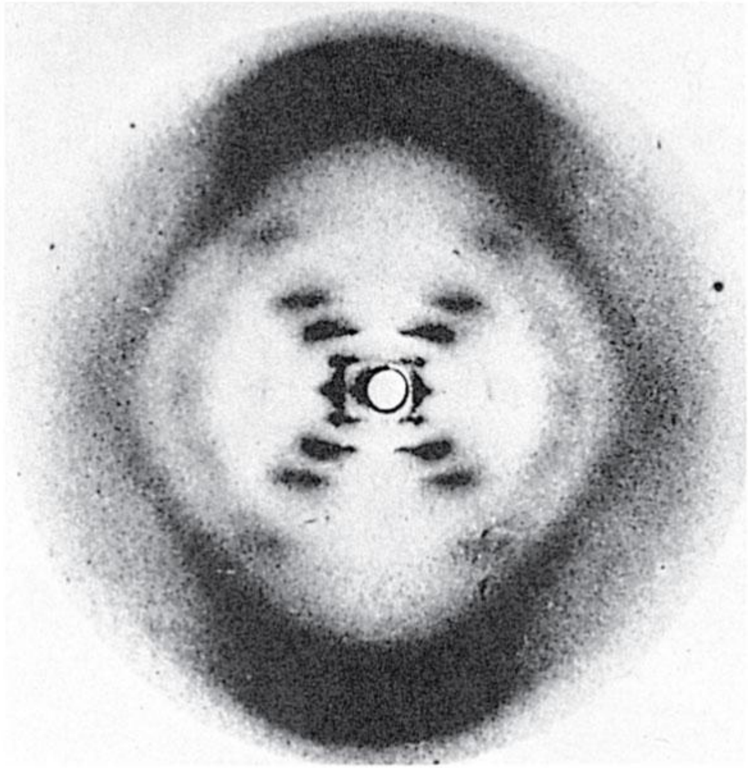
(b) Franklin’s X-ray diffraction photograph of DNA

Figure 16.6a



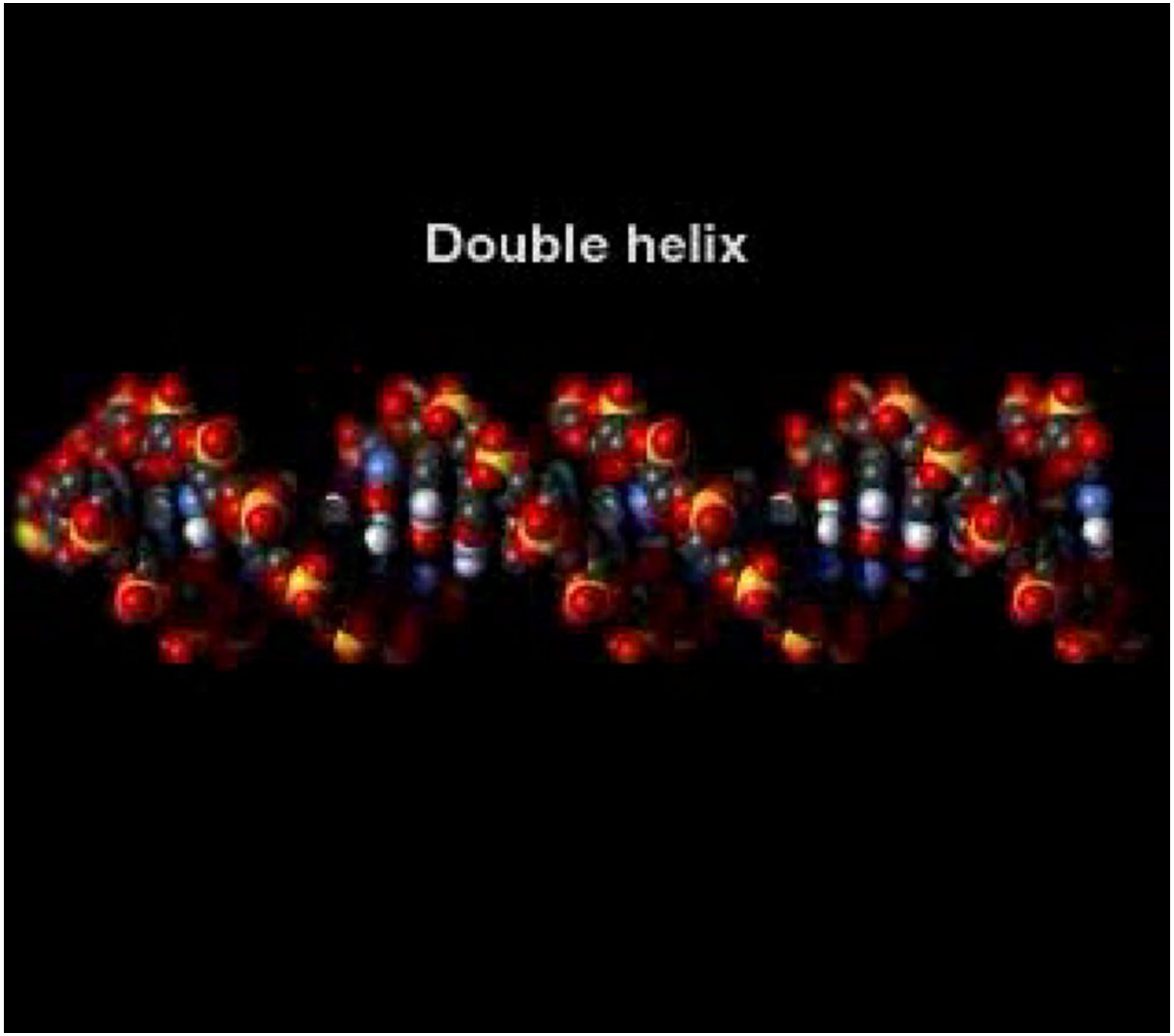
(a) Rosalind Franklin

Figure 16.6b



(b) Franklin's X-ray diffraction photograph of DNA

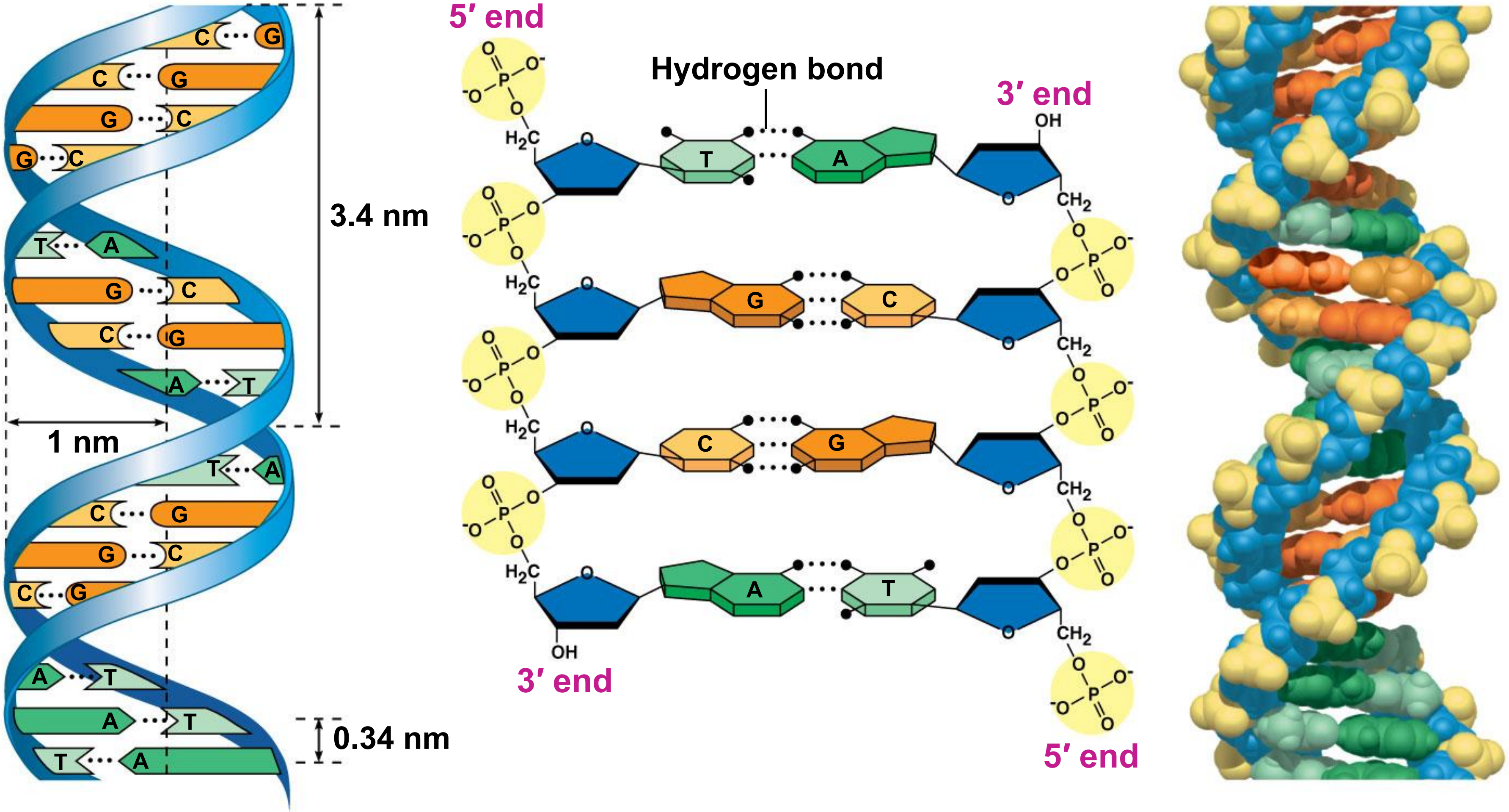
- Franklin’s X-ray crystallographic images of DNA enabled Watson to deduce that DNA was helical
- The X-ray images also enabled Watson to deduce the width of the helix and the spacing of the nitrogenous bases
- The pattern in the photo suggested that the DNA molecule was made up of two strands, forming a **double helix**



Animation: DNA Double Helix

Right-click slide / select “Play”

Figure 16.7

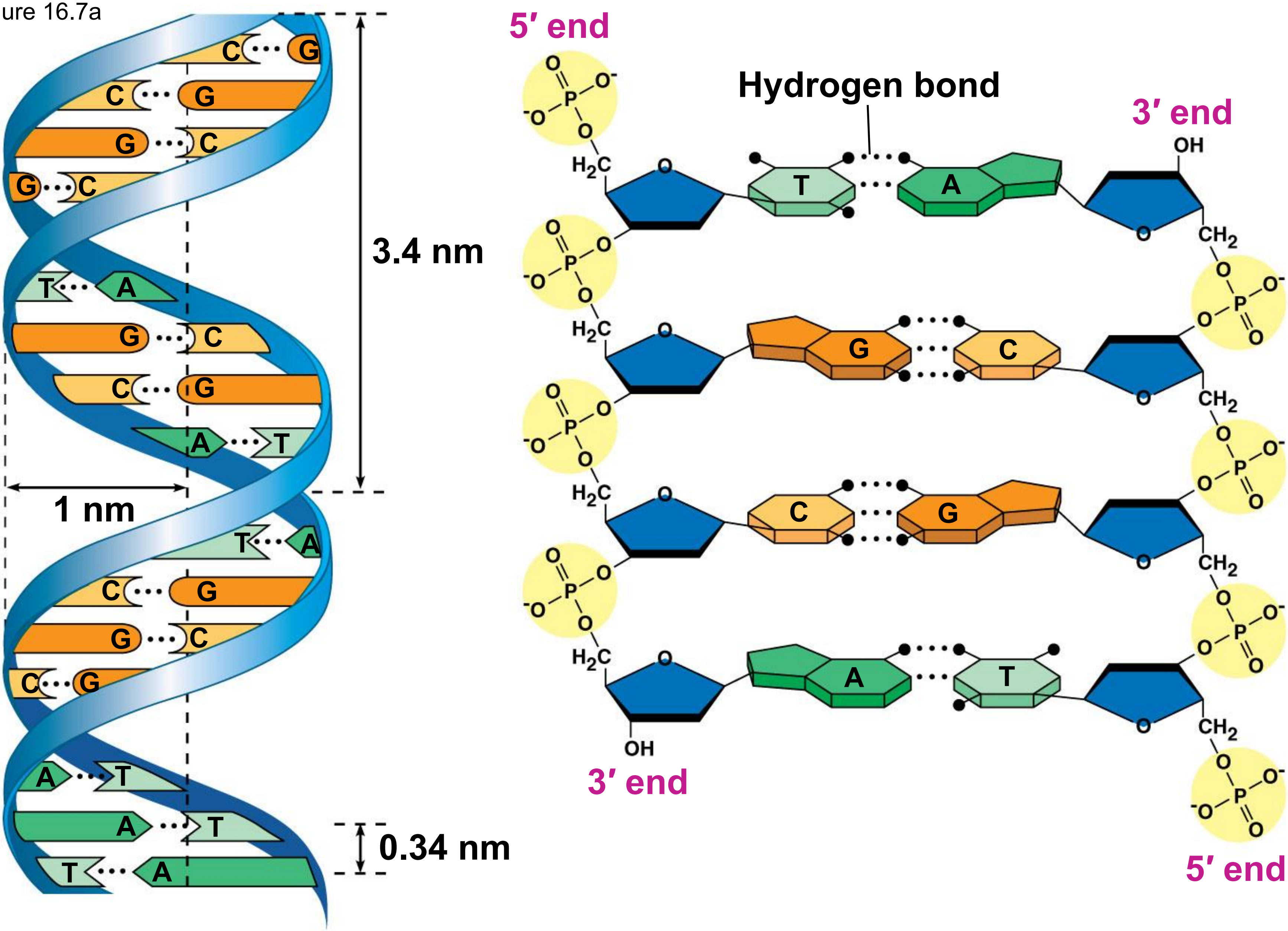


(a) Key features of DNA structure

(b) Partial chemical structure

(c) Space-filling model

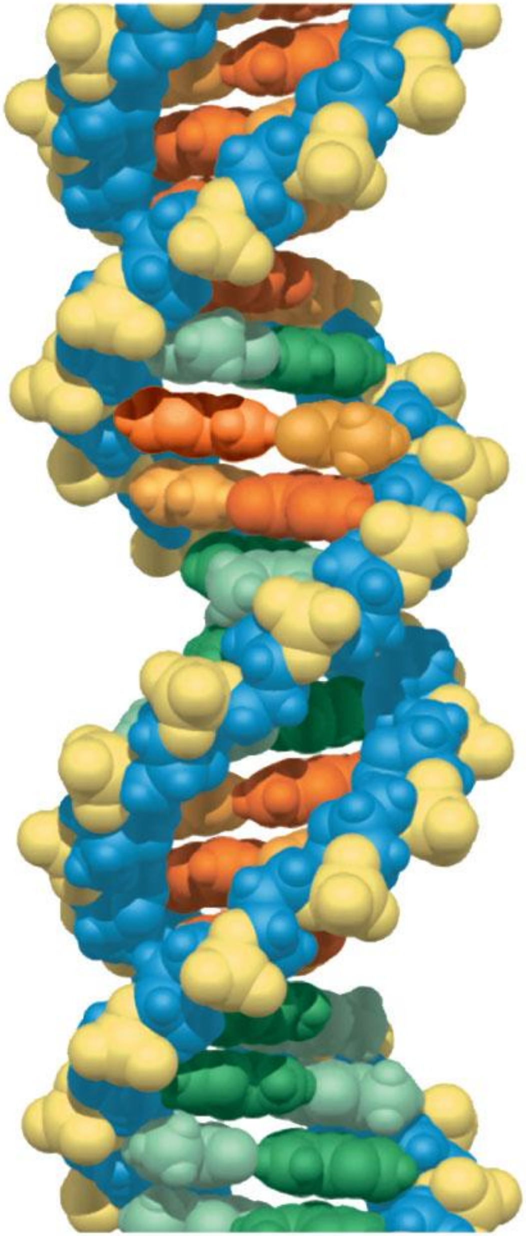
Figure 16.7a



(a) Key features of DNA structure

(b) Partial chemical structure

Figure 16.7b

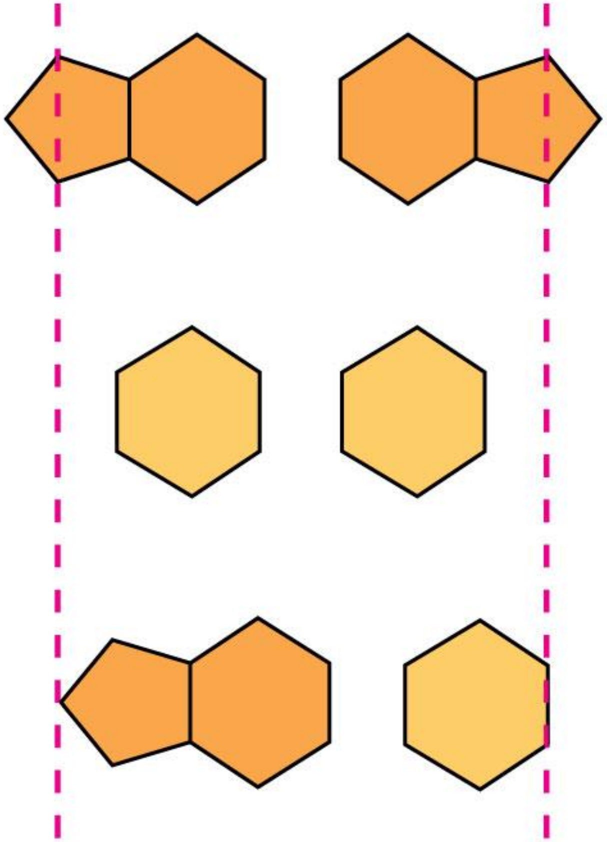


(c) Space-filling model

- Watson and Crick built models of a double helix to conform to the X-rays and chemistry of DNA
- Franklin had concluded that there were two outer sugar-phosphate backbones, with the nitrogenous bases paired in the molecule’s interior
- Watson built a model in which the backbones were **antiparallel** (their subunits run in opposite directions)

- At first, Watson and Crick thought the bases paired like with like (A with A, and so on), but such pairings did not result in a uniform width
- Instead, pairing a purine with a pyrimidine resulted in a uniform width consistent with the X-ray data

Figure 16.UN01



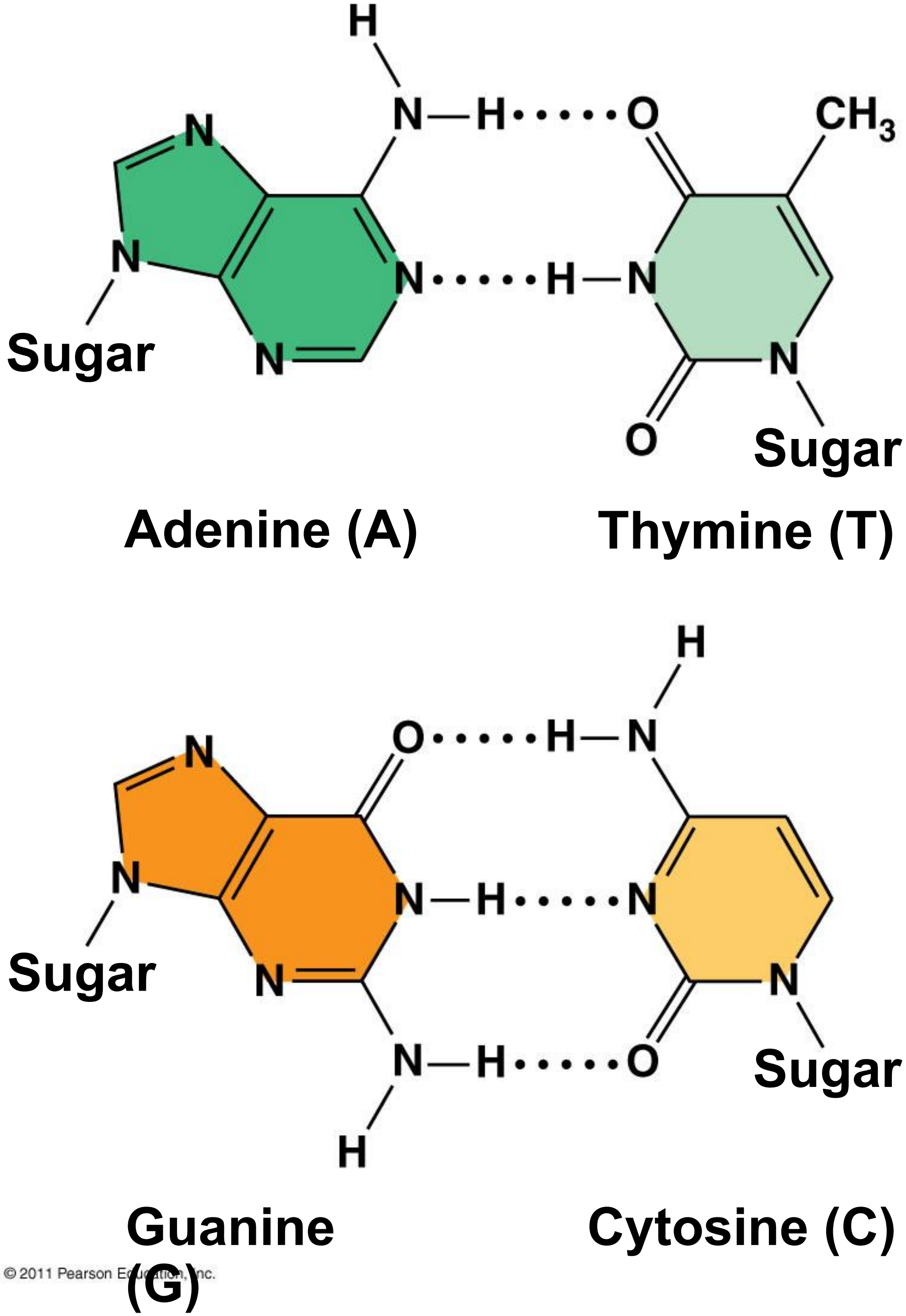
Purine + purine: too wide

Pyrimidine + pyrimidine: too narrow

Purine + pyrimidine: width consistent with X-ray data

- Watson and Crick reasoned that the pairing was more specific, dictated by the base structures
- They determined that adenine (A) paired only with thymine (T), and guanine (G) paired only with cytosine (C)
- The Watson-Crick model explains Chargaff's rules: in any organism the amount of A = T, and the amount of G = C

Figure 16.8

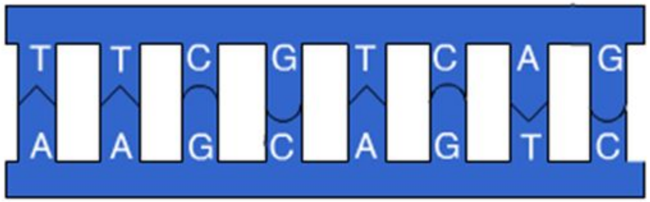

H
N—H·····O
CH3
N
N·····H—N
N
Sugar
N
N
O
Sugar
Adenine (A)
Thymine (T)
H
O·····H—N
N
N
N—H·····N
Sugar
N
N
N—H·····O
Sugar
H
Guanine (G)
Cytosine (C)

Concept 16.2: Many proteins work together in DNA replication and repair

- The relationship between structure and function is manifest in the double helix
- Watson and Crick noted that the specific base pairing suggested a possible copying mechanism for genetic material

The Basic Principle: Base Pairing to a Template Strand

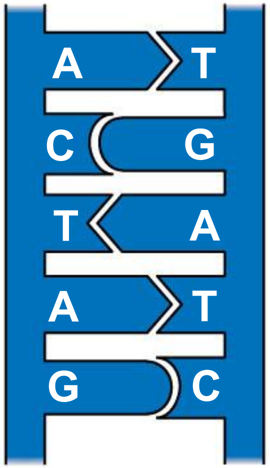
- Since the two strands of DNA are complementary, each strand acts as a template for building a new strand in replication
- In DNA replication, the parent molecule unwinds, and two new daughter strands are built based on base-pairing rules



Animation: DNA Replication Overview

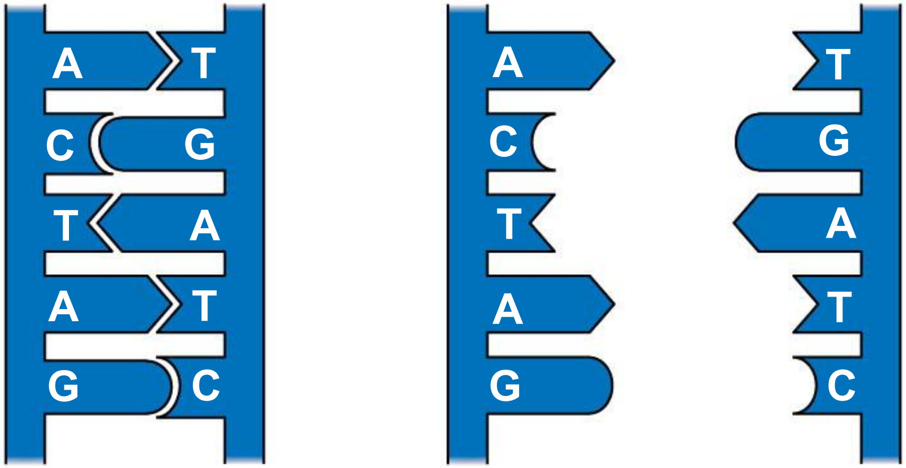
Right-click slide / select “Play”

Figure 16.9-1



(a) Parent molecule

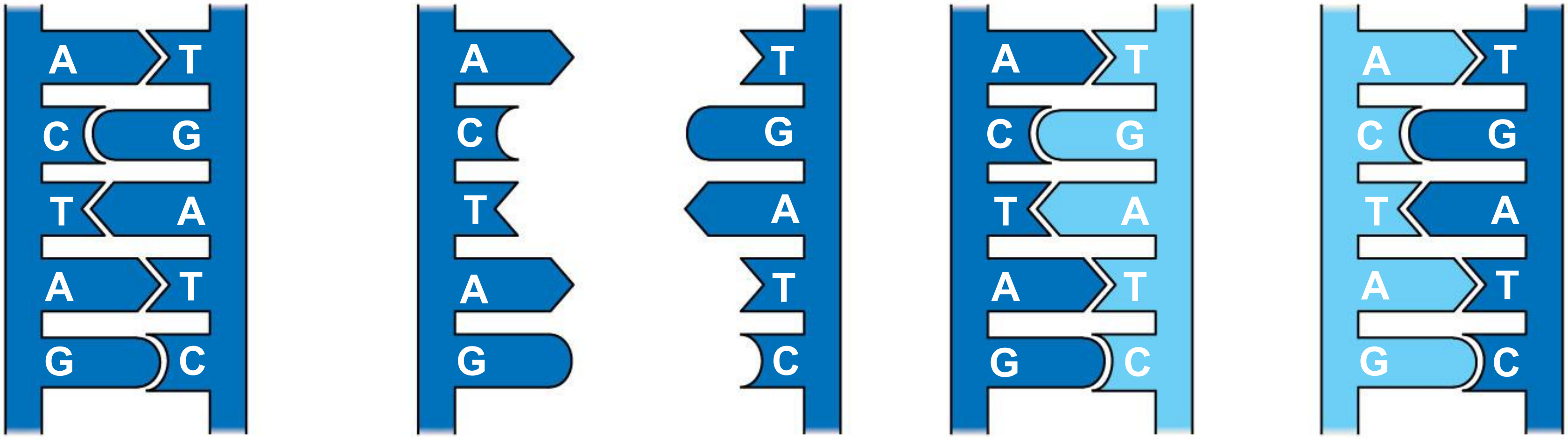
Figure 16.9-2



(a) Parent molecule

(b) Separation of strands

Figure 16.9-3



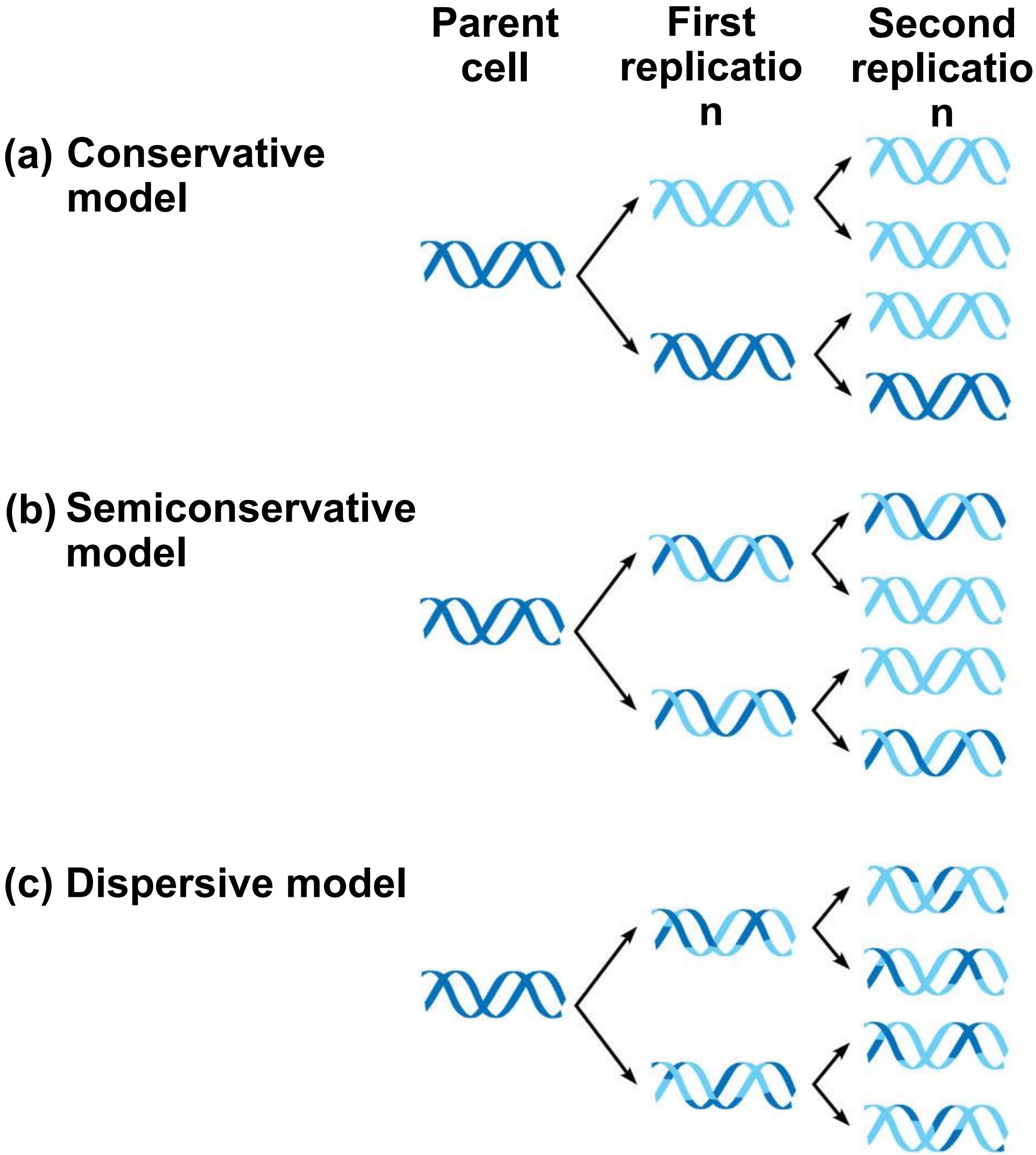
(a) Parent molecule

(b) Separation of strands

(c) "Daughter" DNA molecules, each consisting of one parental strand and one new strand

- Watson and Crick's **semiconservative model** of replication predicts that when a double helix replicates, each daughter molecule will have one old strand (derived or "conserved" from the parent molecule) and one newly made strand
- Competing models were the conservative model (the two parent strands rejoin) and the dispersive model (each strand is a mix of old and new)

Figure 16.10



Parent cell

First replication

Second replication

(a) Conservative model

(b) Semiconservative model

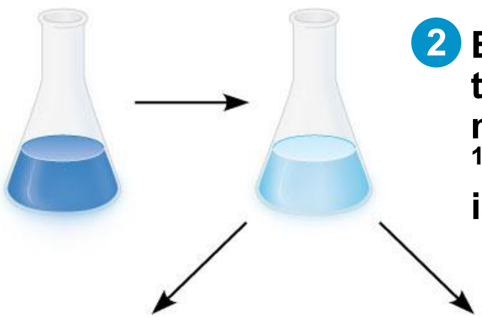
(c) Dispersive model

- Experiments by Matthew Meselson and Franklin Stahl supported the semiconservative model
- They labeled the nucleotides of the old strands with a heavy isotope of nitrogen, while any new nucleotides were labeled with a lighter isotope

- The first replication produced a band of hybrid DNA, eliminating the conservative model
- A second replication produced both light and hybrid DNA, eliminating the dispersive model and supporting the semiconservative model

Figure 16.11

EXPERIMENT



① Bacteria cultured in medium with ^{15}N (heavy isotope)

② Bacteria transferred to medium with ^{14}N (lighter isotope)

RESULTS

③ DNA sample centrifuged after first replication

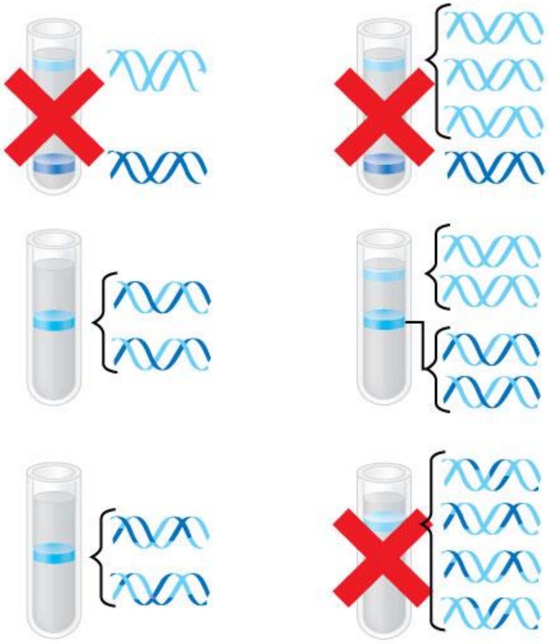
④ DNA sample centrifuged after second replication

Less dense

More dense

CONCLUSION

Predictions: First replication | Second replication



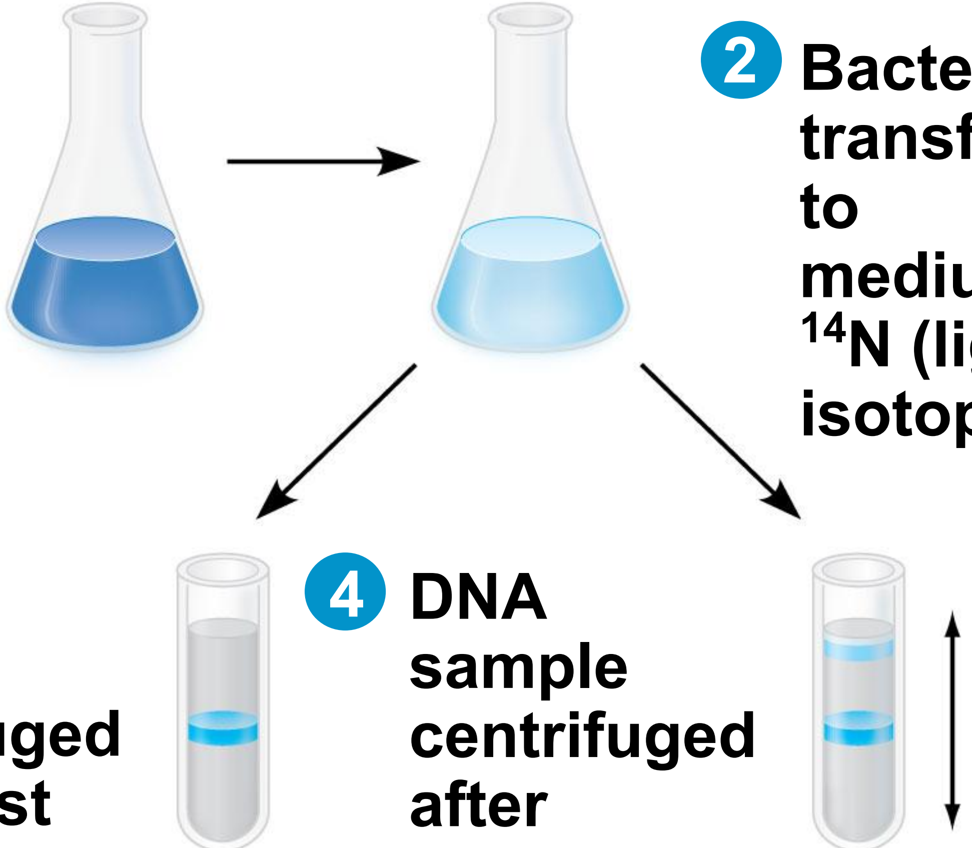
Conservative model

Semiconservative model

Dispersive model

Figure 16.11a

EXPERIMENT



① Bacteria cultured in medium with ^{15}N (heavy isotope)

② Bacteria transferred to medium with ^{14}N (lighter isotope)

RESULTS

③ DNA sample centrifuged after first replication

④ DNA sample centrifuged after second replication

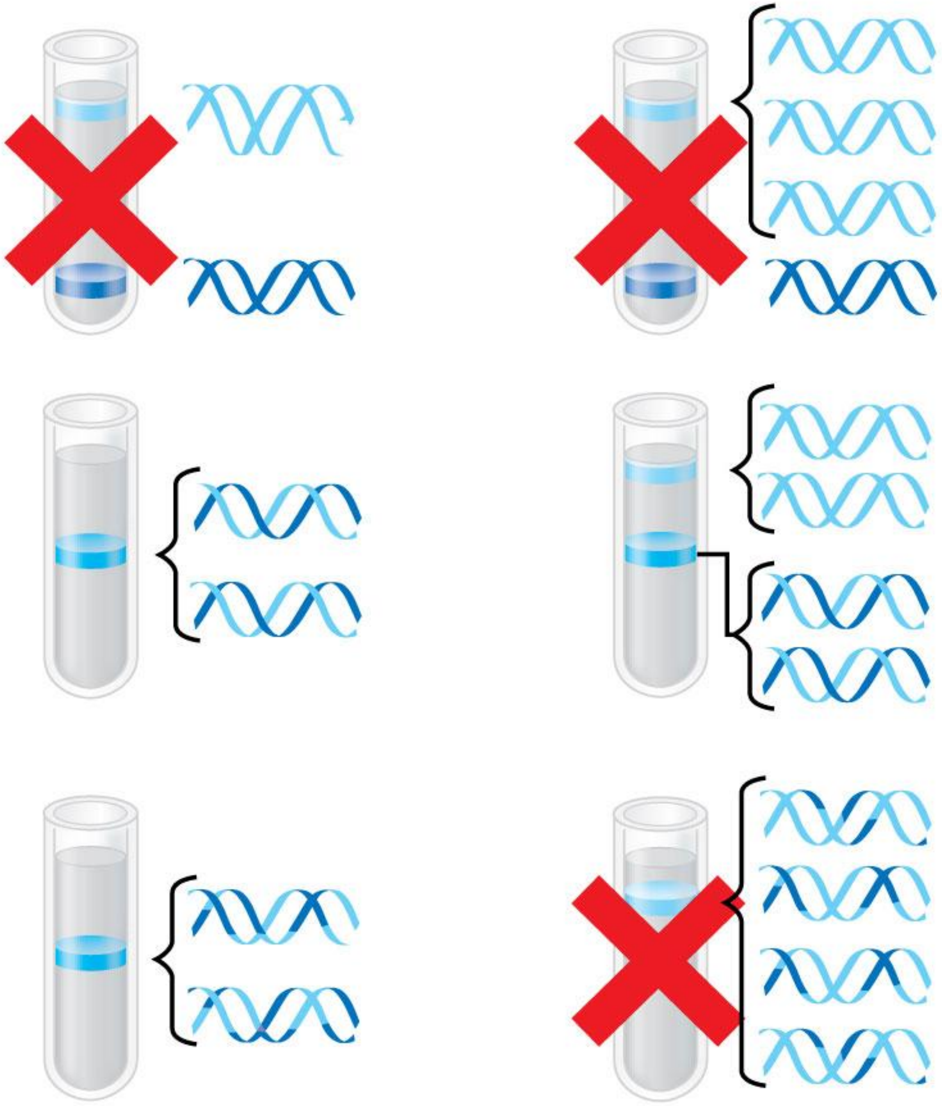
Less dense

More dense

Figure 16.11b

CONCLUSION

Predictions: **First replication** **Second replication**



Conservative model

Semiconservative model

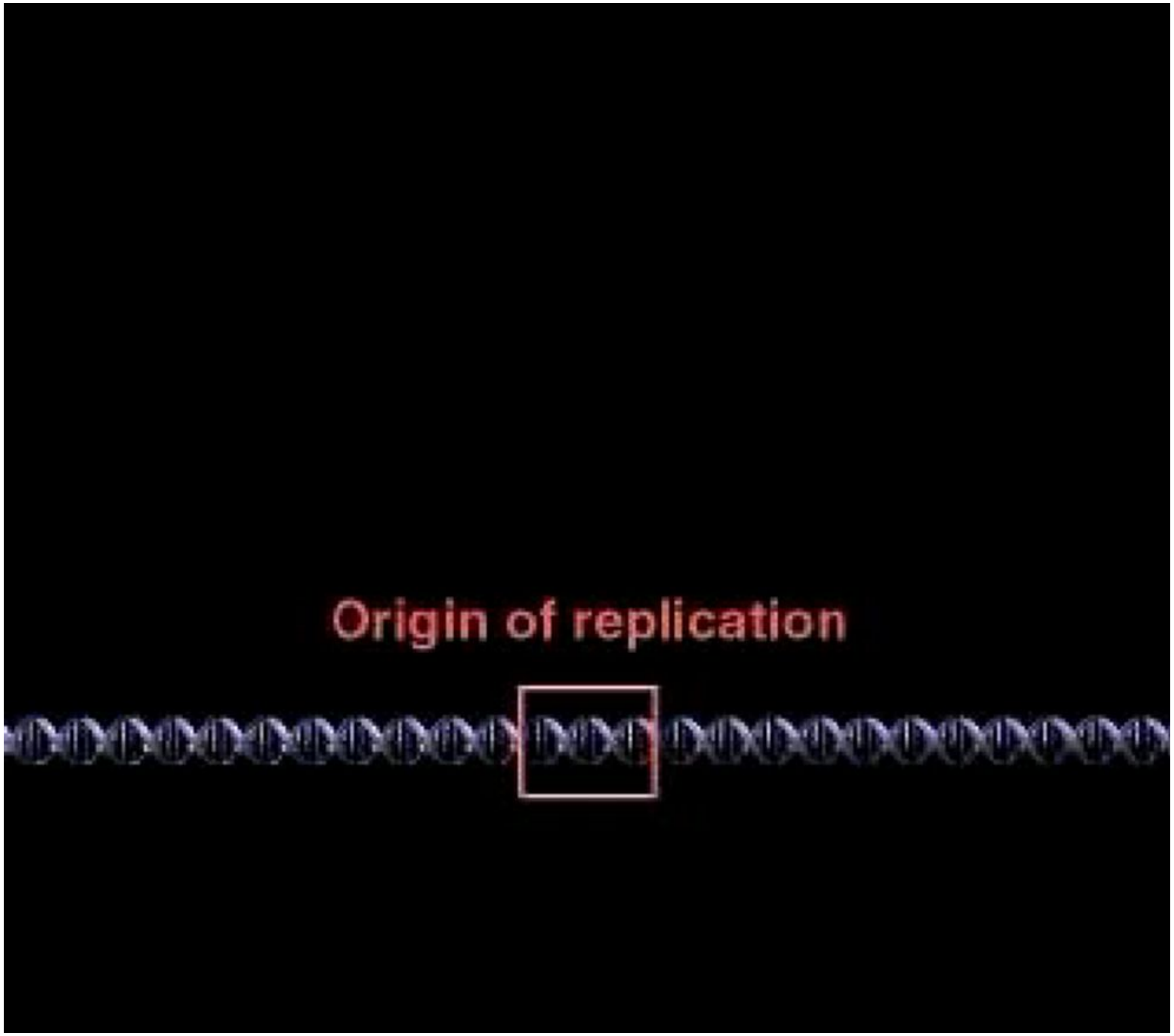
Dispersive model

DNA Replication: *A Closer Look*

- The copying of DNA is remarkable in its speed and accuracy
- More than a dozen enzymes and other proteins participate in DNA replication

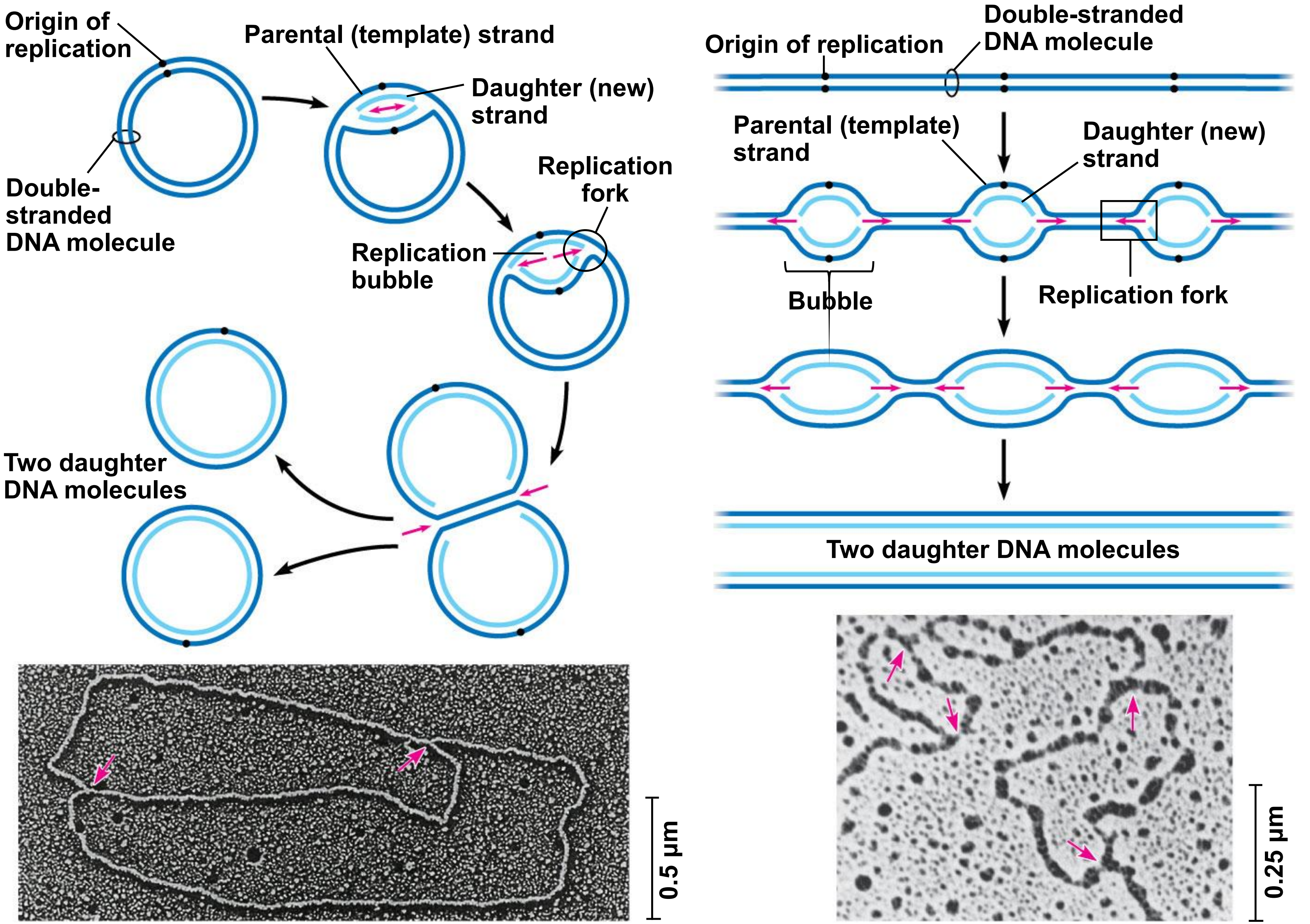
Getting Started

- Replication begins at particular sites called **origins of replication**, where the two DNA strands are separated, opening up a replication "bubble"
- A eukaryotic chromosome may have hundreds or even thousands of origins of replication
- Replication proceeds in both directions from each origin, until the entire molecule is copied



Animation: Origins of Replication
Right-click slide / select “Play”

Figure 16.12

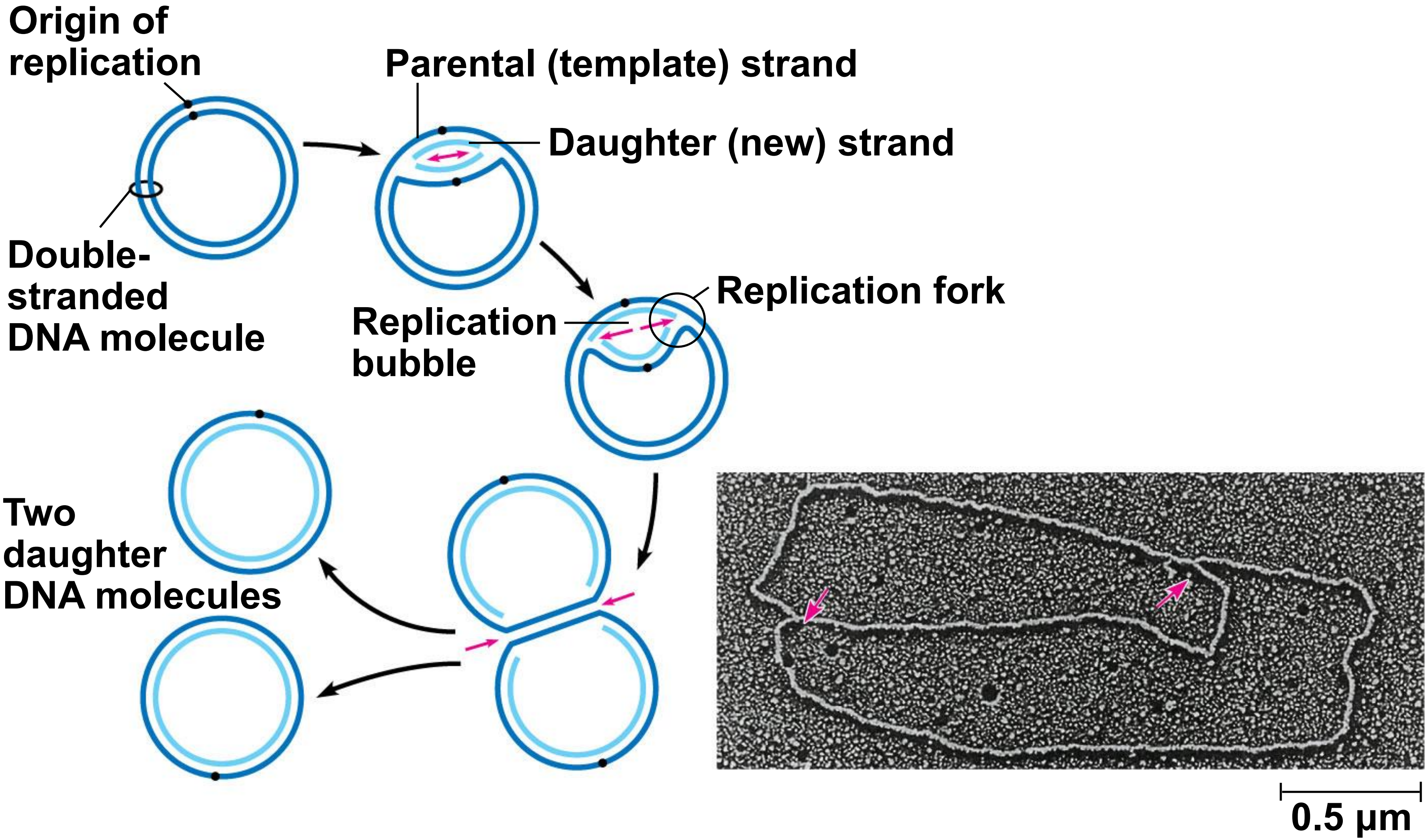


(a) Origin of replication in an *E. coli* cell

(b) Origins of replication in a eukaryotic cell

Figure 16.12a

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



Origin of replication

Parental (template) strand

Daughter (new) strand

Double-stranded DNA molecule

Replication fork

Replication bubble

Two daughter DNA molecules

Figure 16.12b

(b) Origins of replication in a eukaryotic cell

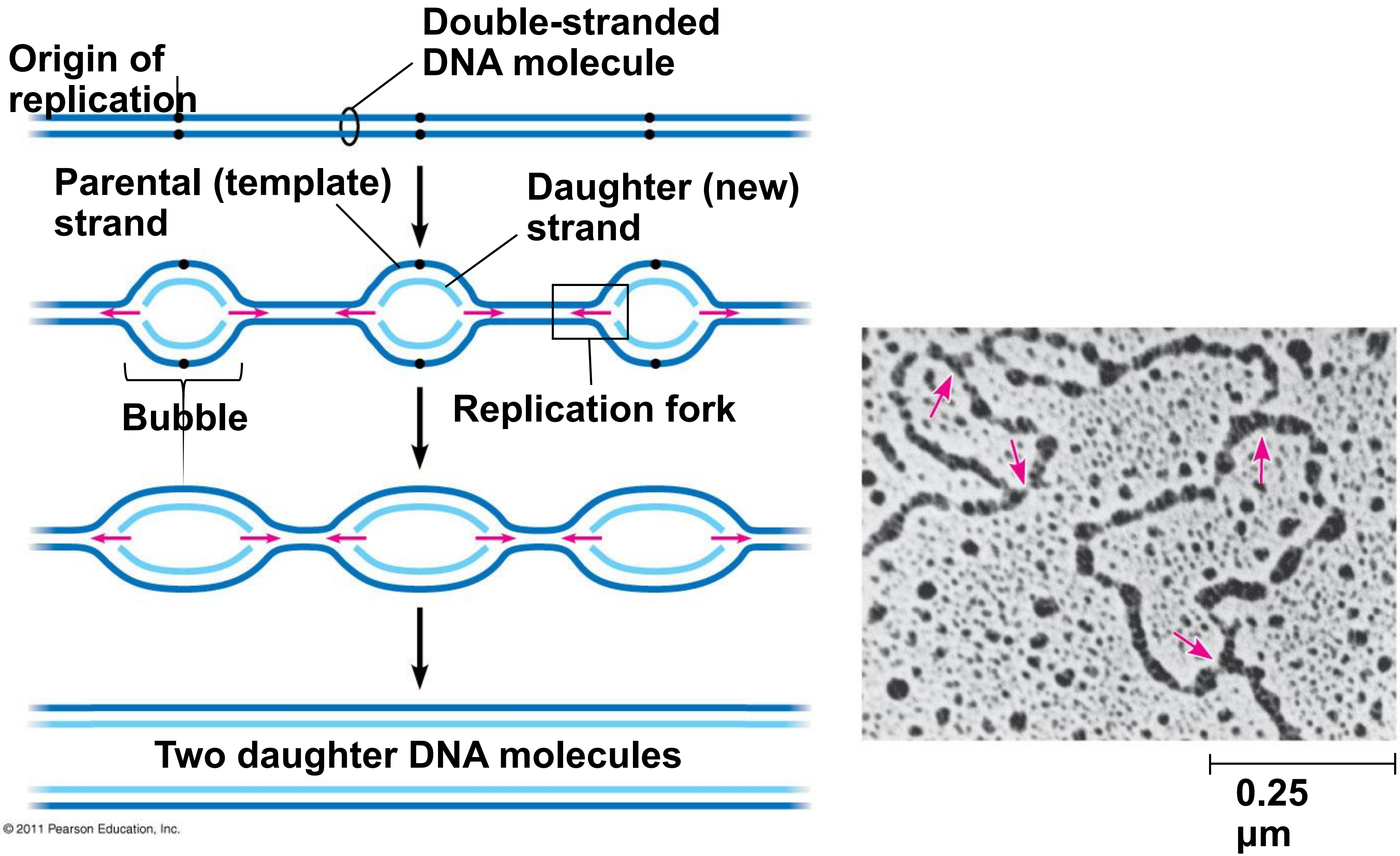


Figure 16.12c

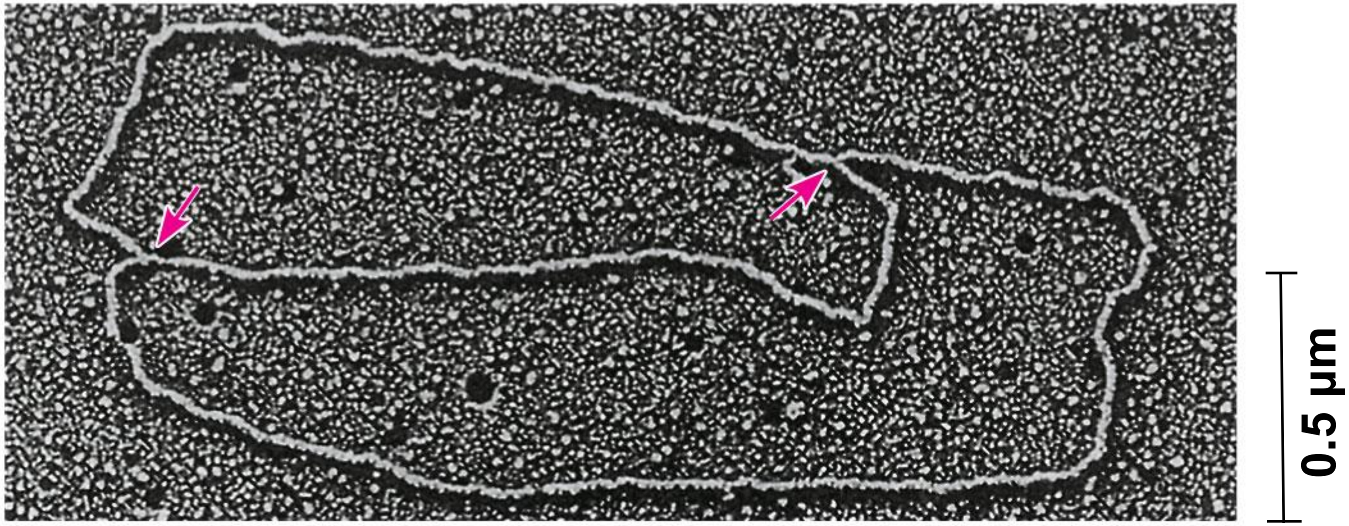
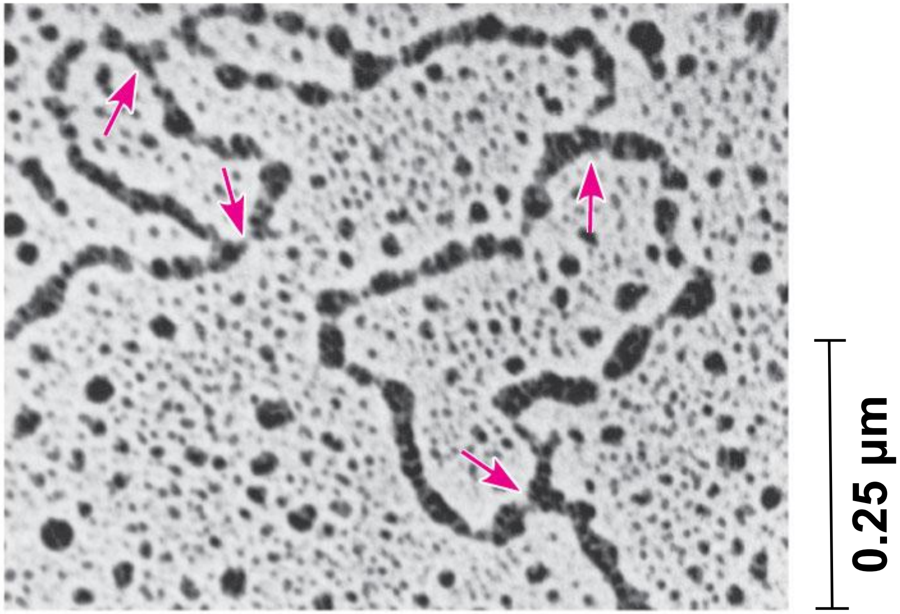
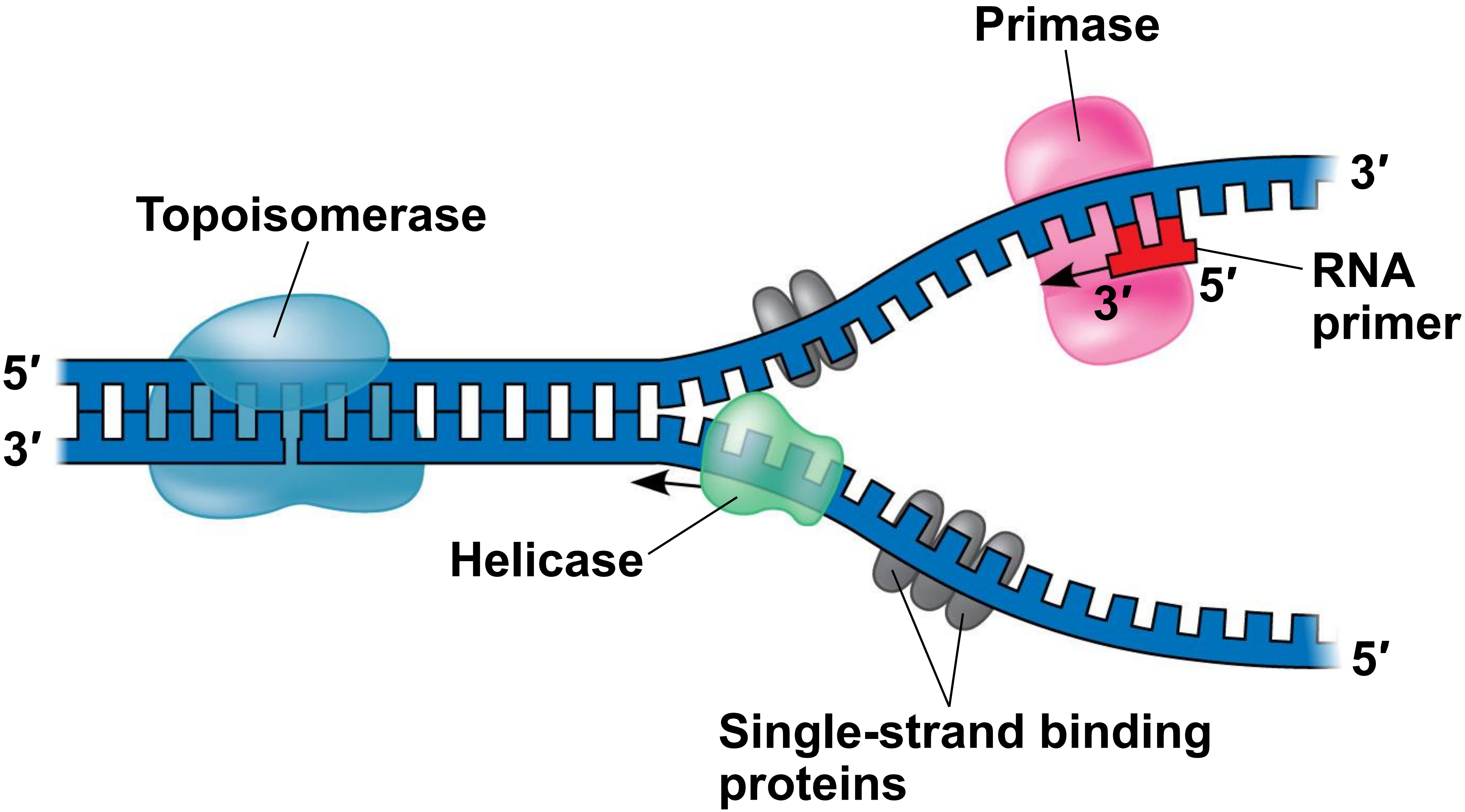


Figure 16.12d



- At the end of each replication bubble is a **replication fork**, a Y-shaped region where new DNA strands are elongating
- **Helicases** are enzymes that untwist the double helix at the replication forks
- **Single-strand binding proteins** bind to and stabilize single-stranded DNA
- **Topoisomerase** corrects “overwinding” ahead of replication forks by breaking, swiveling, and rejoining DNA strands

Figure 16.13


Primase
Topoisomerase
3′
RNA
primer
5′
3′
5′
3′
Helicase
5′
Single-strand binding
proteins

- DNA polymerases cannot initiate synthesis of a polynucleotide; they can only add nucleotides to the 3′ end
- The initial nucleotide strand is a short RNA **primer**

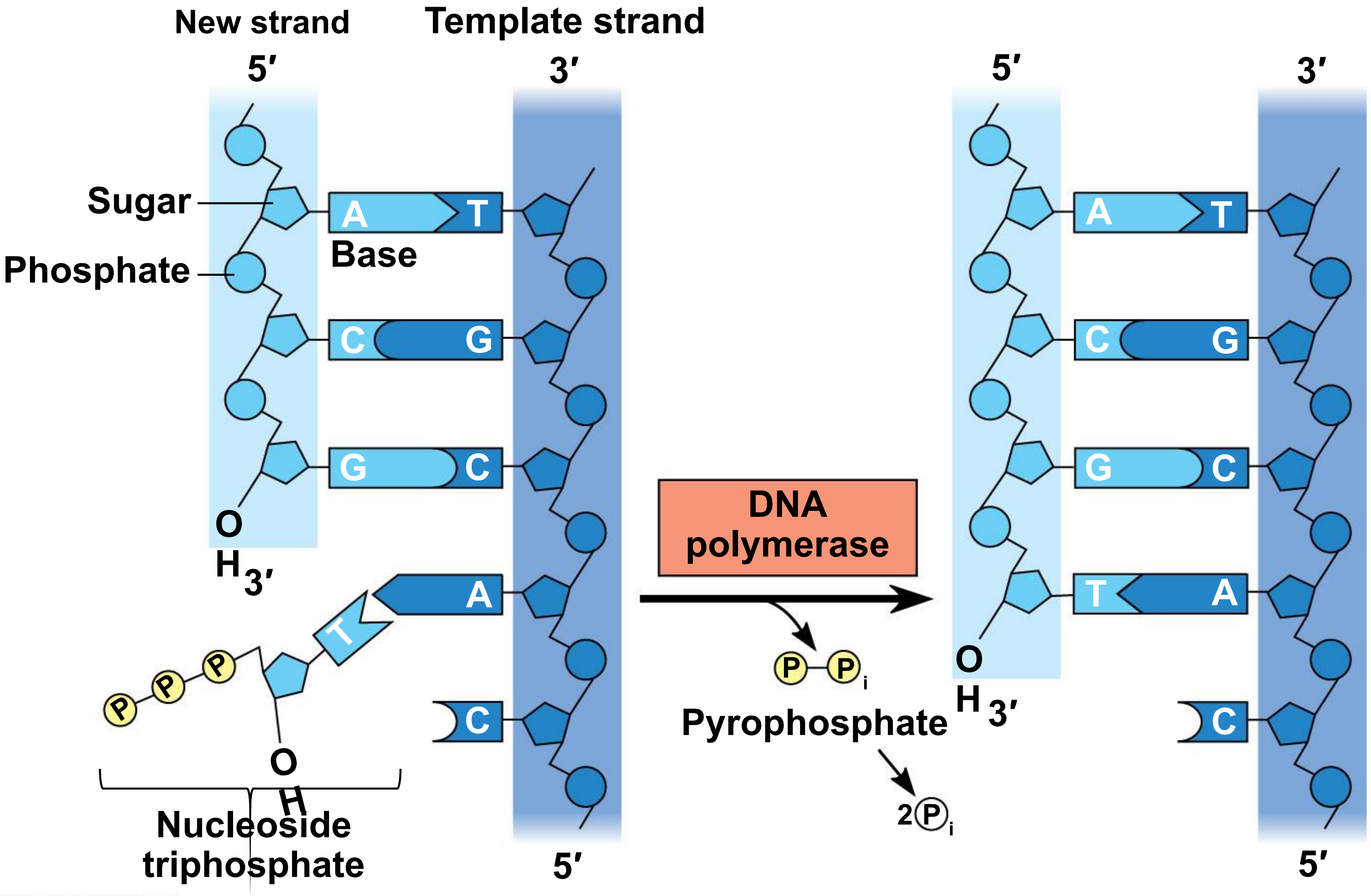
- An enzyme called **primase** can start an RNA chain from scratch and adds RNA nucleotides one at a time using the parental DNA as a template
- The primer is short (5–10 nucleotides long), and the 3′ end serves as the starting point for the new DNA strand

Synthesizing a New DNA Strand

- Enzymes called **DNA polymerases** catalyze the elongation of new DNA at a replication fork
- Most DNA polymerases require a primer and a DNA template strand
- The rate of elongation is about 500 nucleotides per second in bacteria and 50 per second in human cells

- Each nucleotide that is added to a growing DNA strand is a nucleoside triphosphate
- dATP supplies adenine to DNA and is similar to the ATP of energy metabolism
- The difference is in their sugars: dATP has deoxyribose while ATP has ribose
- As each monomer of dATP joins the DNA strand, it loses two phosphate groups as a molecule of pyrophosphate

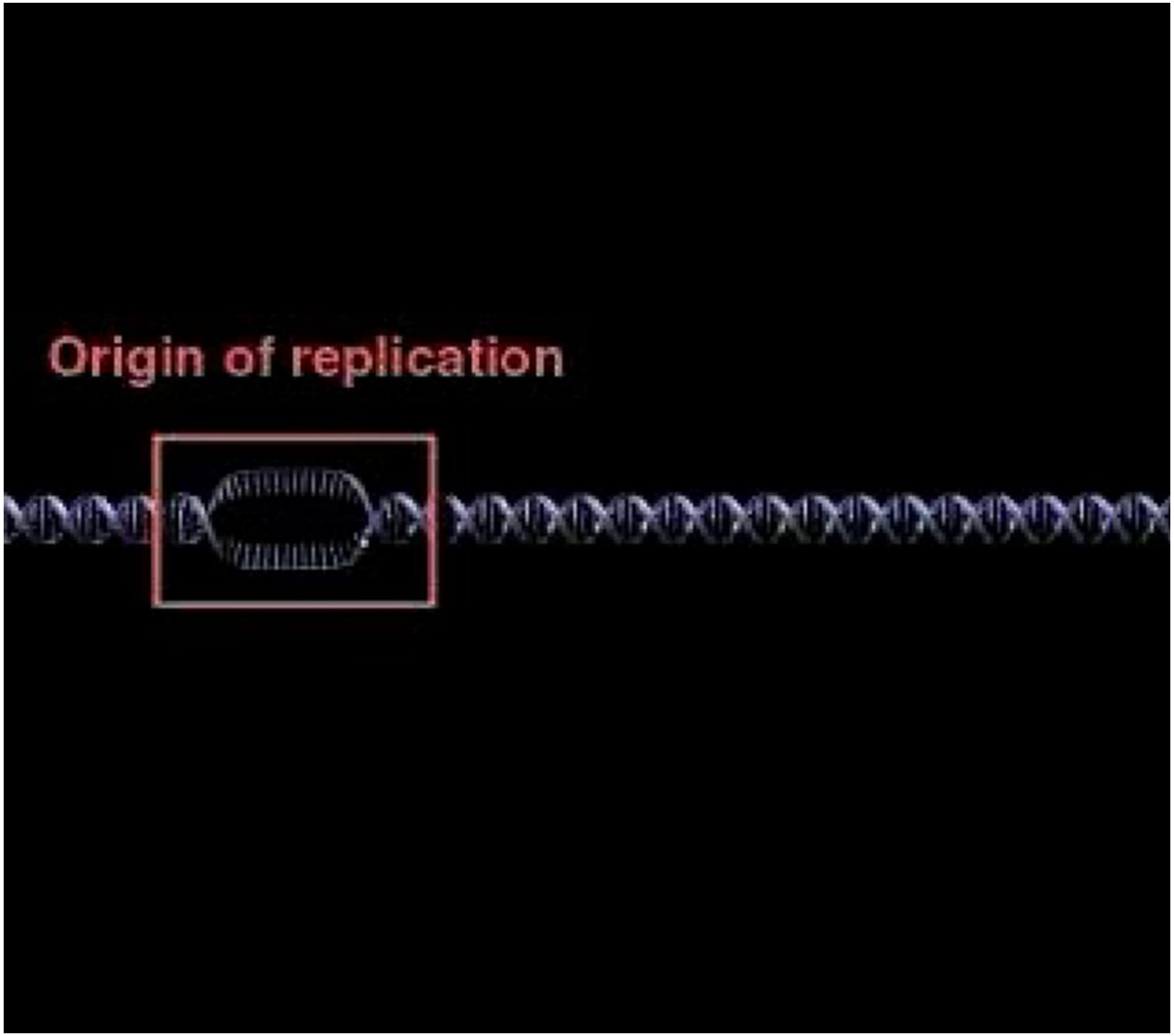
Figure 16.14


New strand
Template strand
5′
3′
Sugar
Phosphate
Base
A
T
C
G
G
C
O
H
3′
A
T
P
P
P
O
H
C
Nucleoside triphosphate
5′
DNA polymerase
P
Pi
Pyrophosphate
2 Pi
5′
3′
A
T
C
G
G
C
T
A
O
H
3′
C
5′

Antiparallel Elongation

- The antiparallel structure of the double helix affects replication
- DNA polymerases add nucleotides only to the free 3′ end of a growing strand; therefore, a new DNA strand can elongate only in the 5′ to 3′ direction

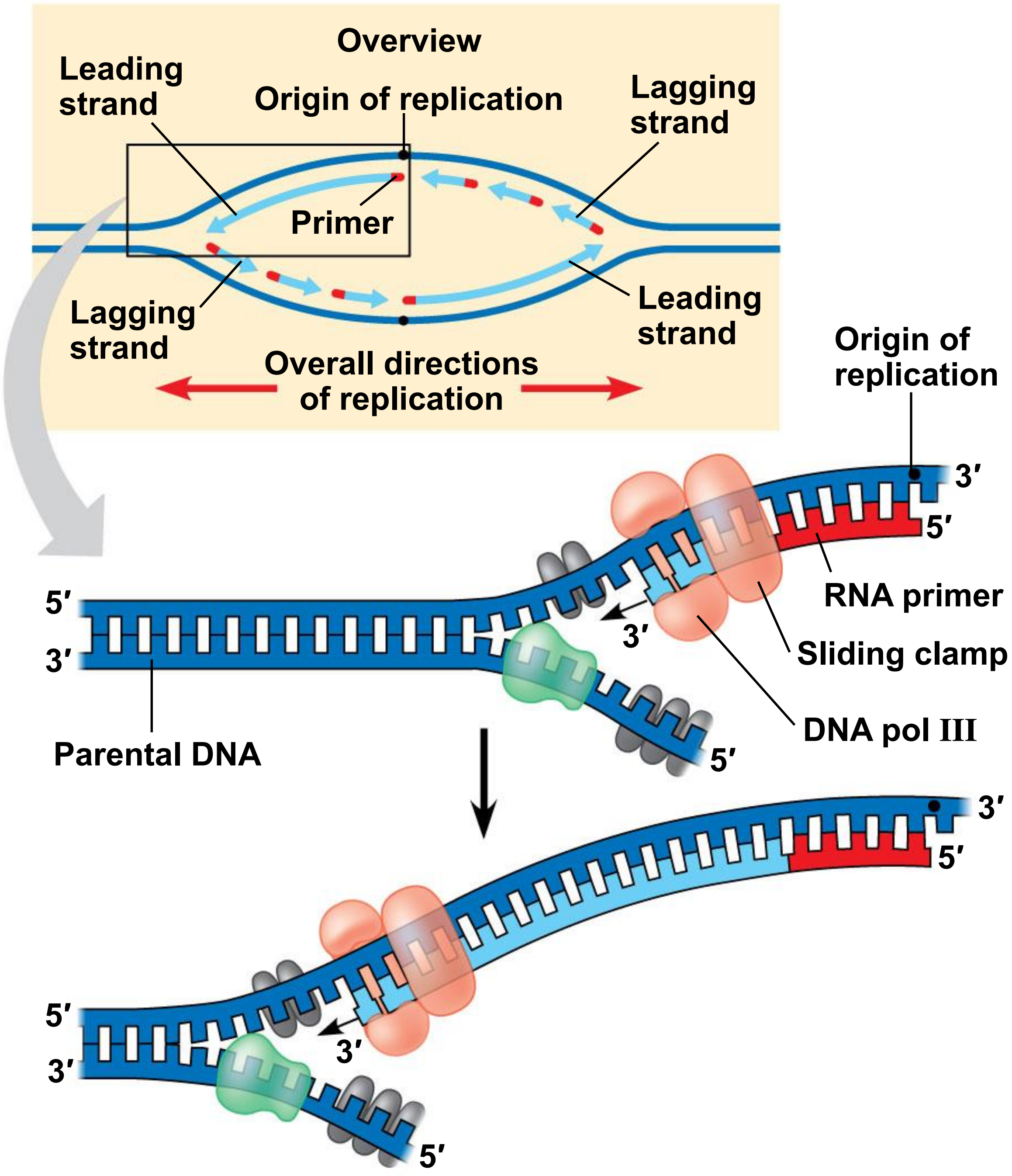
- Along one template strand of DNA, the DNA polymerase synthesizes a **leading strand** continuously, moving toward the replication fork



Animation: Leading Strand

Right-click slide / select “Play”

Figure 16.15



Overview
Leading strand
Origin of replication
Lagging strand
Primer
Lagging strand
Leading strand
Overall directions of replication
Origin of replication
3′
5′
RNA primer
Sliding clamp
DNA pol III
5′
3′
3′
Parental DNA
5′
3′
5′
5′
3′
3′
5′

Figure 16.15a

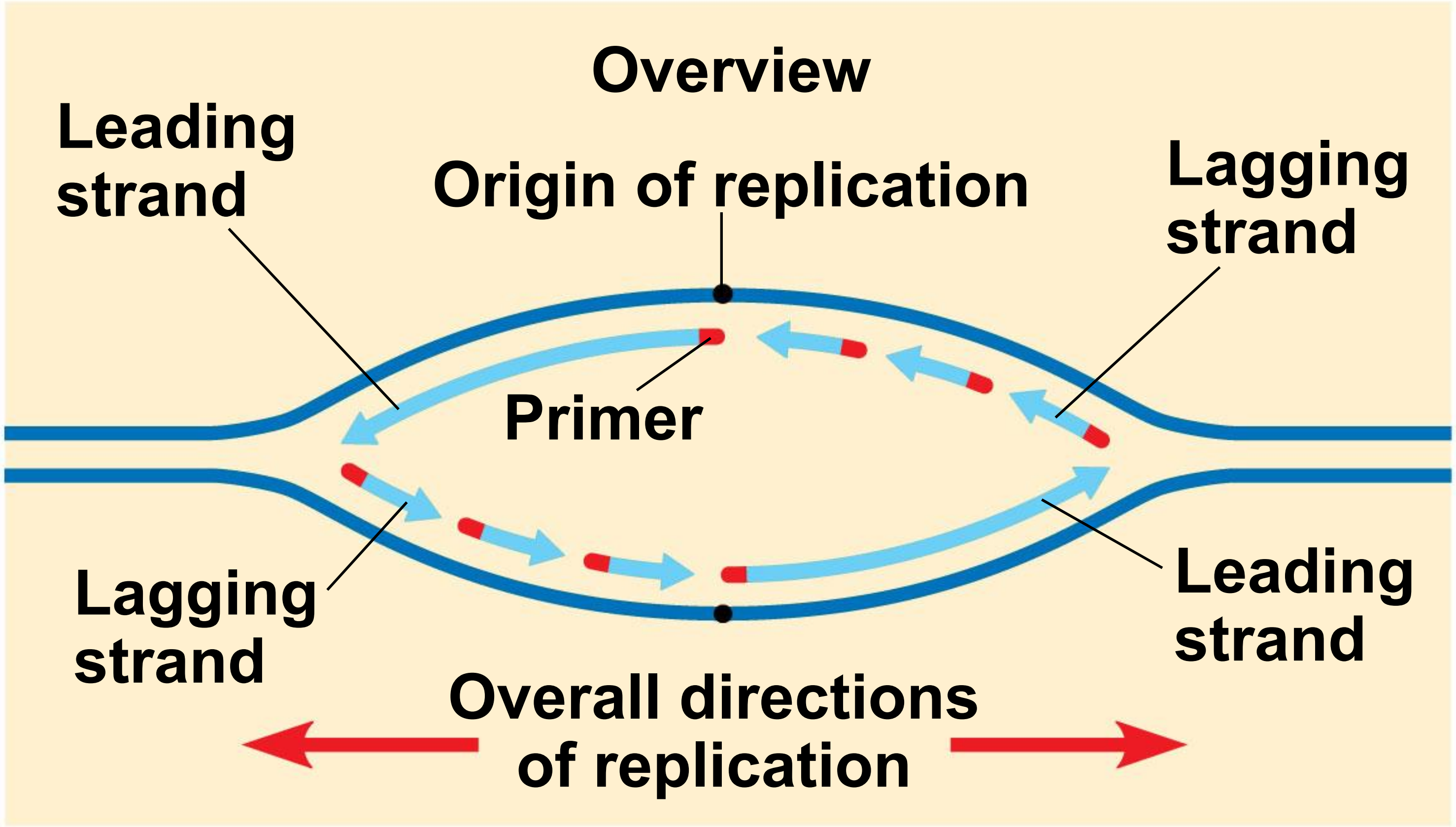
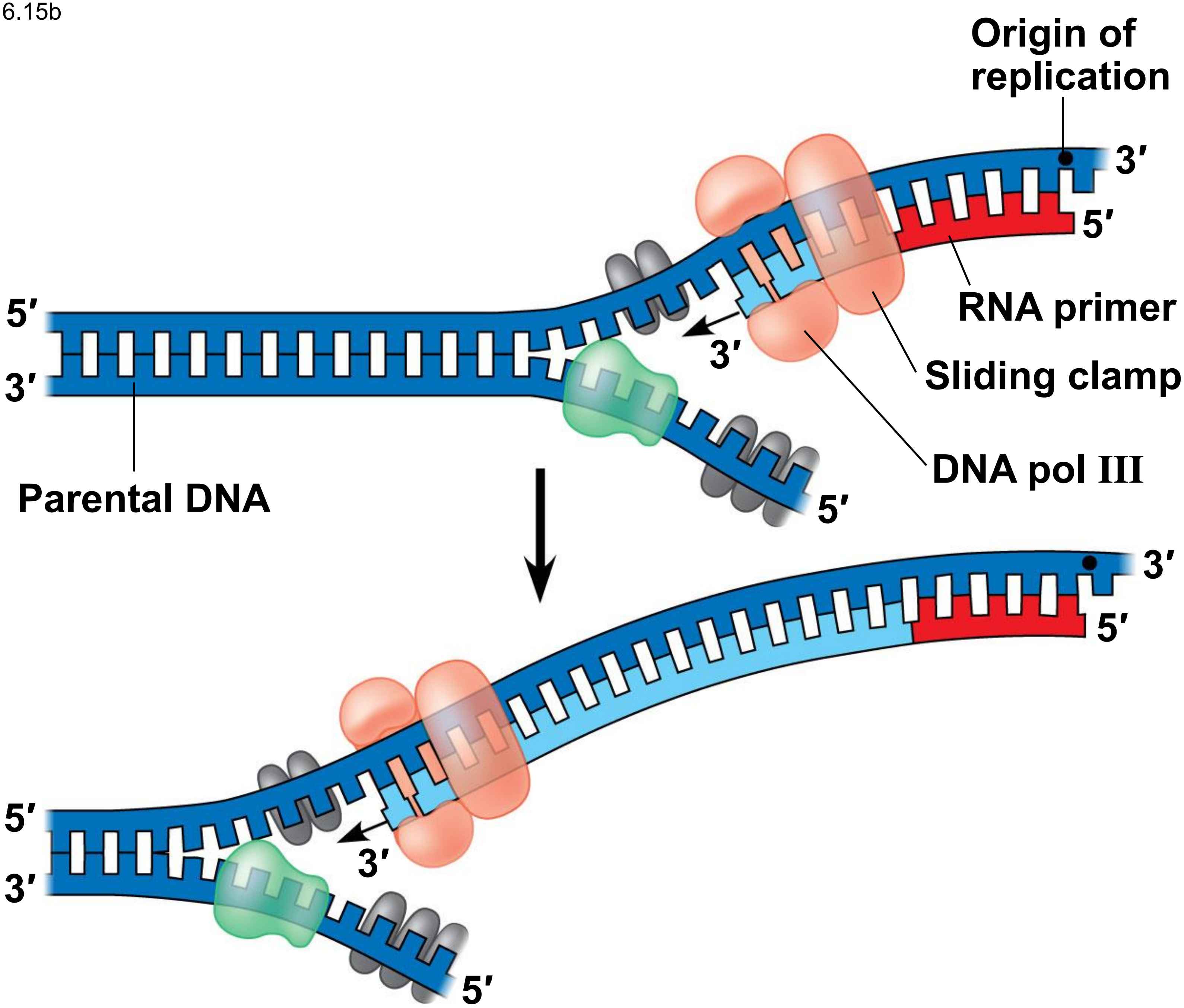
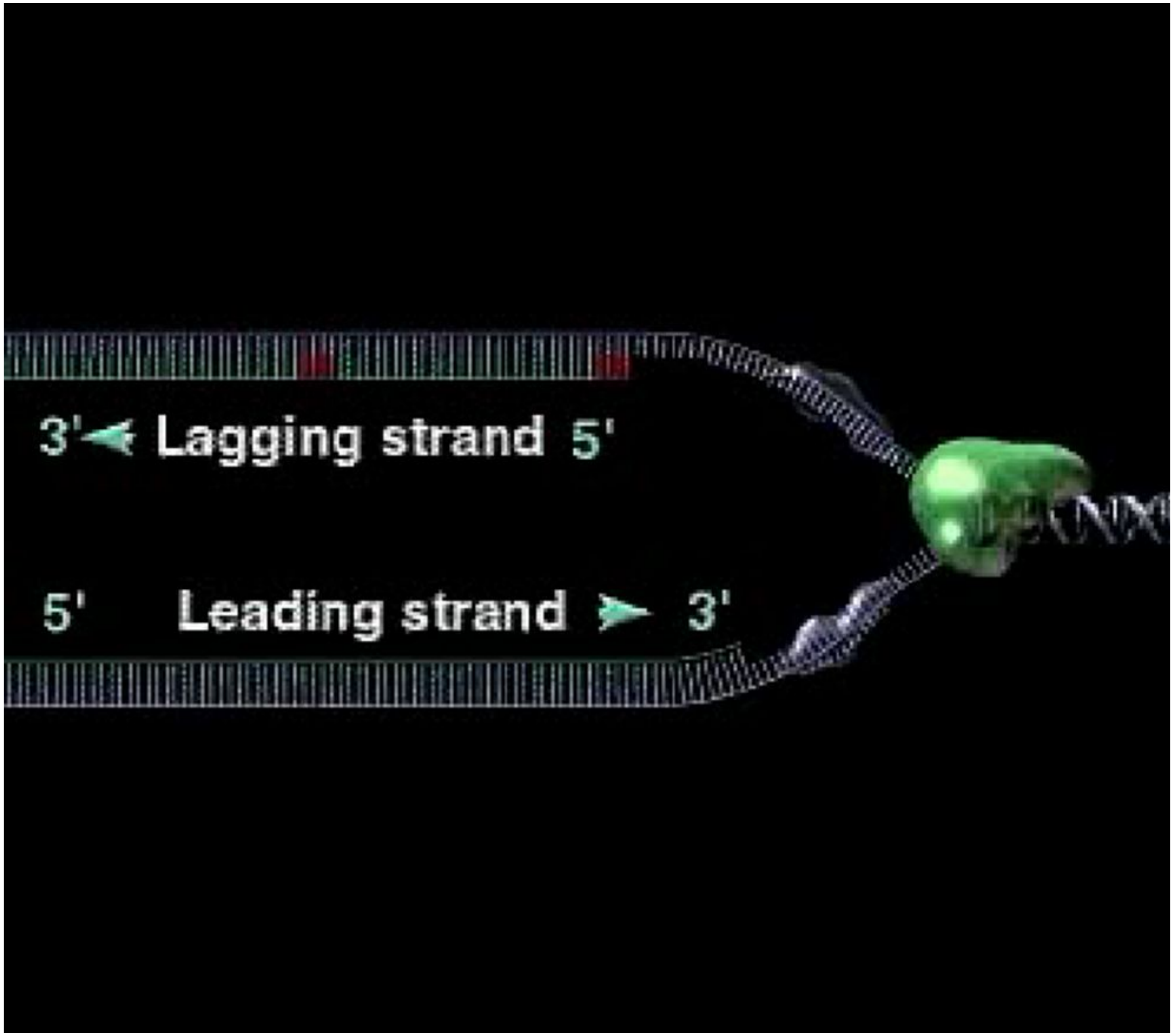


Figure 16.15b

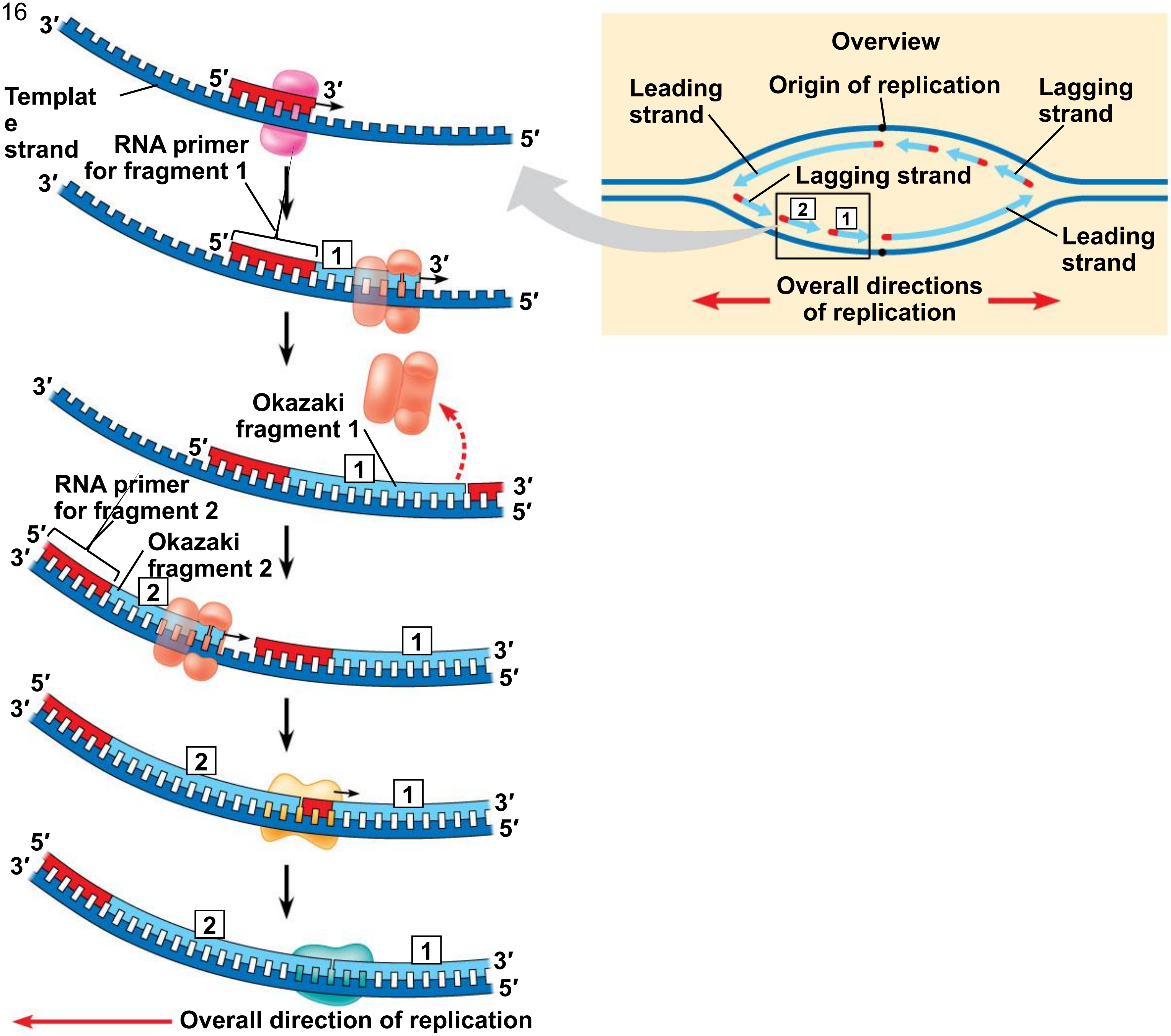


- To elongate the other new strand, called the **lagging strand**, DNA polymerase must work in the direction away from the replication fork
- The lagging strand is synthesized as a series of segments called **Okazaki fragments**, which are joined together by **DNA ligase**



Animation: Lagging Strand
Right-click slide / select "Play"

Figure 16.16



Overview
Leading strand
Origin of replication
Lagging strand
Lagging strand
2
1
Leading strand
Overall directions of replication
3′
5′
3′
5′
Template strand
RNA primer for fragment 1
3′
5′
1
3′
5′
3′
Okazaki fragment 1
5′
1
3′
5′
RNA primer for fragment 2
5′
3′
Okazaki fragment 2
2
1
3′
5′
5′
3′
2
1
3′
5′
5′
3′
2
1
3′
5′
Overall direction of replication

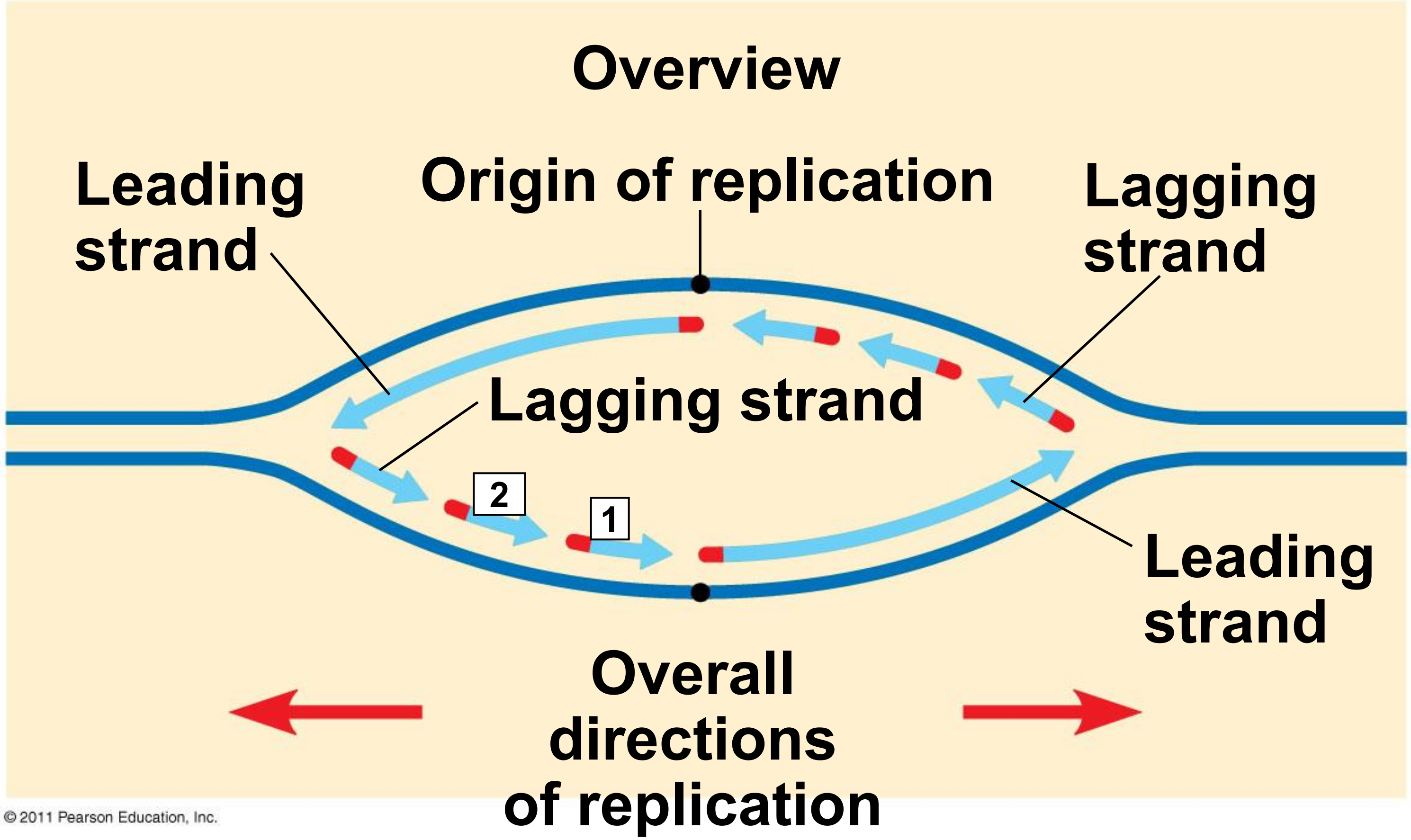

Overview
Origin of replication
Leading strand
Lagging strand
Lagging strand
Leading strand
2
1
Overall directions of replication

Figure 16.16b-1

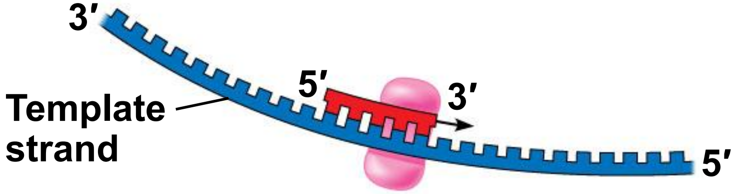


Figure 16.16b-2

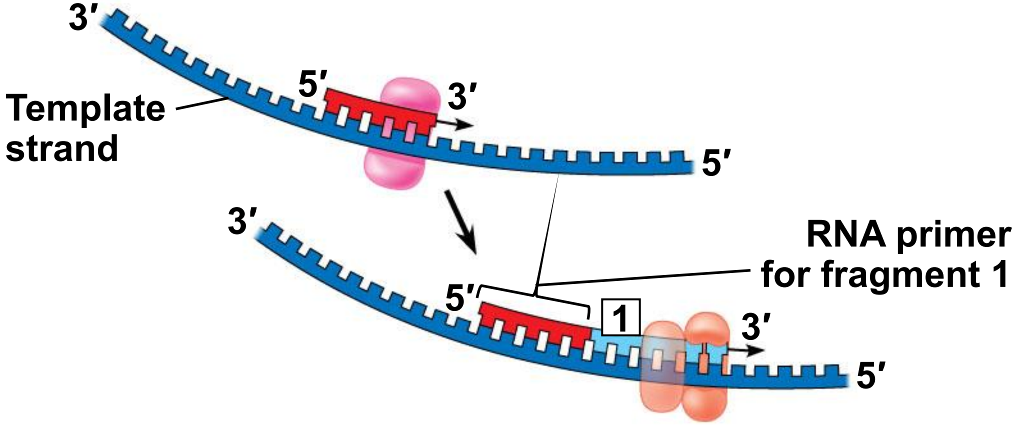


Figure 16.16b-3

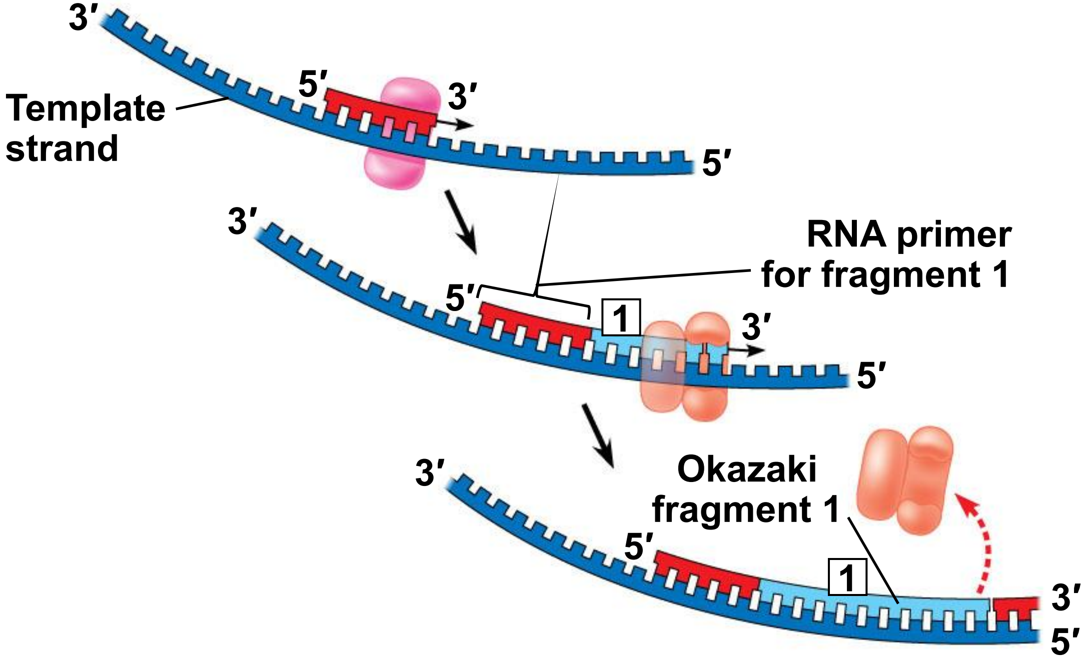


Figure 16.16b-4

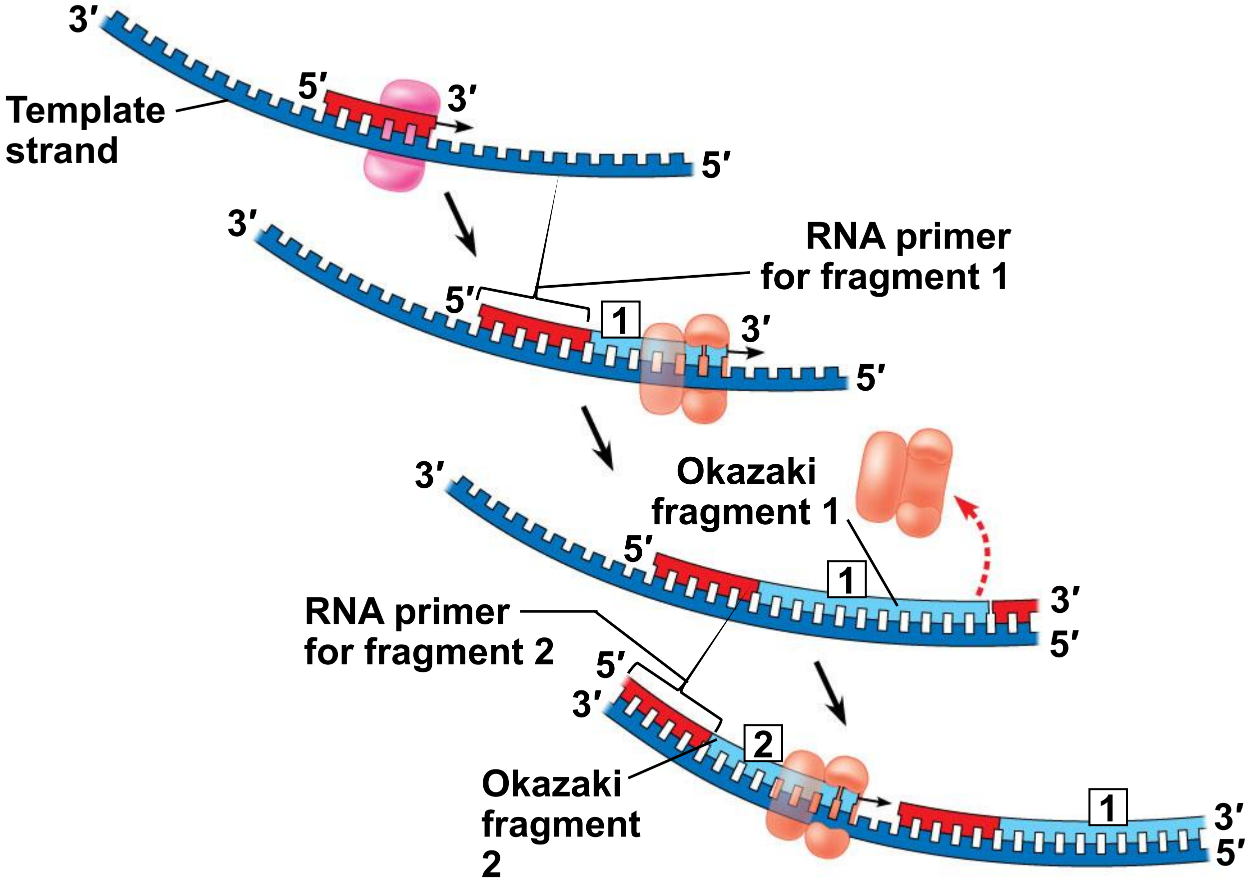


Figure 16.16b-5

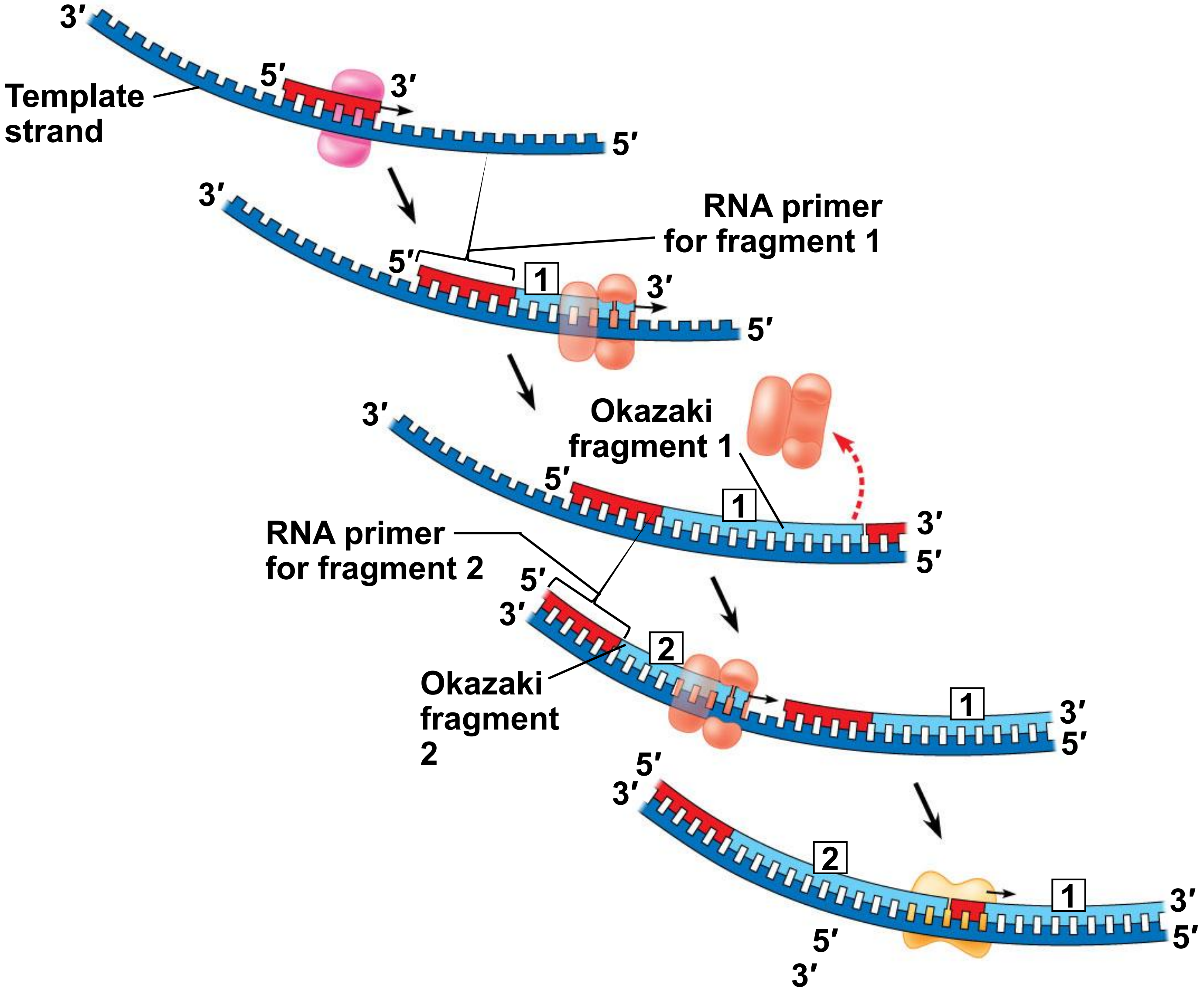


Figure 16.16b-6

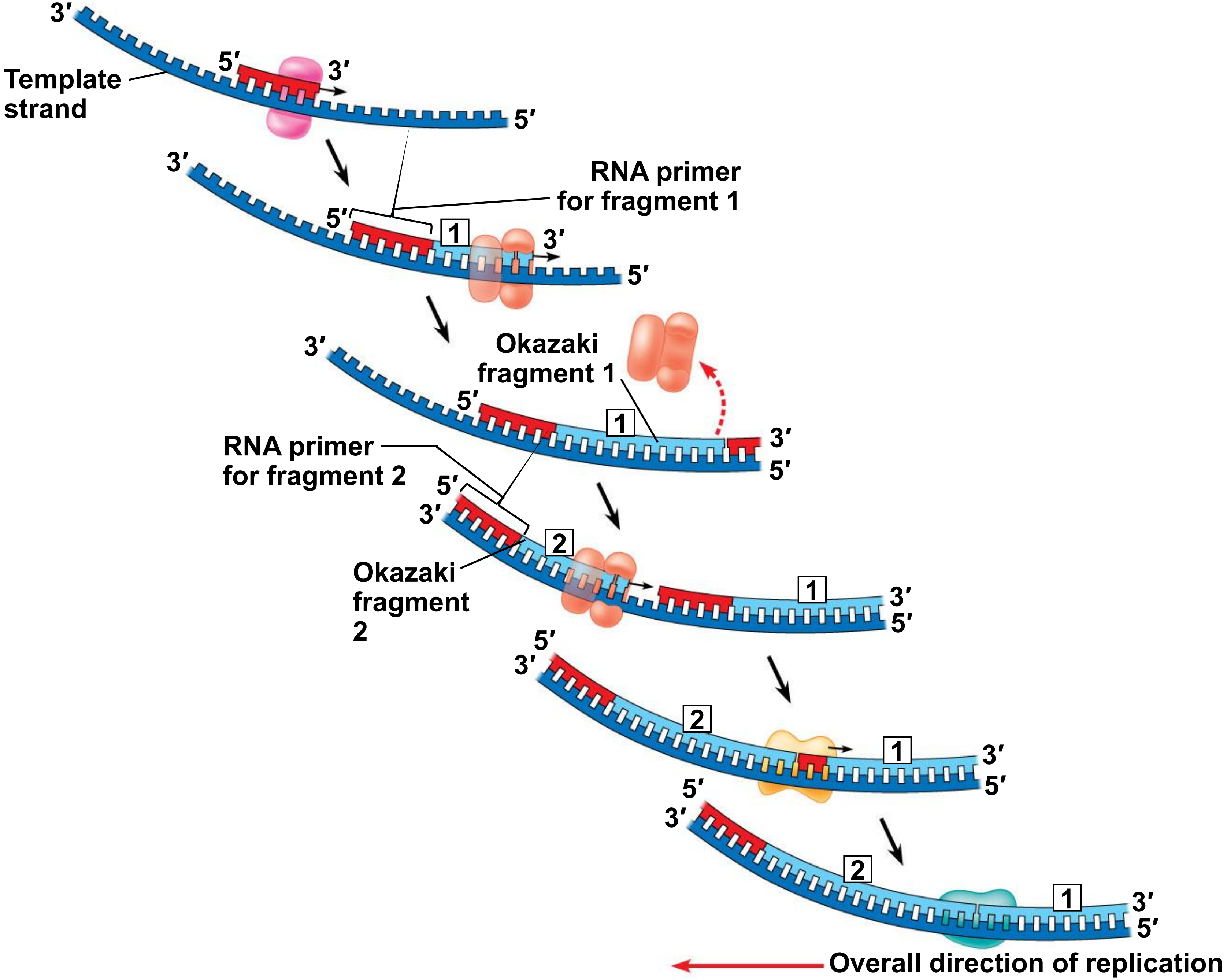
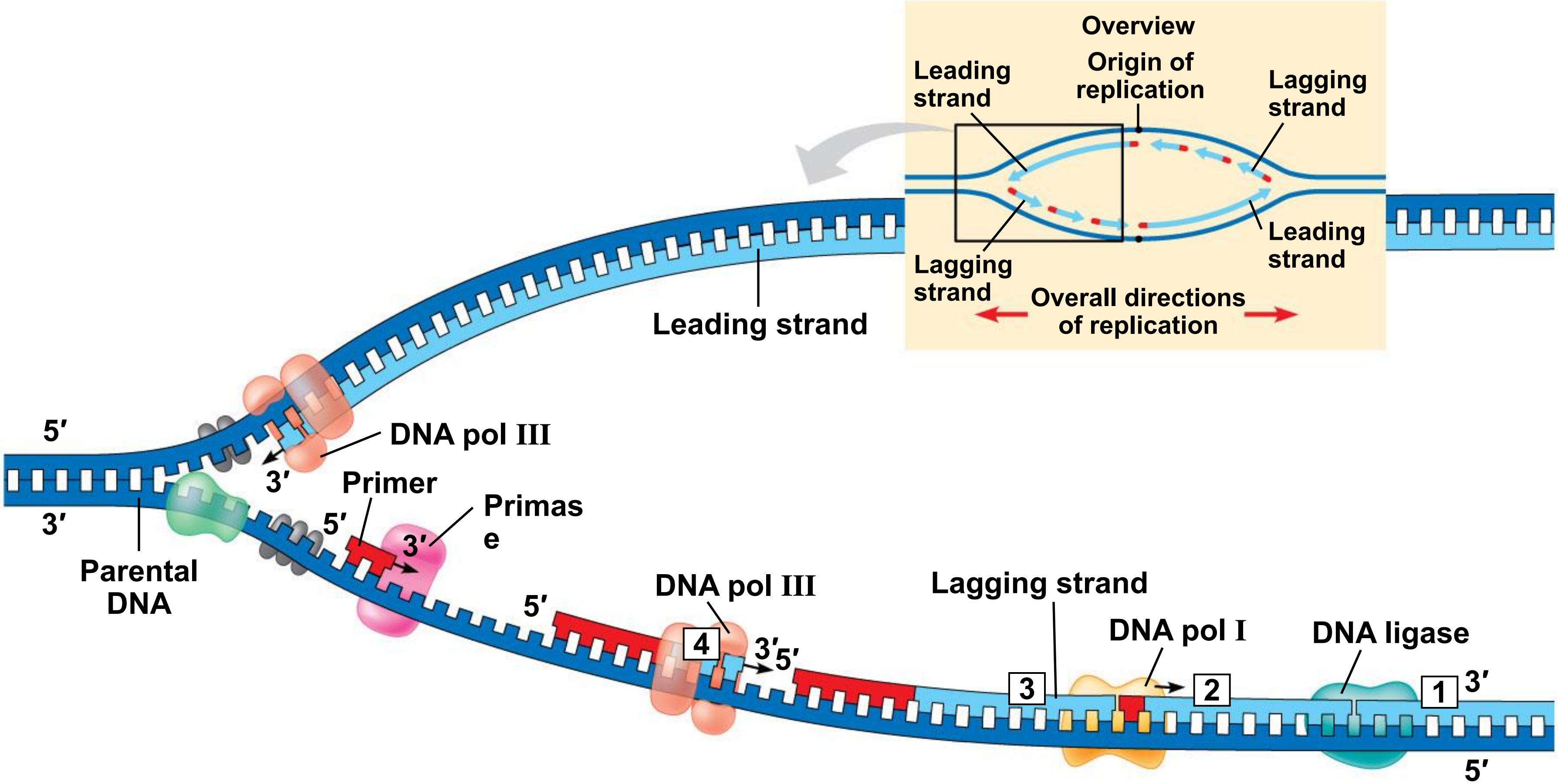


Figure 16.17



Overview
Leading strand
Origin of replication
Lagging strand
Lagging strand
Leading strand
Overall directions of replication
Leading strand
5′
3′
DNA pol III
3′
Primer
Primas
e
5′
3′
Parental DNA
5′
DNA pol III
4
3′
5′
Lagging strand
DNA pol I
DNA ligase
3
2
1
3′
5′

Figure 16.17a

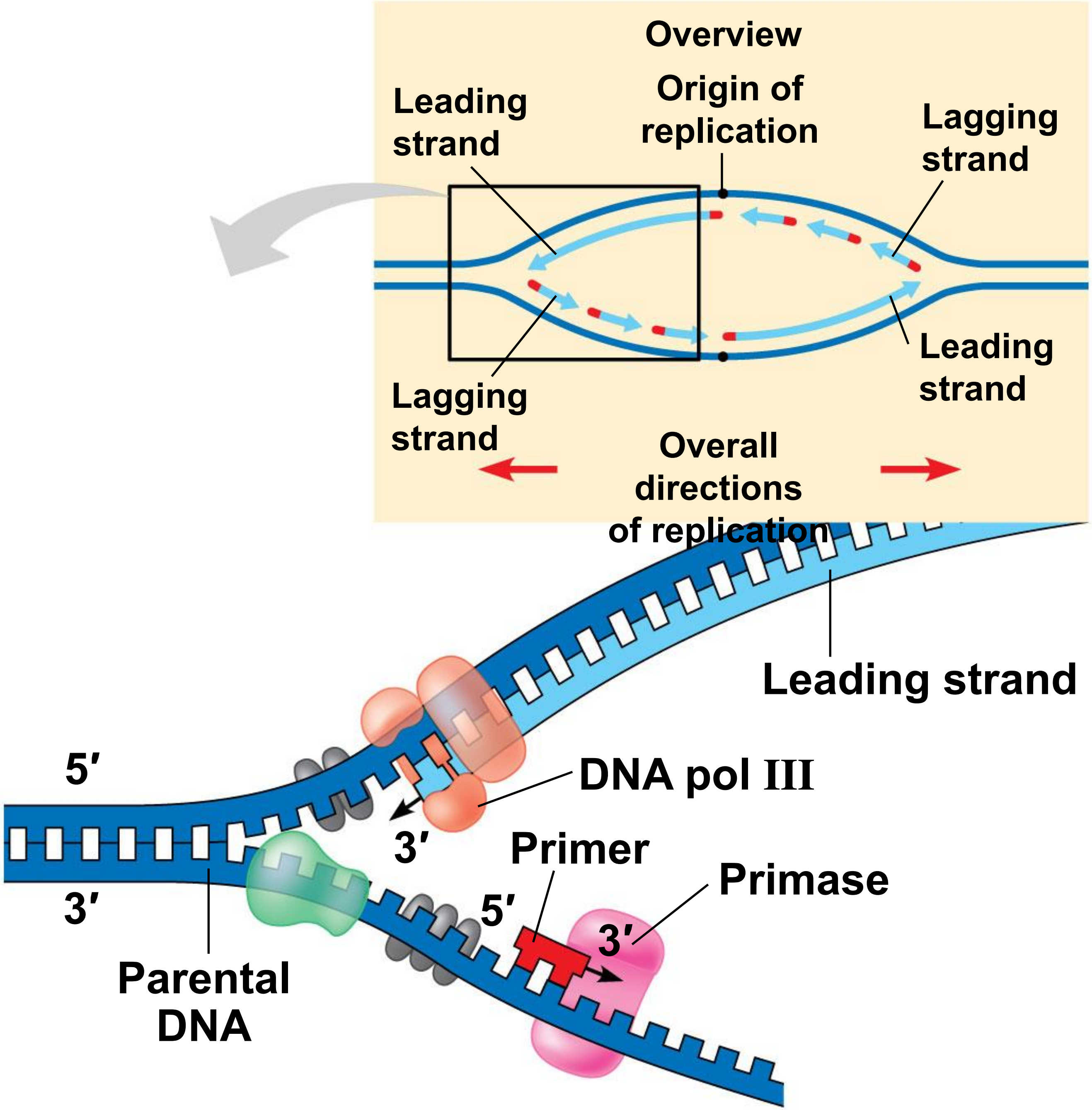
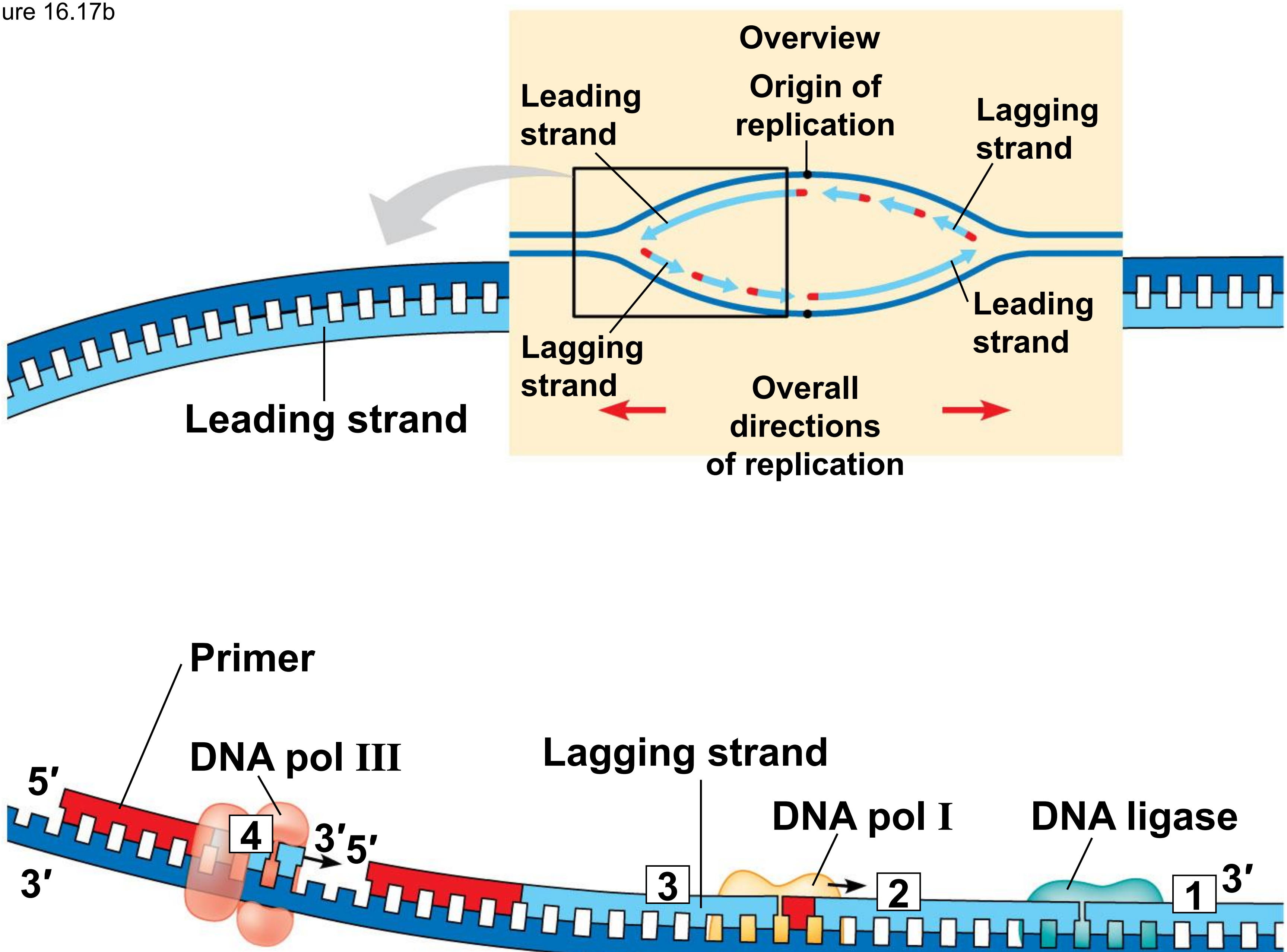


Figure 16.17b



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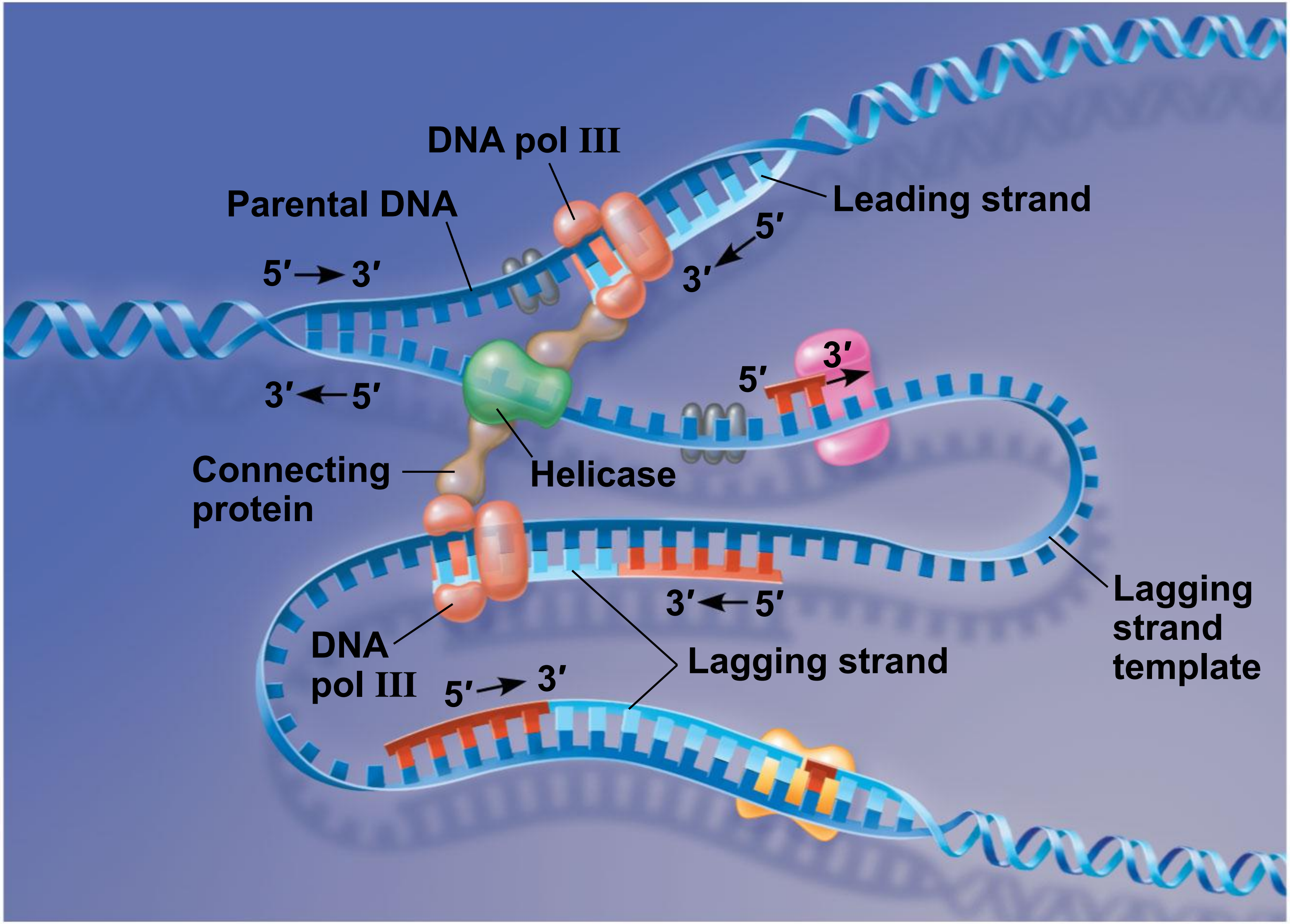
The DNA Replication Complex

- The proteins that participate in DNA replication form a large complex, a “DNA replication machine”
- The DNA replication machine may be stationary during the replication process
- Recent studies support a model in which DNA polymerase molecules “reel in” parental DNA and “extrude” newly made daughter DNA molecules

Animation: DNA Replication Review

Right-click slide / select “Play”

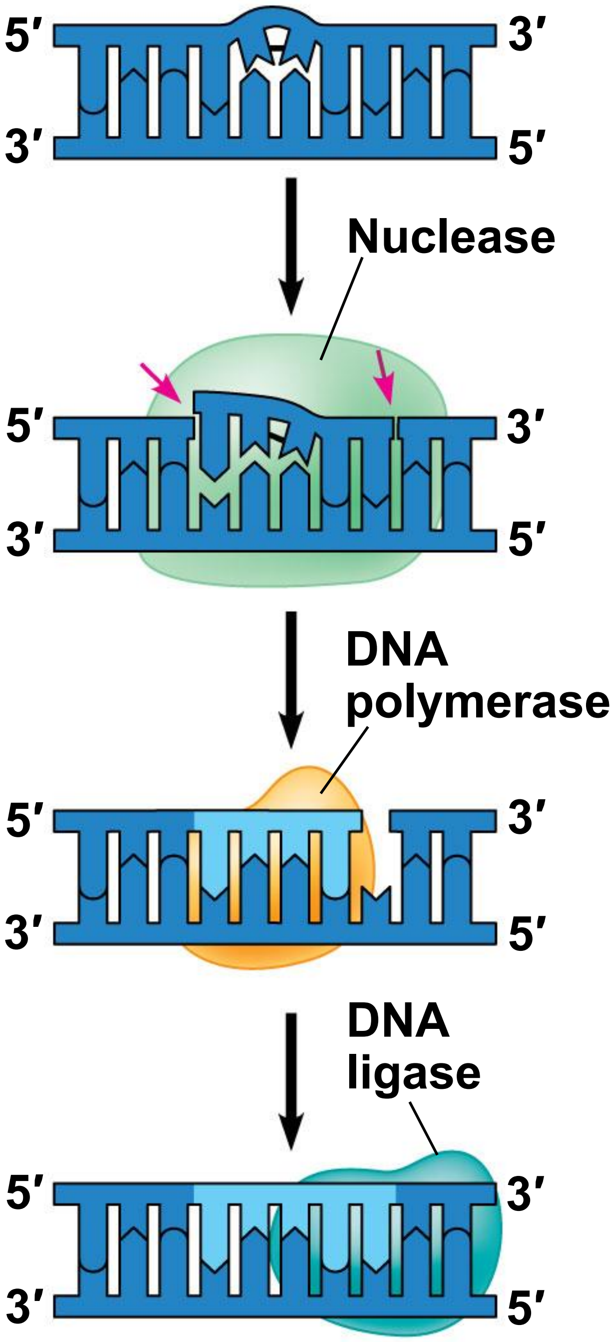
Figure 16.18


DNA pol III
Parental DNA
Leading strand
5′
3′
5′ → 3′
3′
5′
3′ ← 5′
Connecting protein
Helicase
3′ ← 5′
Lagging strand template
DNA pol III
5′ → 3′
Lagging strand

Proofreading and Repairing DNA

- DNA polymerases proofread newly made DNA, replacing any incorrect nucleotides
- In **mismatch repair** of DNA, repair enzymes correct errors in base pairing
- DNA can be damaged by exposure to harmful chemical or physical agents such as cigarette smoke and X-rays; it can also undergo spontaneous changes
- In **nucleotide excision repair**, a **nuclease** cuts out and replaces damaged stretches of DNA

Figure 16.19



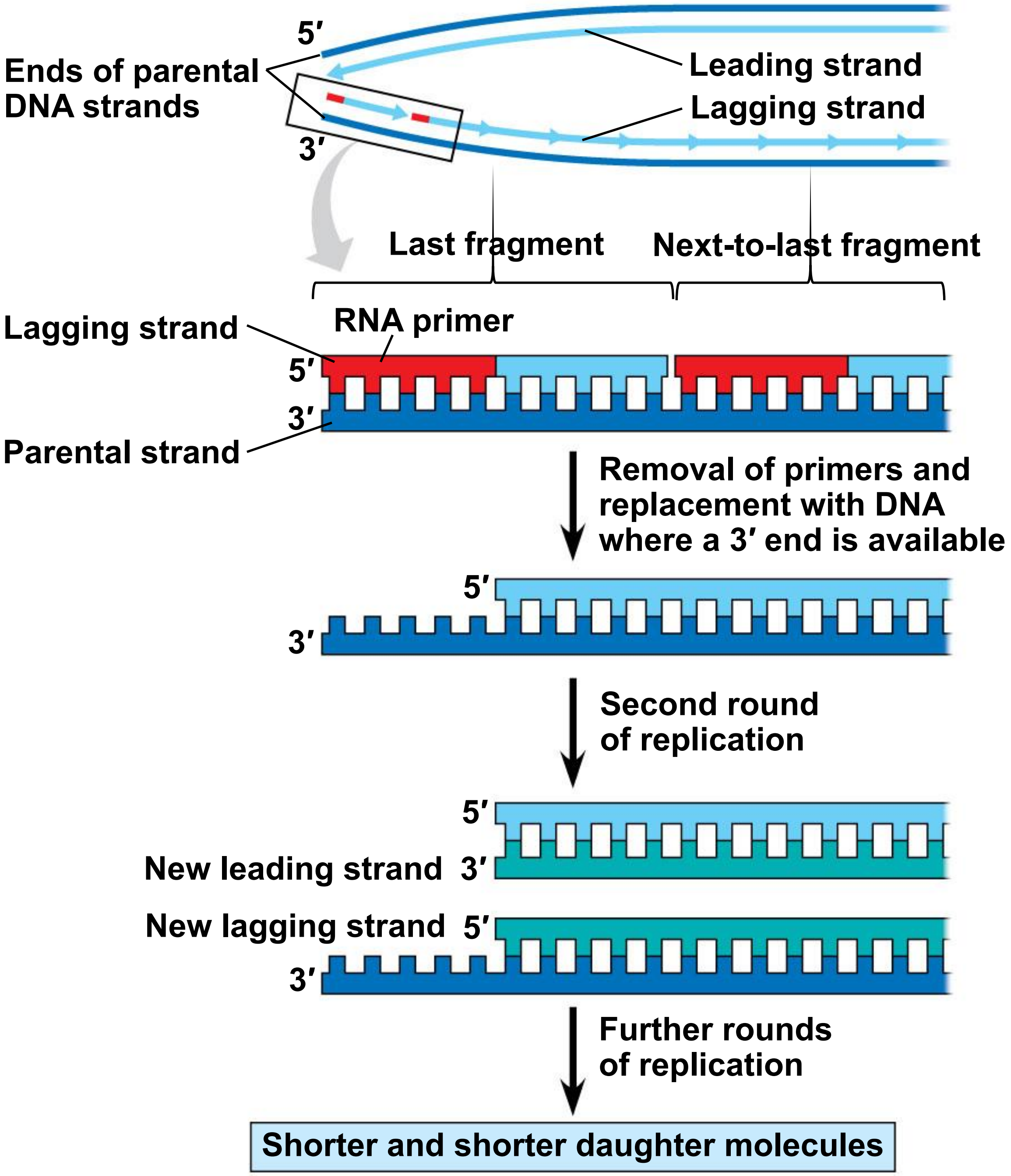
Evolutionary Significance of Altered DNA Nucleotides

- Error rate after proofreading repair is low but not zero
- Sequence changes may become permanent and can be passed on to the next generation
- These changes (mutations) are the source of the genetic variation upon which natural selection operates

Replicating the Ends of DNA Molecules

- Limitations of DNA polymerase create problems for the linear DNA of eukaryotic chromosomes
- The usual replication machinery provides no way to complete the 5′ ends, so repeated rounds of replication produce shorter DNA molecules with uneven ends
- This is not a problem for prokaryotes, most of which have circular chromosomes

Figure 16.20



5′

Ends of parental DNA strands

3′

Leading strand

Lagging strand

Last fragment

Next-to-last fragment

Lagging strand

RNA primer

5′

3′

Parental strand

Removal of primers and replacement with DNA where a 3′ end is available

5′

3′

Second round of replication

5′

New leading strand 3′

New lagging strand 5′

3′

Further rounds of replication

Shorter and shorter daughter molecules

Figure 16.20a

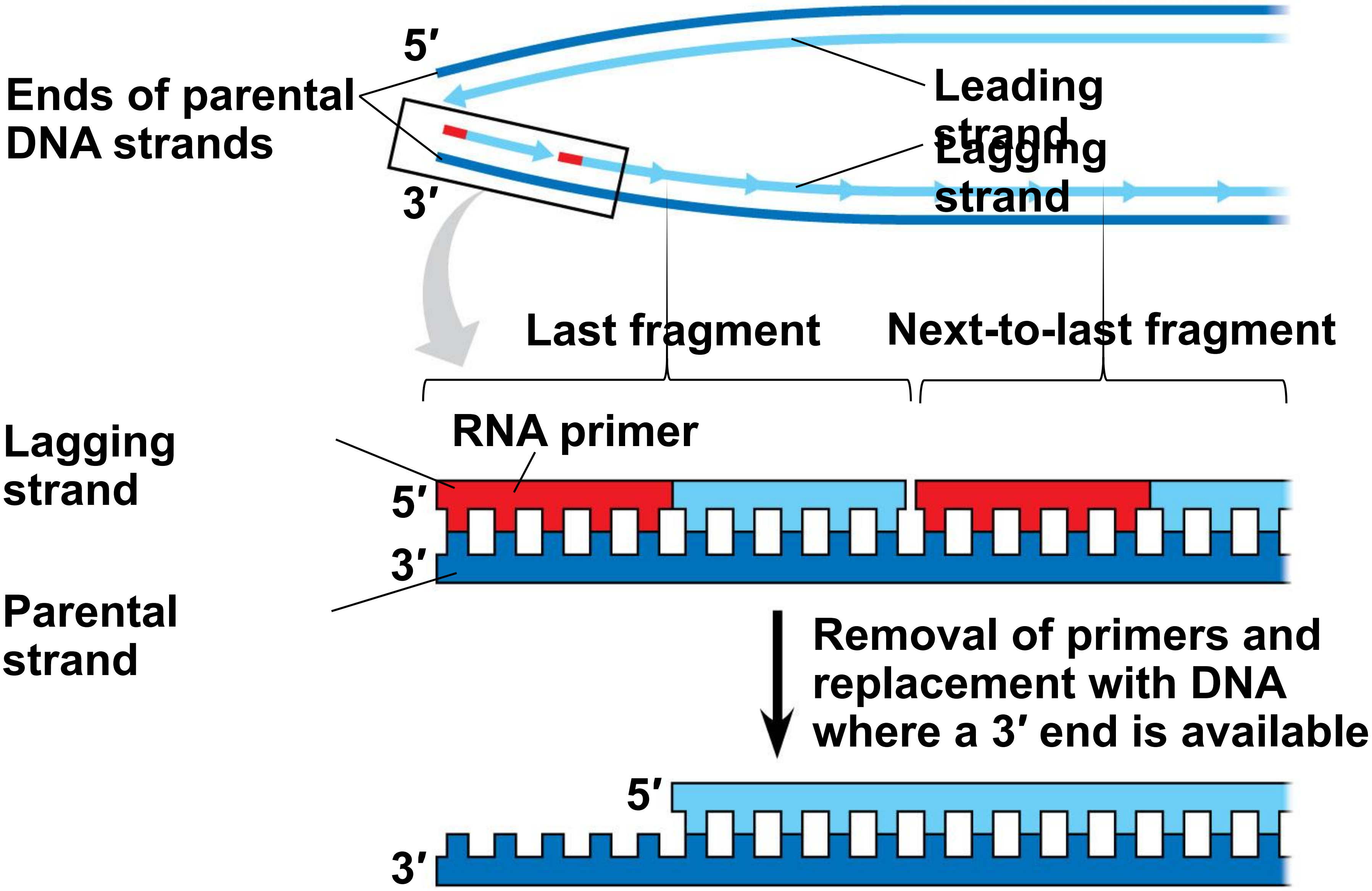
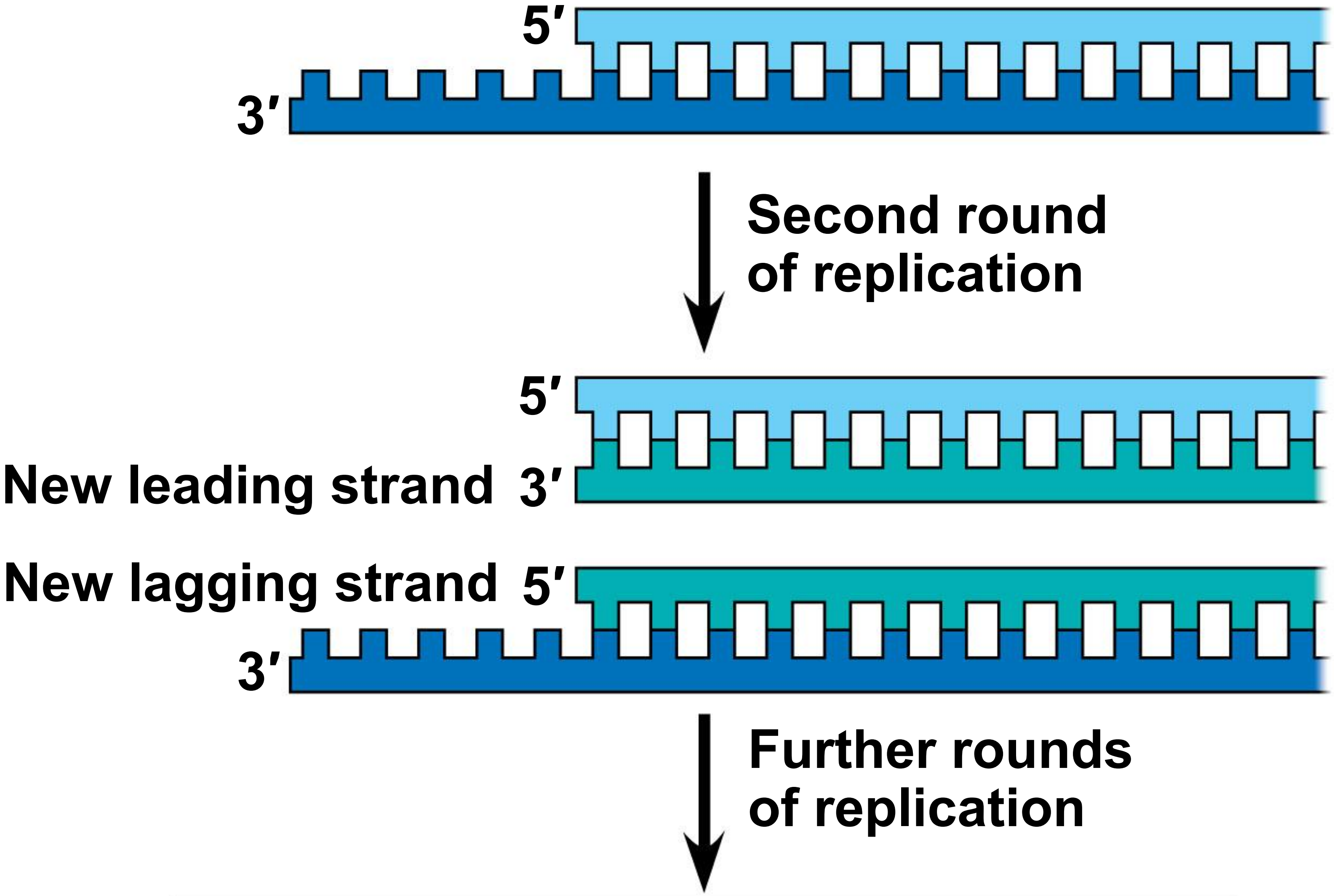


Figure 16.20b



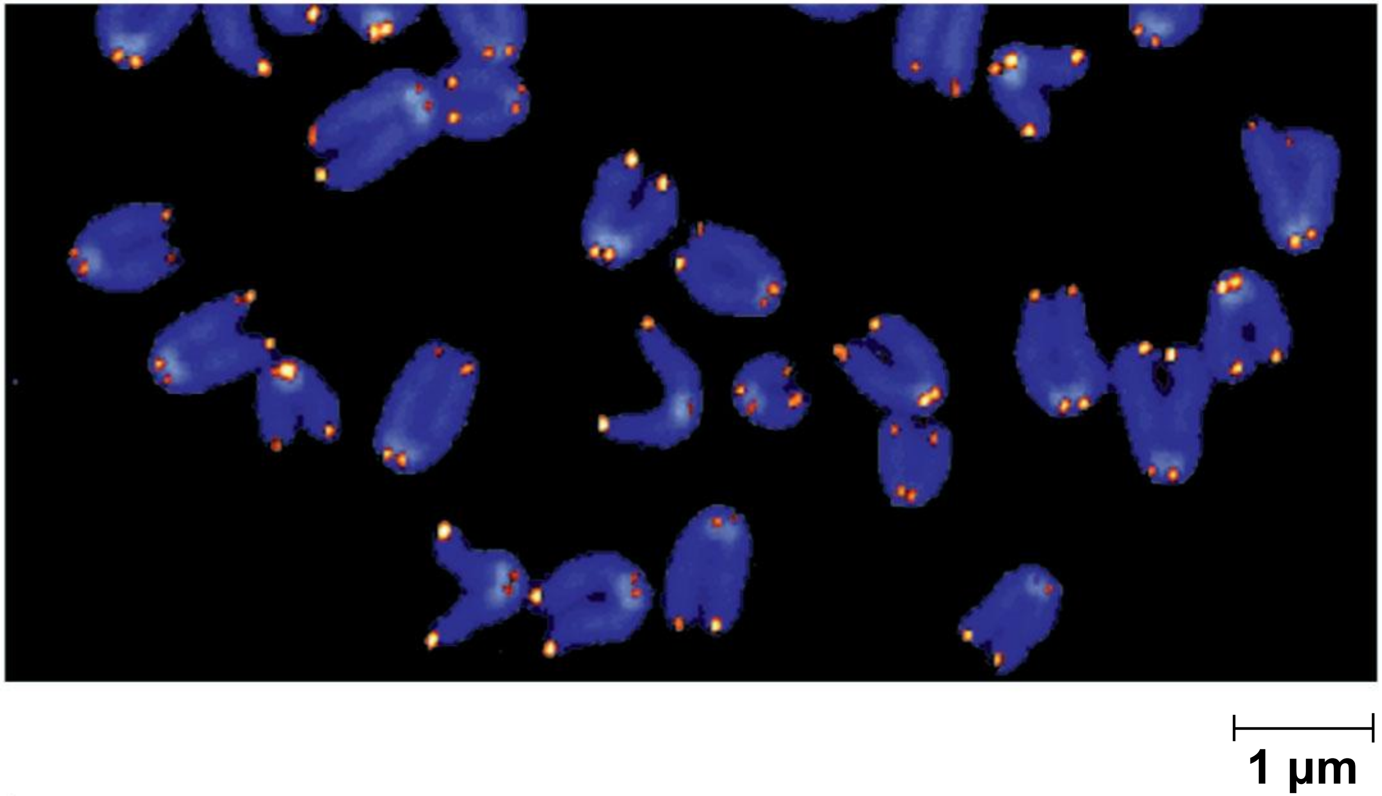
Second round of replication

Further rounds of replication

Shorter and shorter daughter molecules

- Eukaryotic chromosomal DNA molecules have special nucleotide sequences at their ends called **telomeres**
- Telomeres do not prevent the shortening of DNA molecules, but they do postpone the erosion of genes near the ends of DNA molecules
- It has been proposed that the shortening of telomeres is connected to aging

Figure 16.21



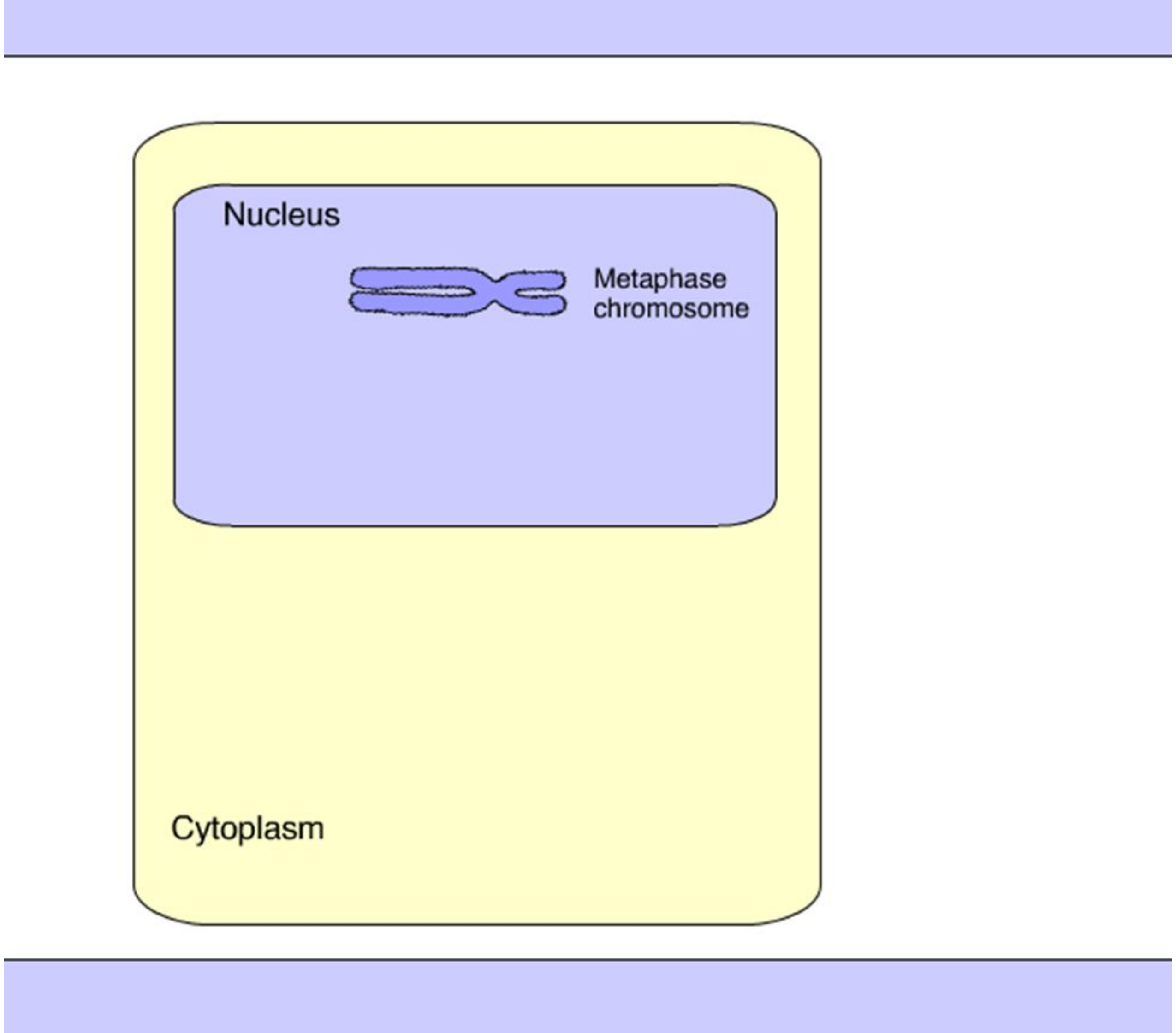
- If chromosomes of germ cells became shorter in every cell cycle, essential genes would eventually be missing from the gametes they produce
- An enzyme called **telomerase** catalyzes the lengthening of telomeres in germ cells

- The shortening of telomeres might protect cells from cancerous growth by limiting the number of cell divisions
- There is evidence of telomerase activity in cancer cells, which may allow cancer cells to persist

Concept 16.3 A chromosome consists of a DNA molecule packed together with proteins

- The bacterial chromosome is a double-stranded, circular DNA molecule associated with a small amount of protein
- Eukaryotic chromosomes have linear DNA molecules associated with a large amount of protein
- In a bacterium, the DNA is “supercoiled” and found in a region of the cell called the **nucleoid**

- **Chromatin**, a complex of DNA and protein, is found in the nucleus of eukaryotic cells
- Chromosomes fit into the nucleus through an elaborate, multilevel system of packing



Animation: DNA Packing

Right-click slide / select "Play"

Figure 16.22a

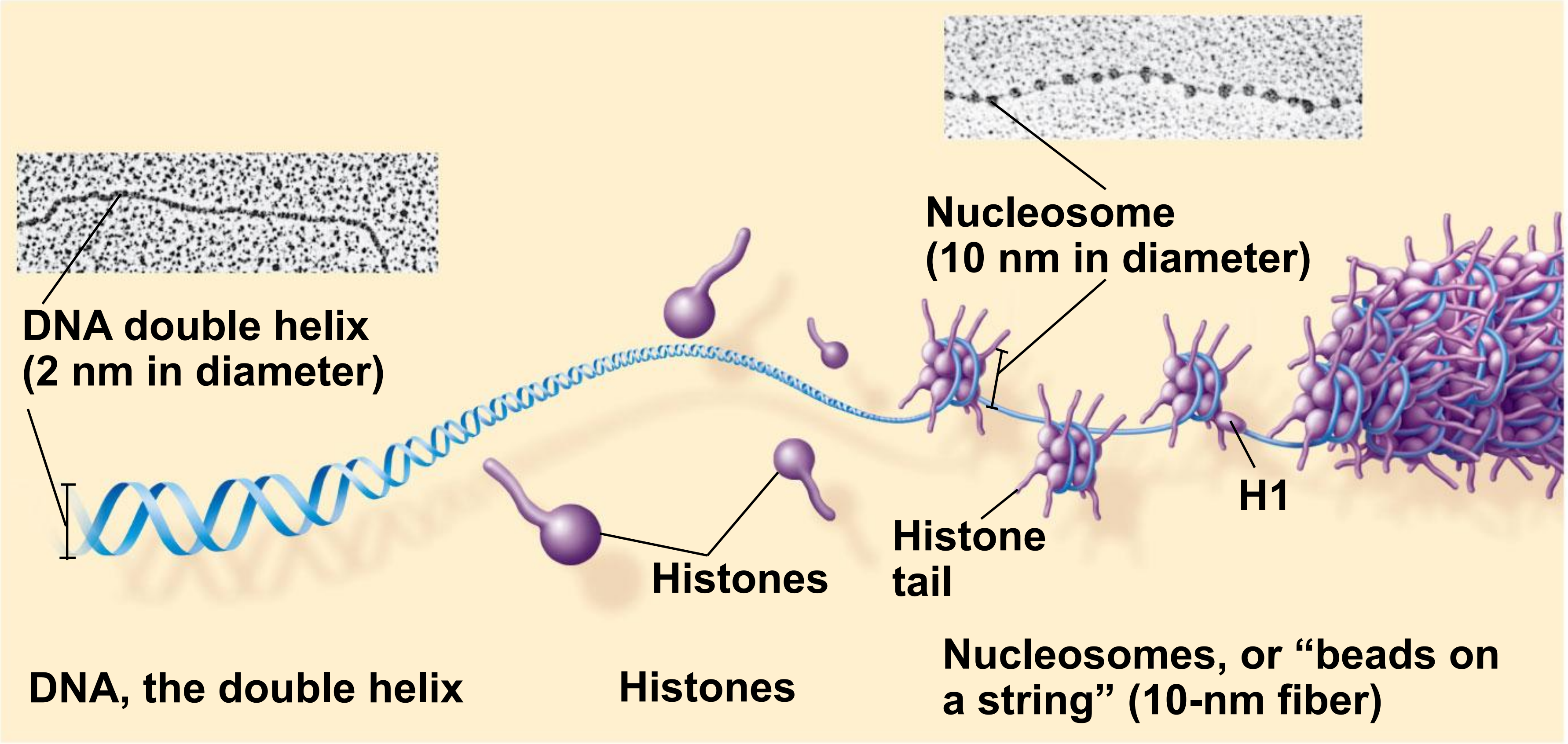


Figure 16.22b

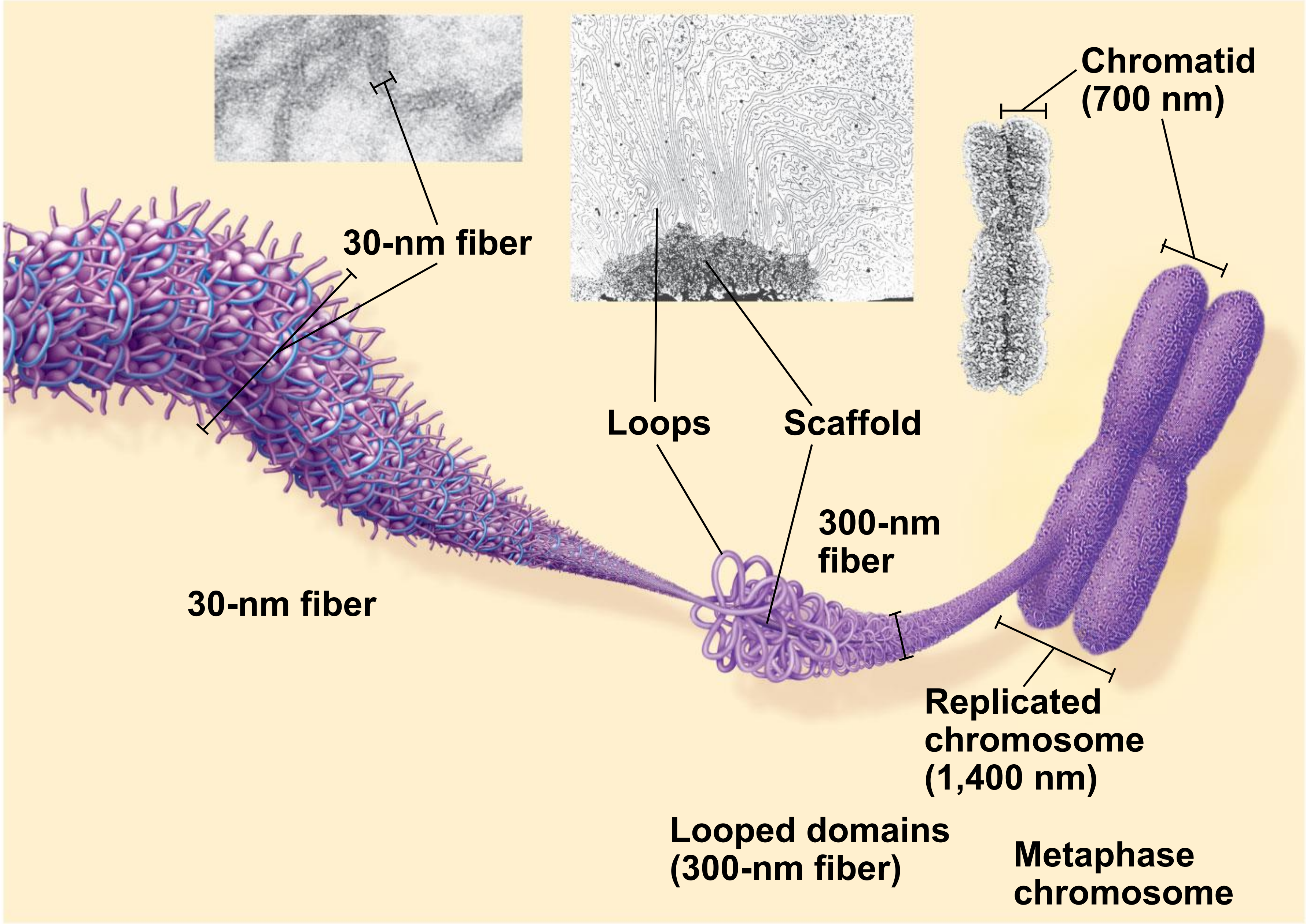
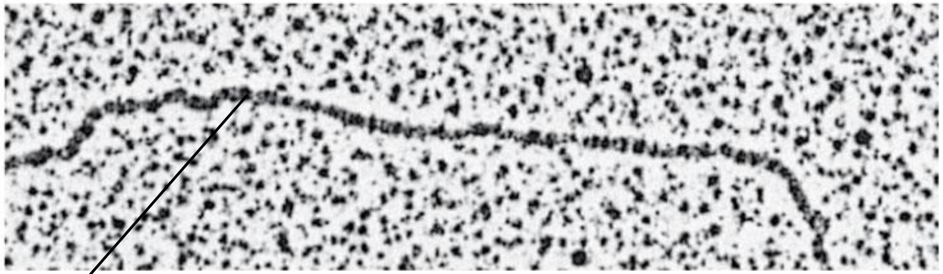
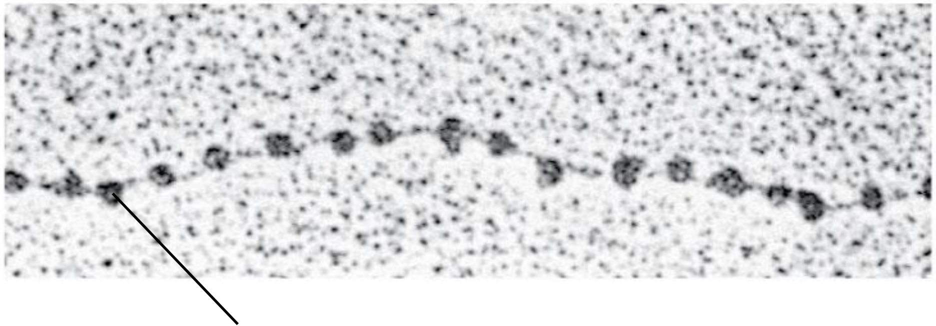


Figure 16.22c



DNA double helix (2 nm in diameter)

Figure 16.22d



Nucleosome (10 nm in diameter)

Figure 16.22e

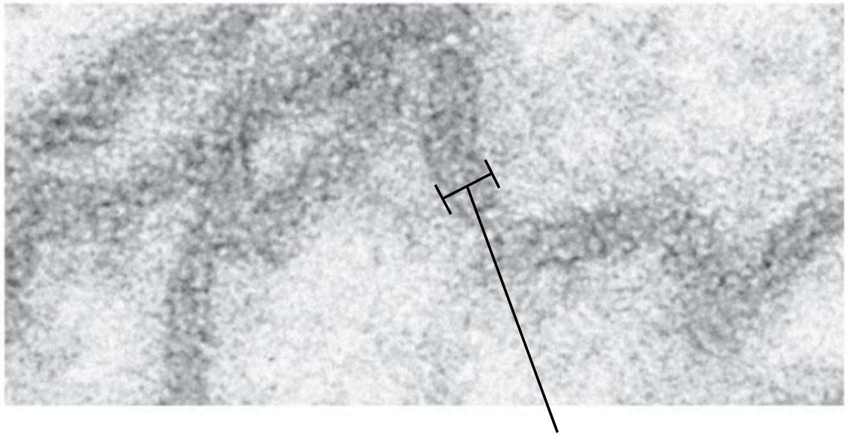


Figure 16.22f

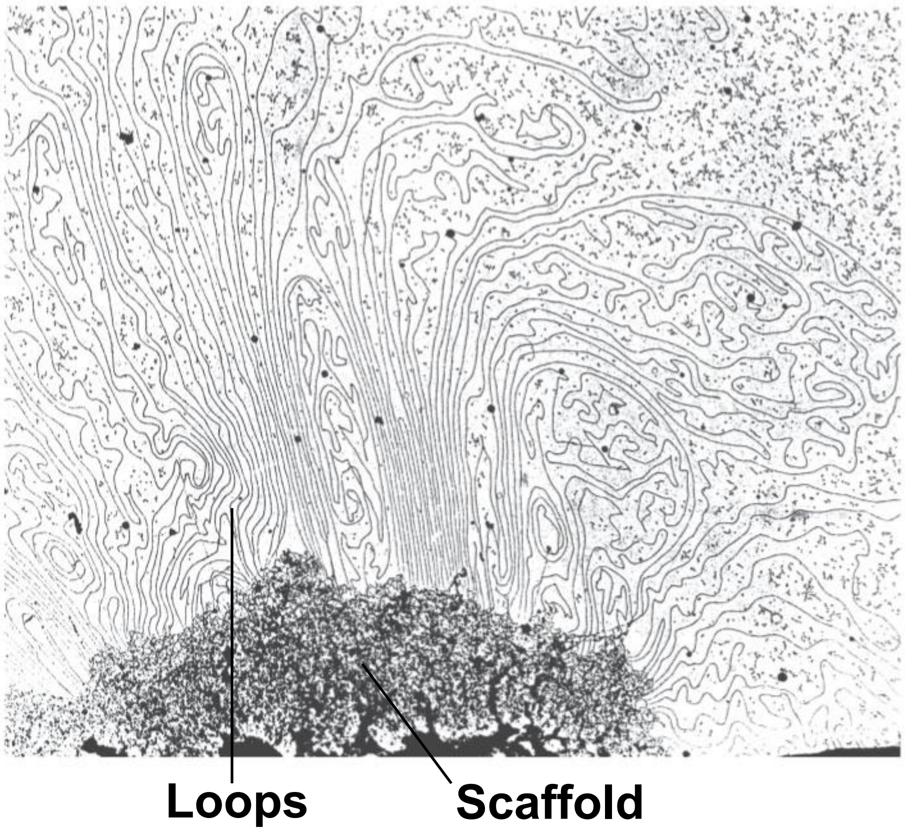
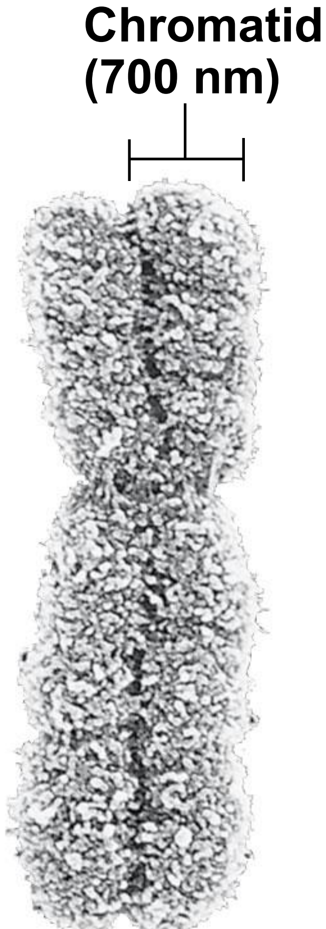


Figure 16.22g



- Chromatin undergoes changes in packing during the cell cycle
- At interphase, some chromatin is organized into a 10-nm fiber, but much is compacted into a 30-nm fiber, through folding and looping
- Though interphase chromosomes are not highly condensed, they still occupy specific restricted regions in the nucleus

Figure 16.23

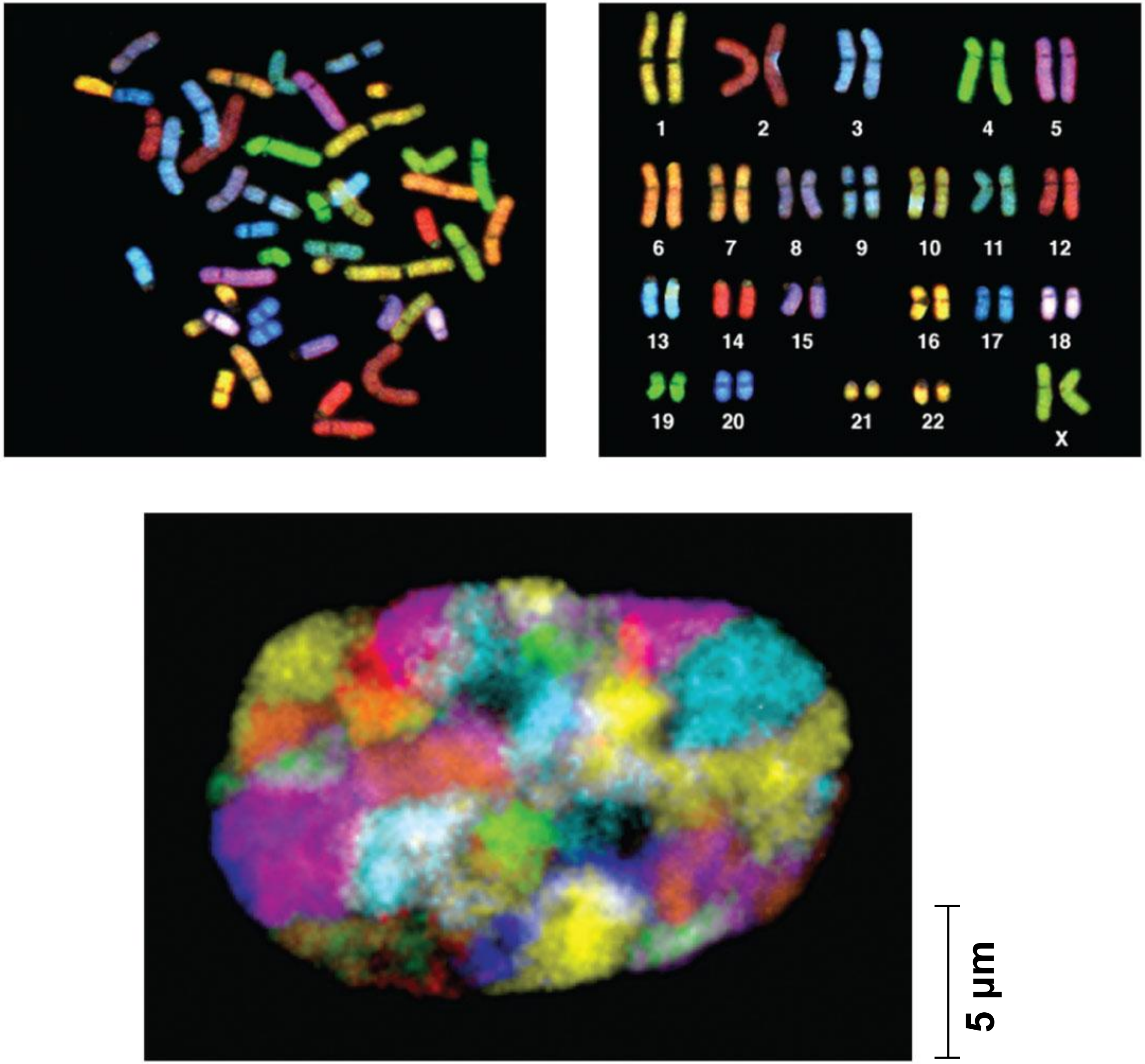


Figure 16.23a

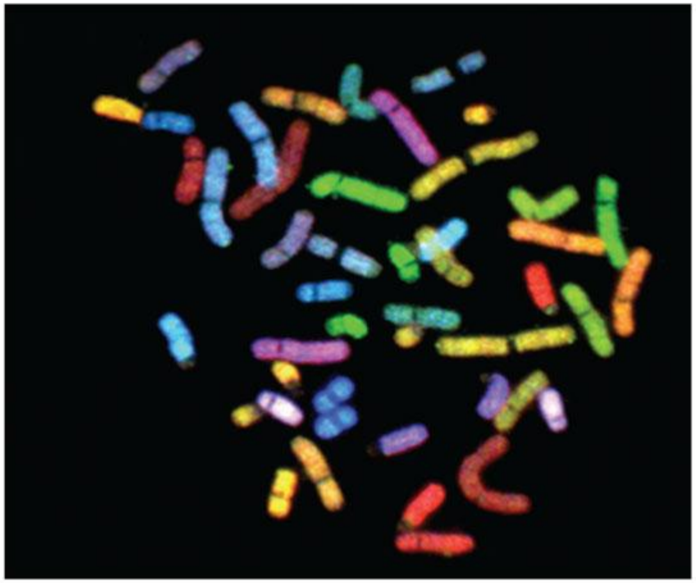


Figure 16.23b

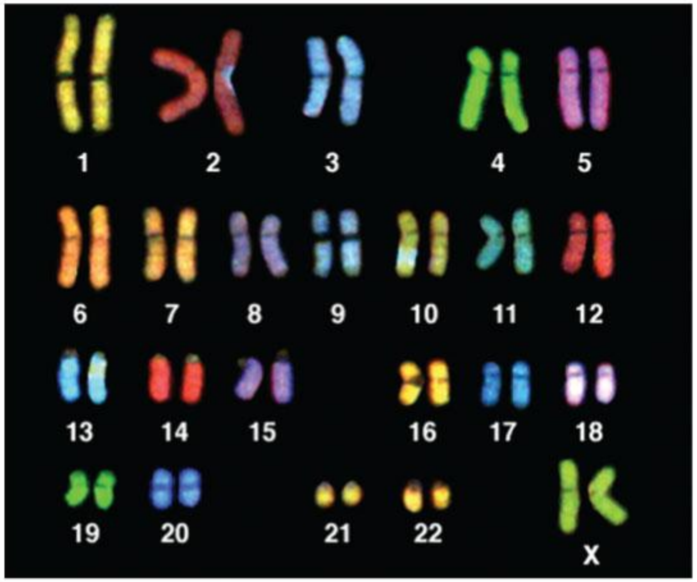
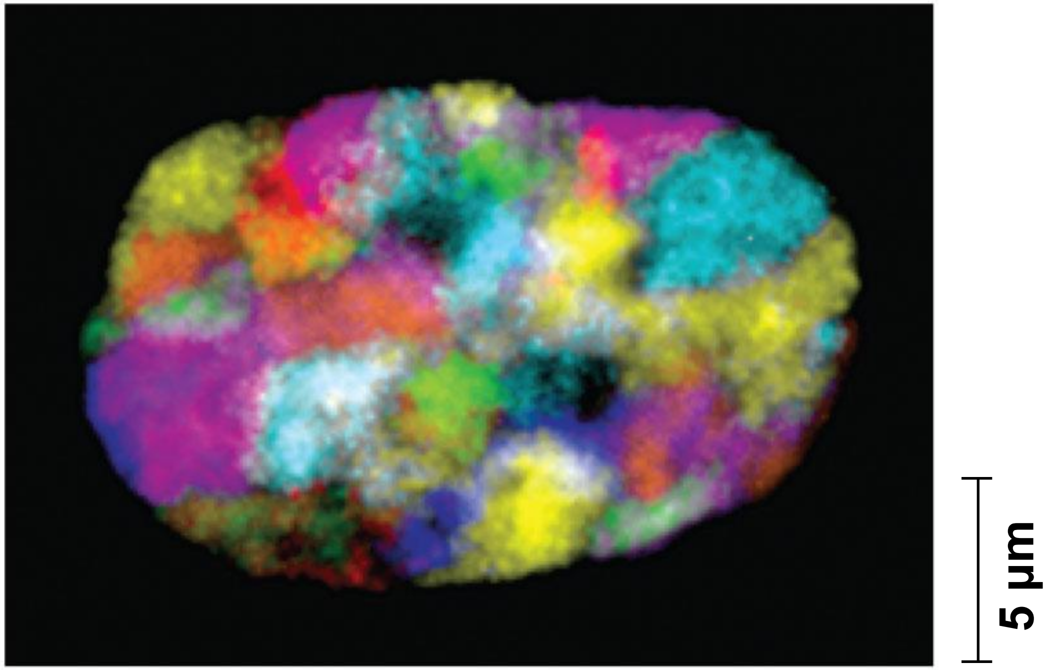


Figure 16.23c



- Most chromatin is loosely packed in the nucleus during interphase and condenses prior to mitosis
- Loosely packed chromatin is called **euchromatin**
- During interphase a few regions of chromatin (centromeres and telomeres) are highly condensed into **heterochromatin**
- Dense packing of the heterochromatin makes it difficult for the cell to express genetic information coded in these regions

- Histones can undergo chemical modifications that result in changes in chromatin organization

Figure 16.UN02

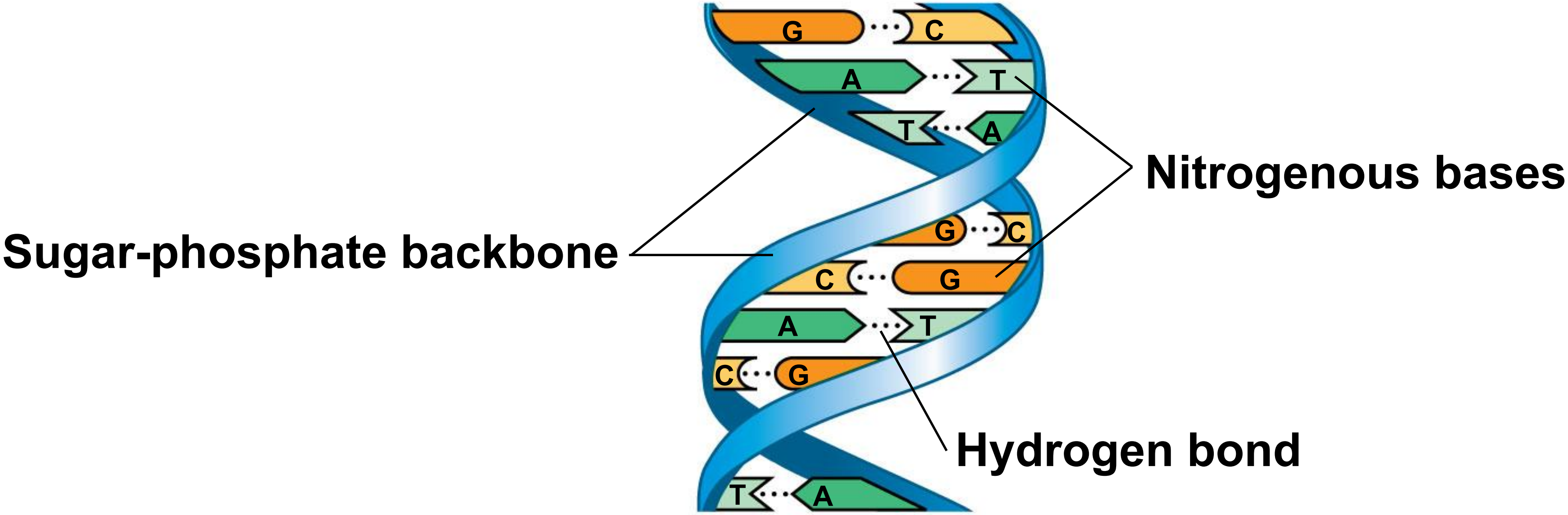


Figure 16.UN03

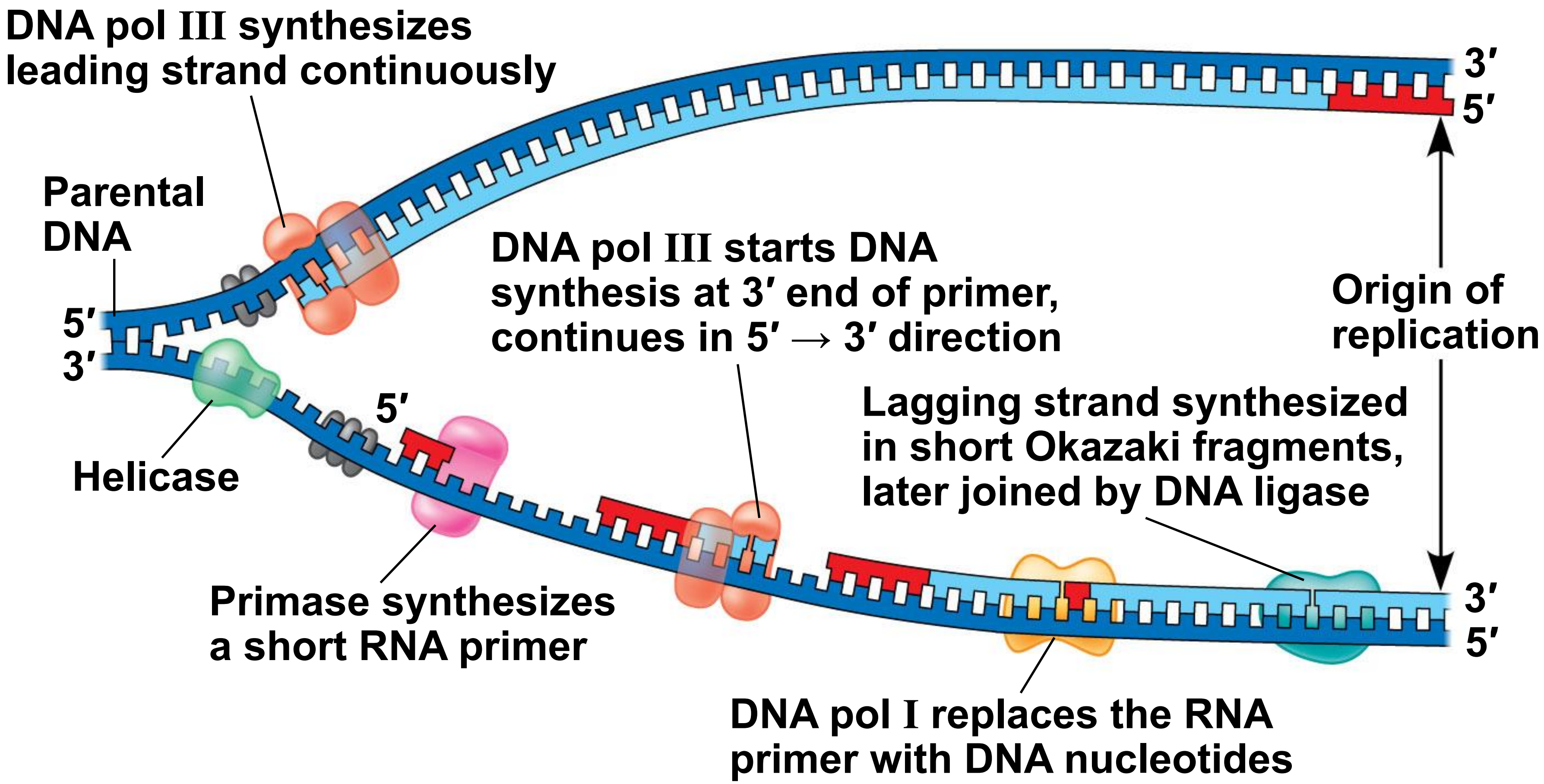
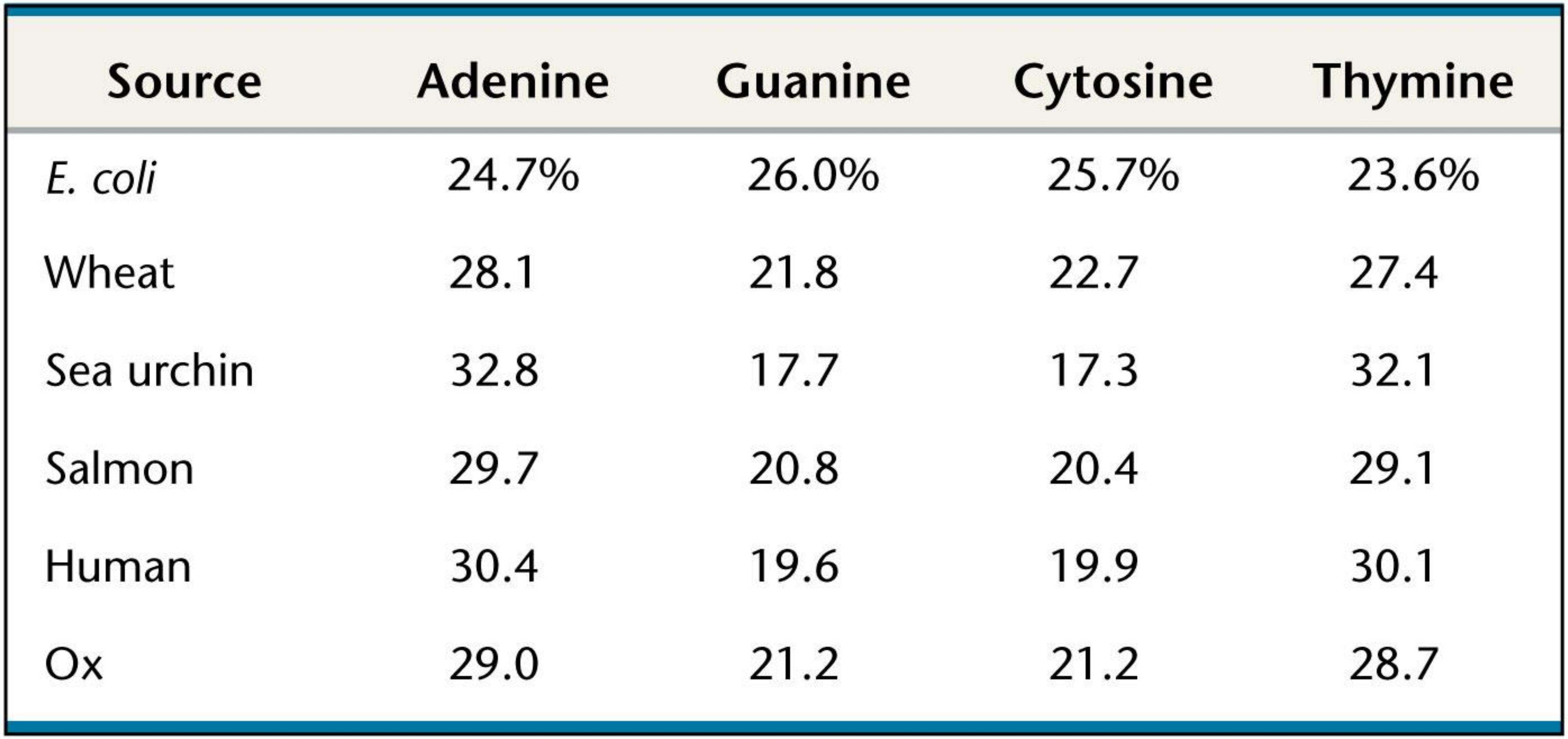


Figure 16.UN04



Source	Adenine	Guanine	Cytosine	Thymine
E. coli	24.7%	26.0%	25.7%	23.6%
Wheat	28.1	21.8	22.7	27.4
Sea urchin	32.8	17.7	17.3	32.1
Salmon	29.7	20.8	20.4	29.1
Human	30.4	19.6	19.9	30.1
Ox	29.0	21.2	21.2	28.7

Figure 16.UN05

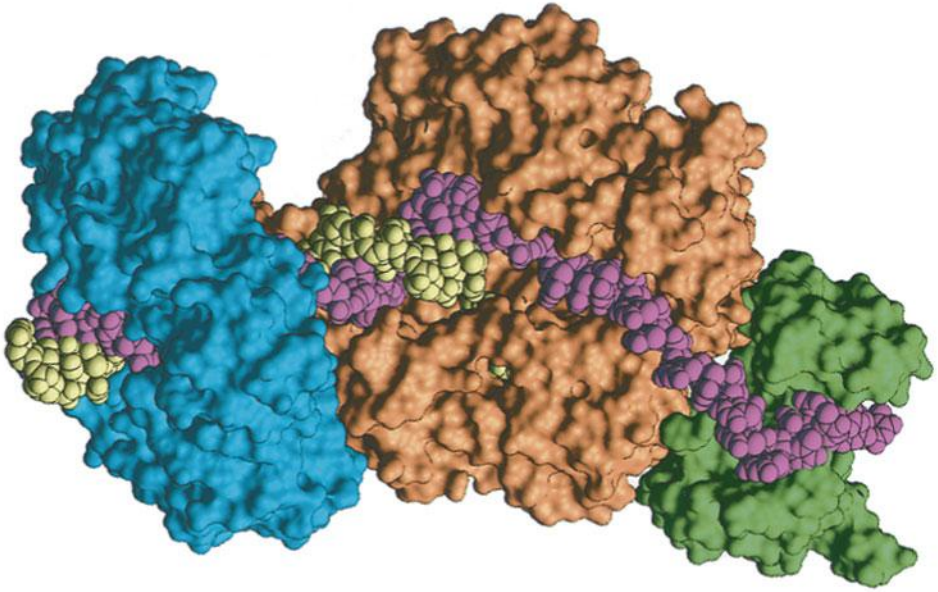


Figure 16.UN06

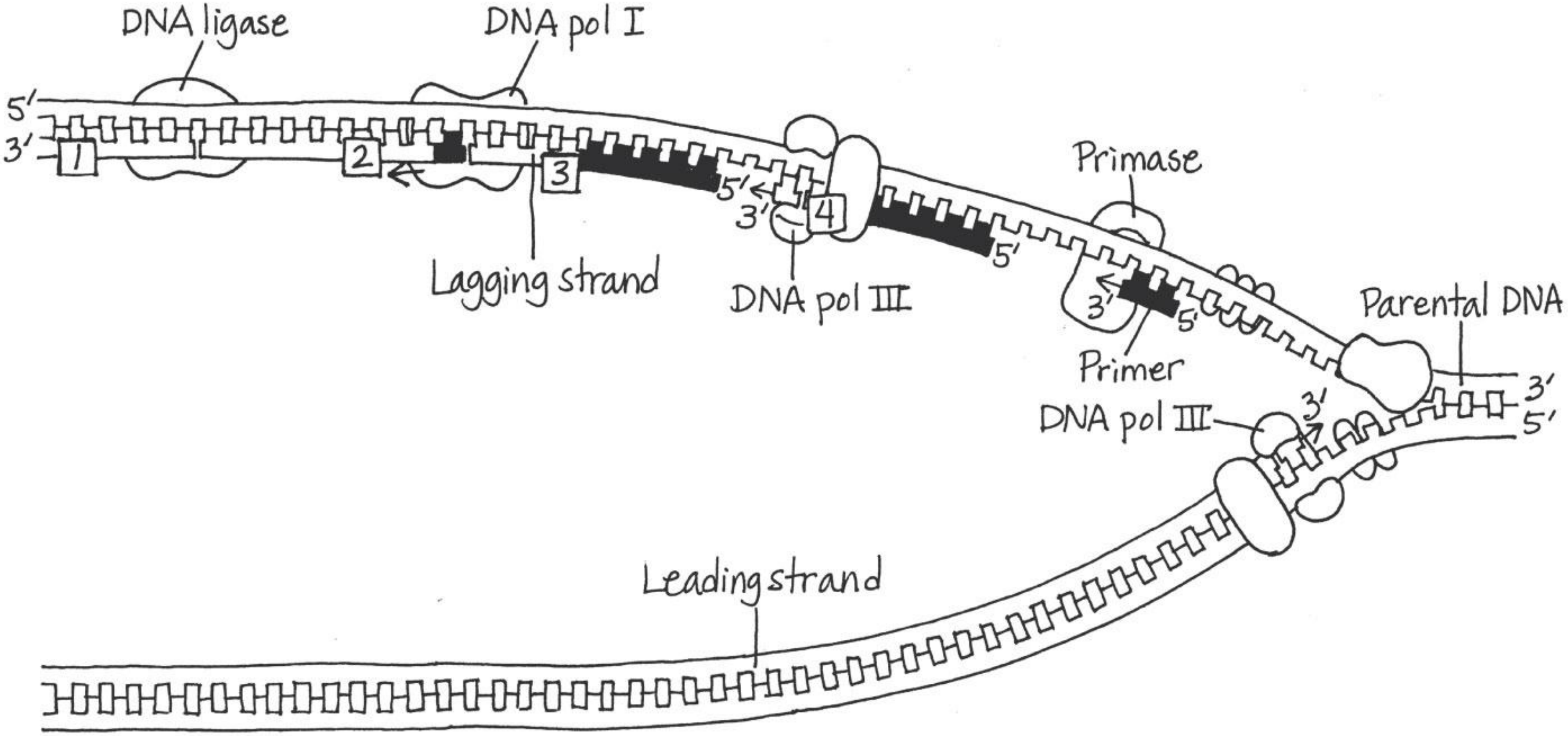


Figure 16.UN07