

Chapter 16

Nucleic Acids and Inheritance

Lecture Presentations by
Nicole Tunbridge and
Kathleen Fitzpatrick

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
- 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



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Figure 16.1a



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- DNA is copied during **DNA replication**, and cells can repair their DNA

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

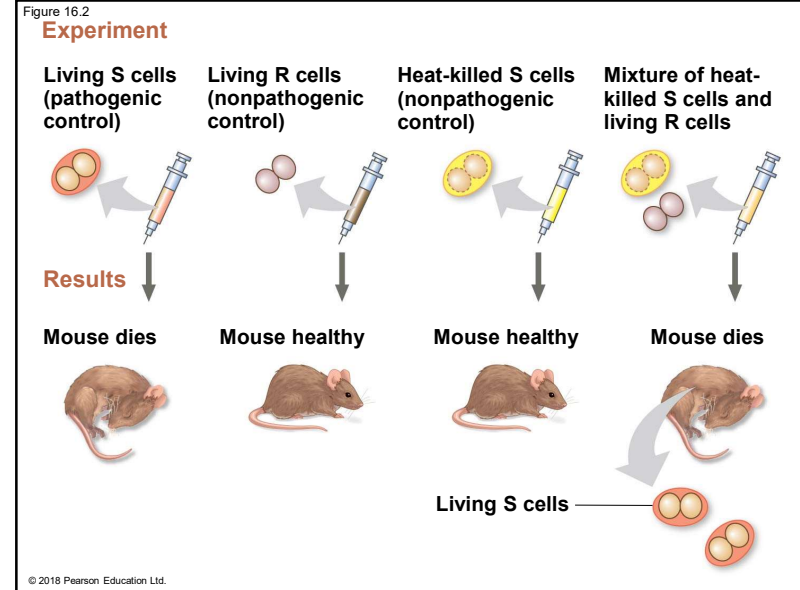
The Search for the Genetic Material: *Scientific Inquiry*

- 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 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

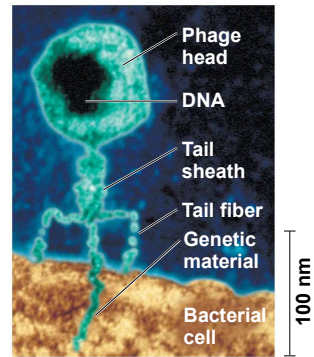


- Later work by Oswald Avery, Maclyn McCarty, and Colin MacLeod identified the transforming substance as DNA
- Many biologists remained skeptical, mainly because little was known about DNA

Evidence That Viral DNA Can Program Cells

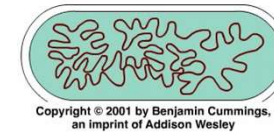
- More evidence for DNA as the genetic material came from studies of viruses that infect bacteria
- Such viruses, called **bacteriophages** (or **phages**), are widely used in molecular genetics research
- A **virus** is DNA (sometimes RNA) enclosed by a protective coat, often simply protein

Figure 16.3



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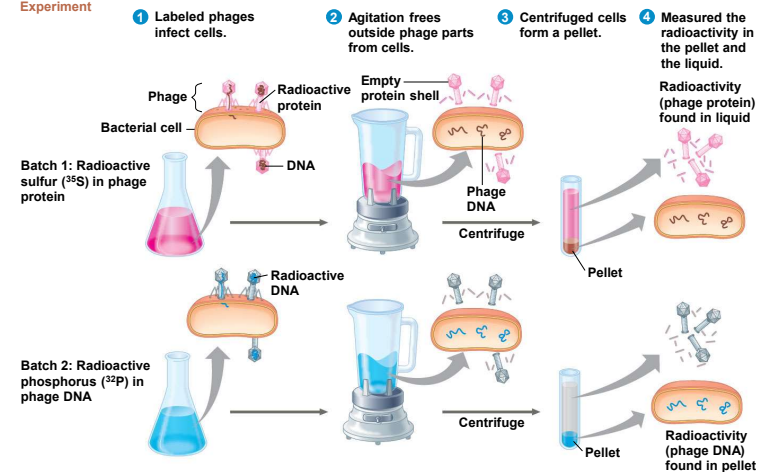
Animation: Phage T2 Reproductive Cycle

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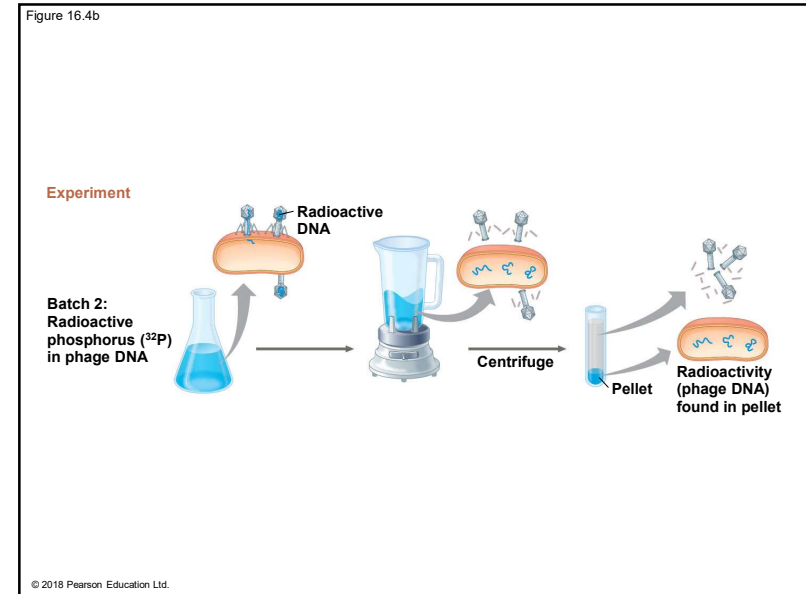
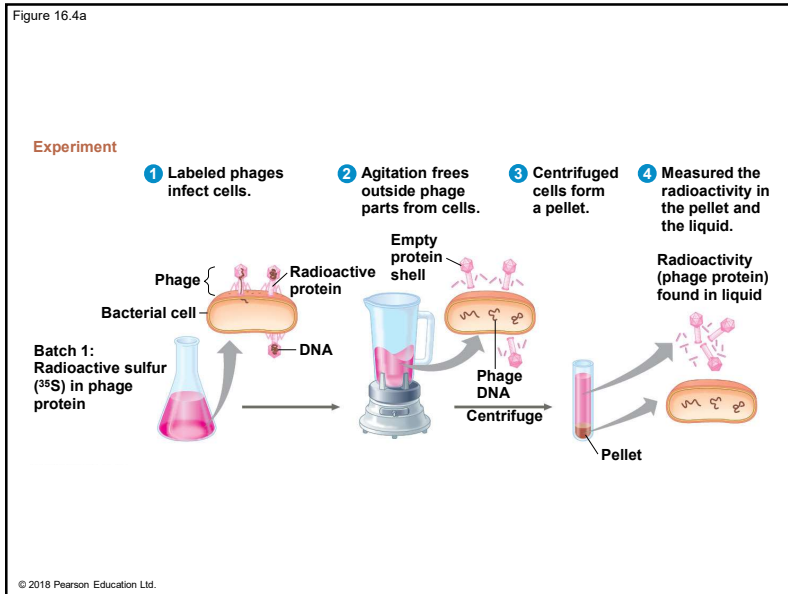
- In 1952, Alfred Hershey and Martha Chase showed that DNA is the genetic material of a phage known as T2
- They designed an experiment showing that only one of the two components of T2 (DNA or protein) enters an *E. coli* cell during infection
- They concluded that the injected DNA of the phage provides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

Figure 16.4

Experiment



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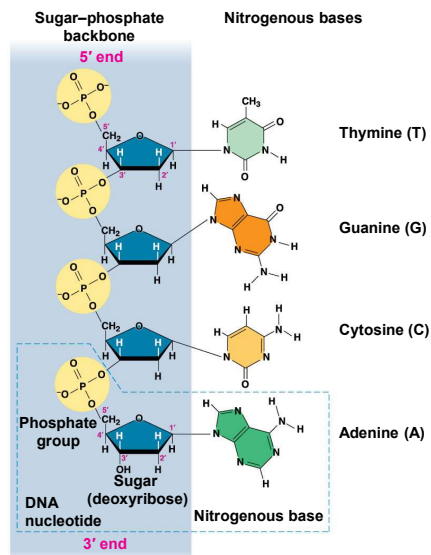


Additional Evidence That DNA Is the Genetic Material

- DNA is a polymer of nucleotides, each consisting of a nitrogenous base, a sugar, and a phosphate group
- The nitrogenous bases can be adenine (A), thymine (T), guanine (G), or cytosine (C)
- 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

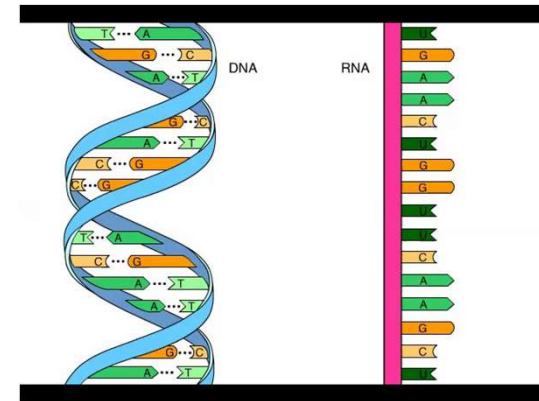
- Two findings became known as Chargaff's rules
 - The base composition of DNA varies between species
 - In any species the number of A and T bases is equal and the number of G and C bases is equal
- The basis for these rules was not understood until the discovery of the double helix

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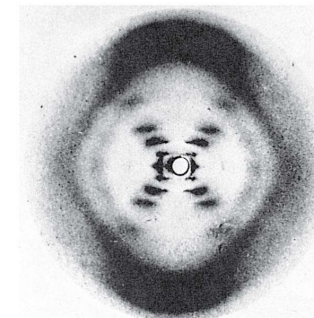
Animation: DNA and RNA Structure



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 16.6b

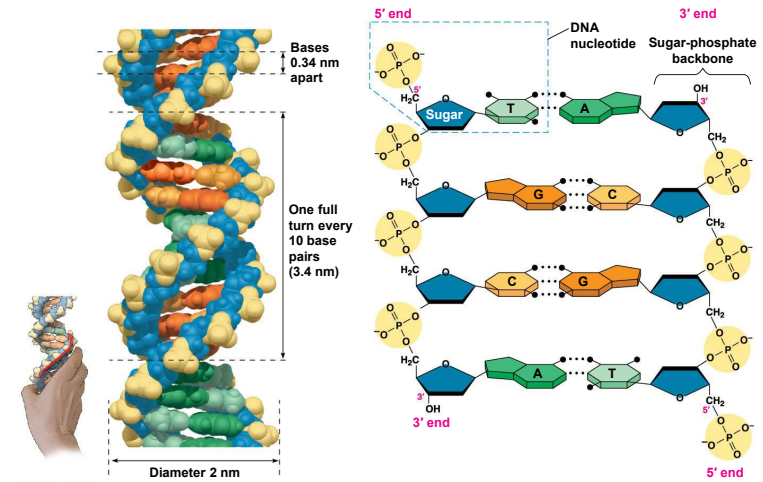


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- Franklin's X-ray crystallographic images of DNA enabled Watson to deduce that DNA was helical
- The X-ray images also enabled Watson to deduce the width of the helix and the spacing of the nitrogenous bases
- The pattern in the photo suggested that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

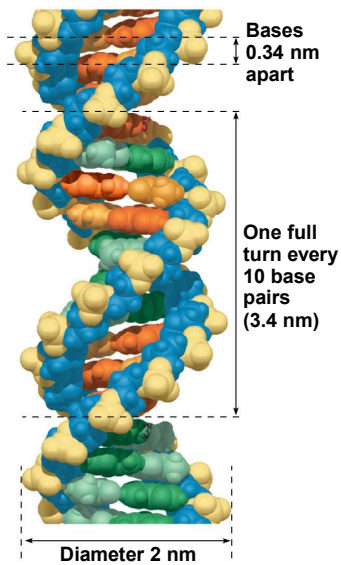
Figure 16.7a

Structural Images



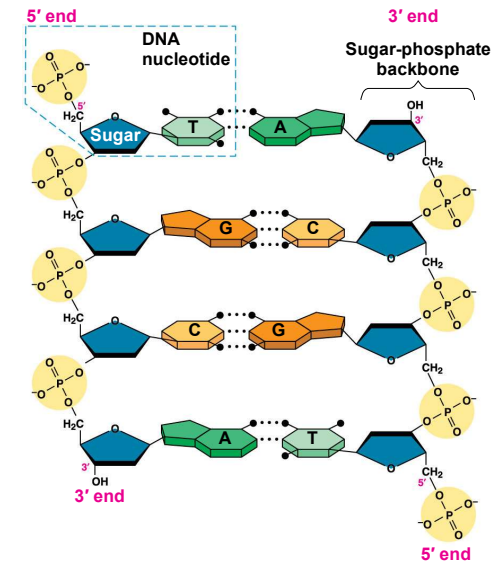
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Figure 16.7aa



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Figure 16.7ab



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Figure 16.7b

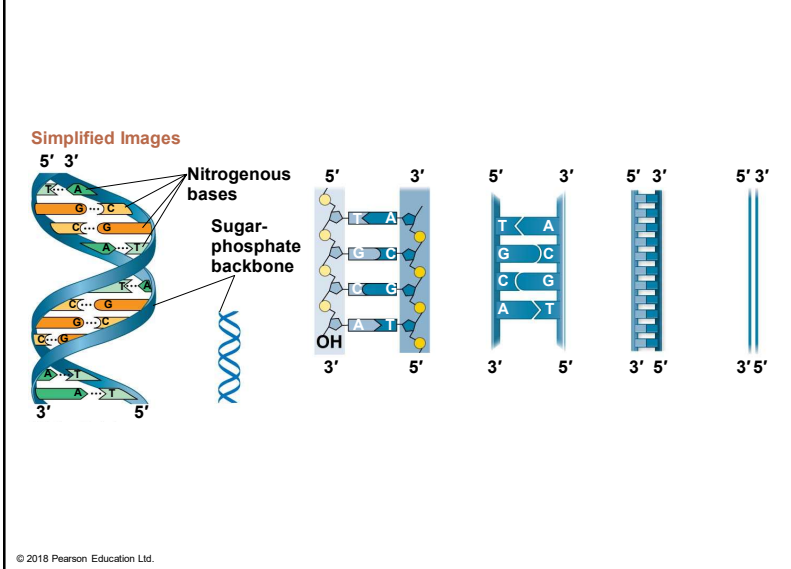


Figure 16.7ba

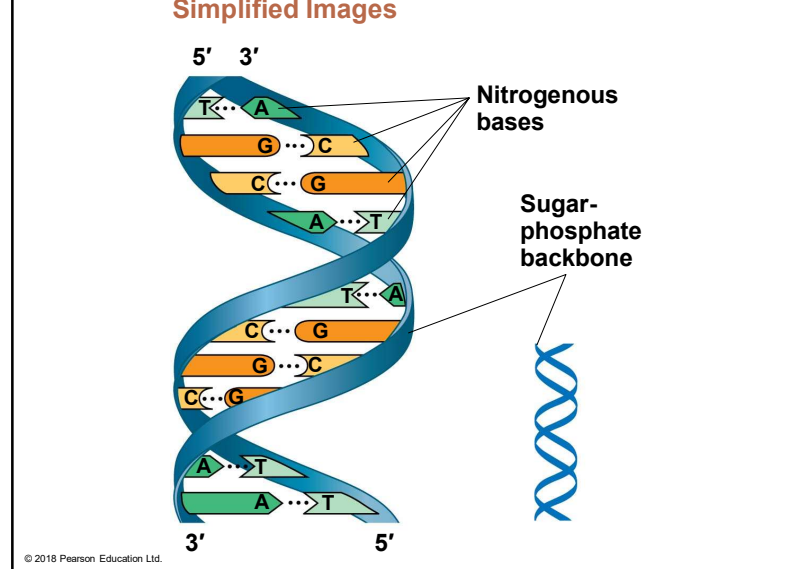
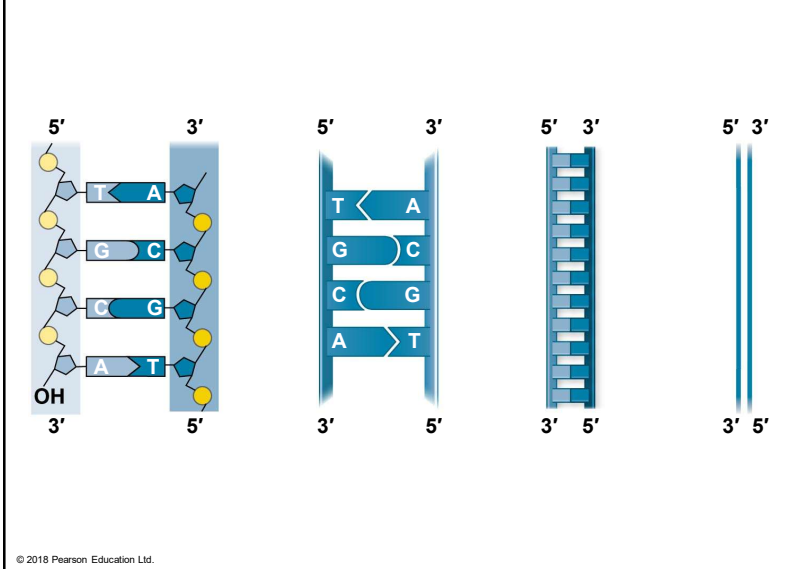


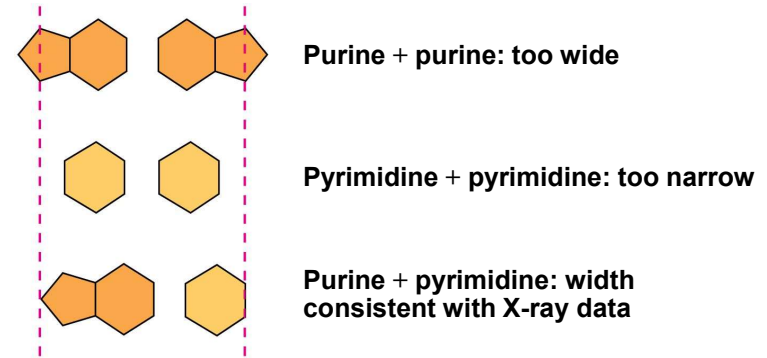
Figure 16.7bb



- 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 (A or G) with a pyrimidine (C or T) resulted in a uniform width consistent with the X-ray data

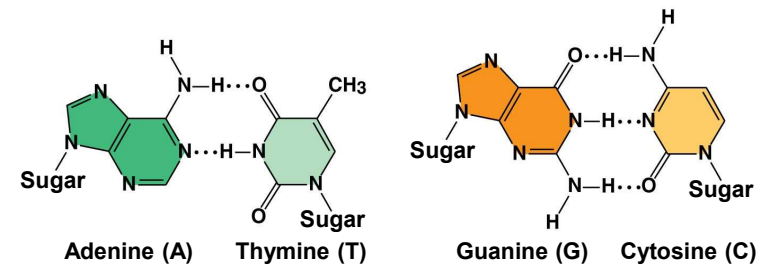
Figure 16.UN02



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- 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



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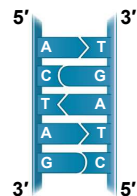
Concept 16.2: Many proteins work together in DNA replication and repair

- 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

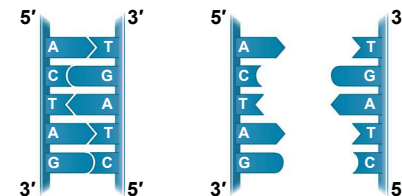
Figure 16.9_1



(a) Parental molecule

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Figure 16.9_2

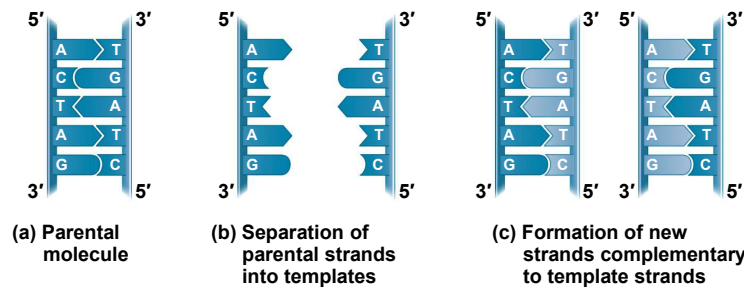


(a) Parental molecule

(b) Separation of parental strands into templates

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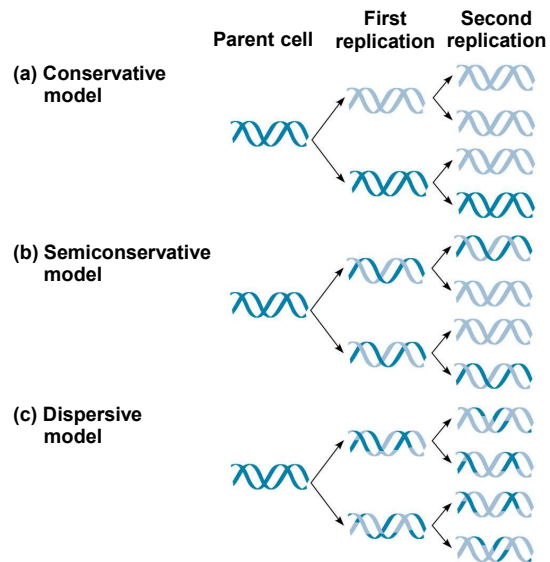
Figure 16.9_3



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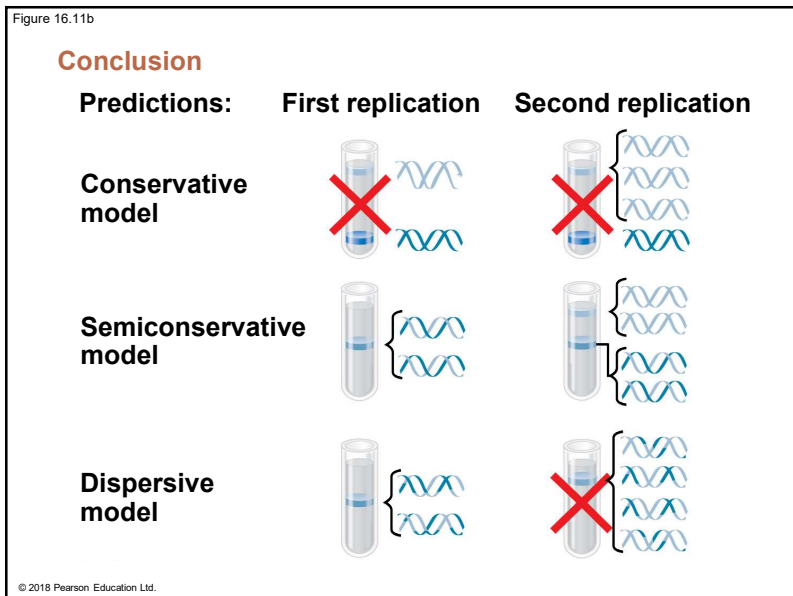
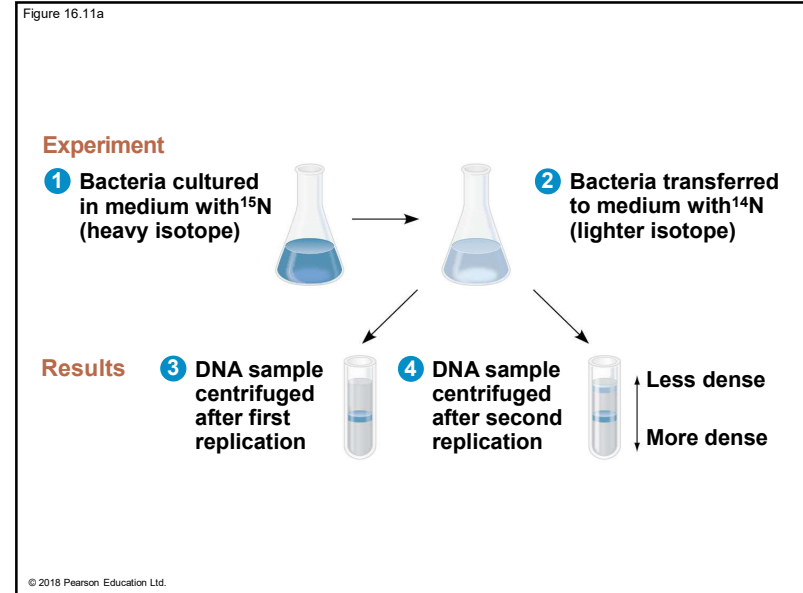
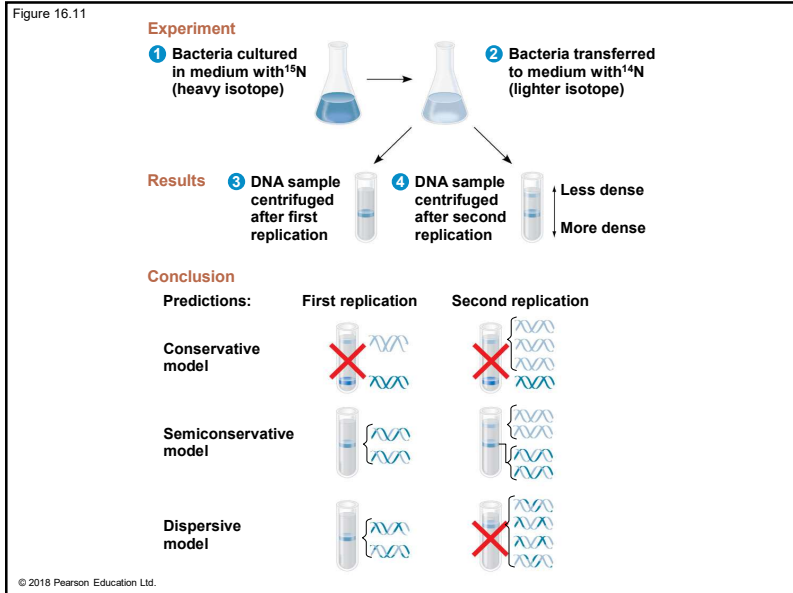
- Watson and Crick's **semiconservative model** of replication predicts that when a double helix replicates, each daughter molecule will have one old strand (derived or "conserved" from the parent molecule) and one newly made strand
- Competing models were the conservative model (the two parent strands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

Figure 16.10



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- Experiments by Matthew Meselson and Franklin Stahl supported the semiconservative 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

Figure 16.12

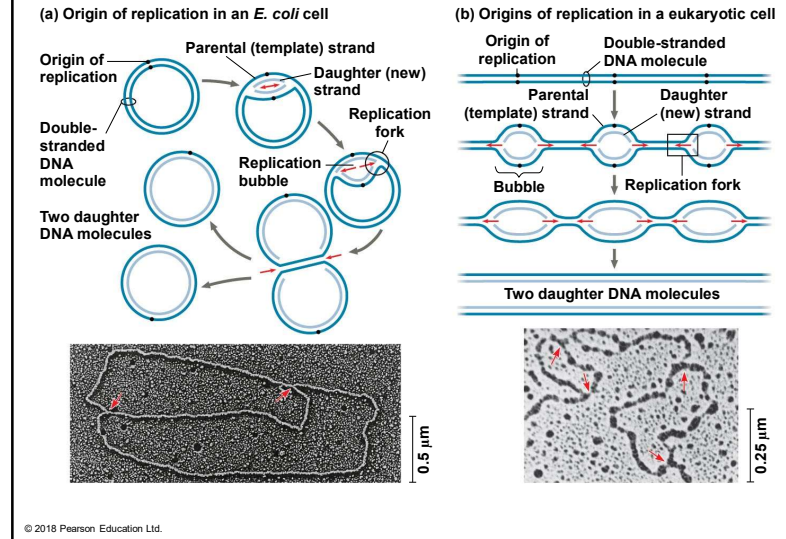


Figure 16.12a

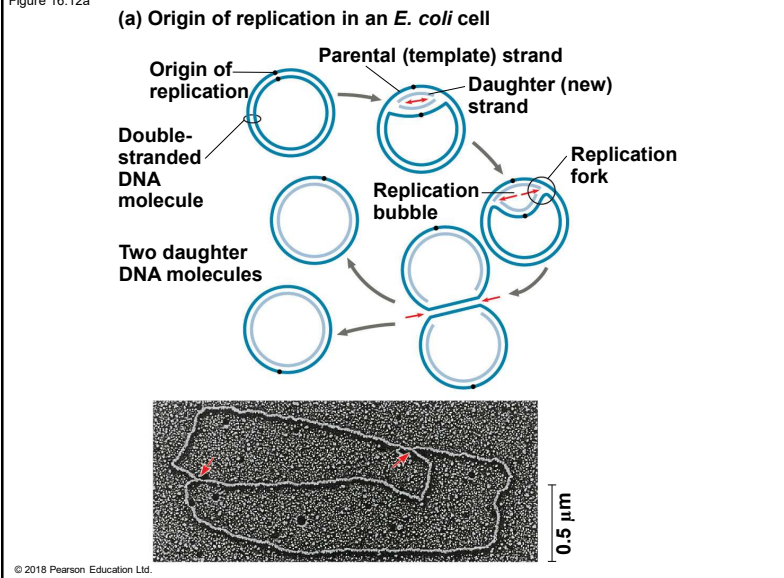


Figure 16.12aa

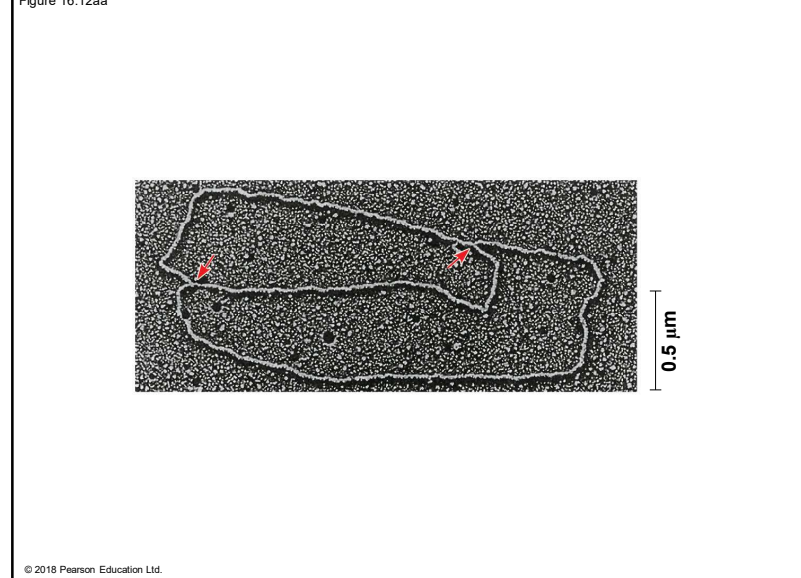
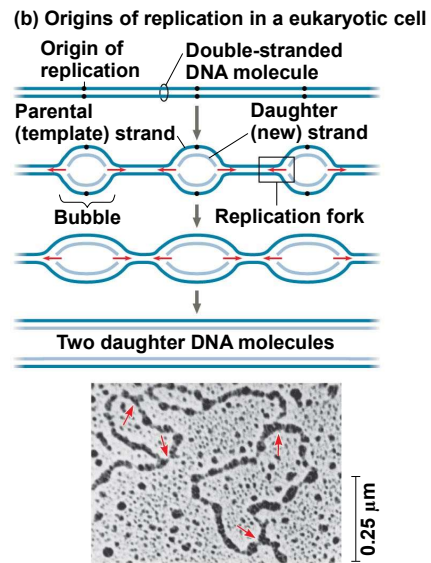
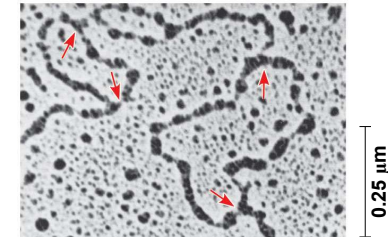


Figure 16.12b



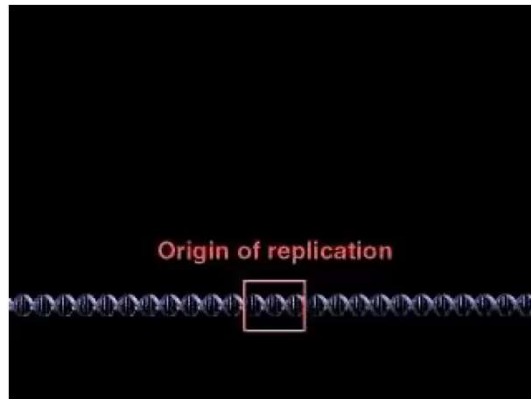
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Figure 16.12ba



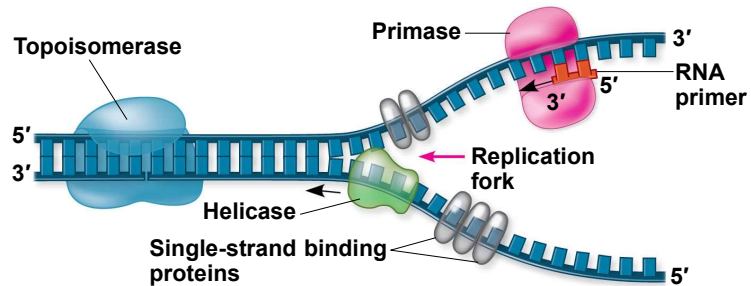
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Animation: Origins of Replication



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

Figure 16.13



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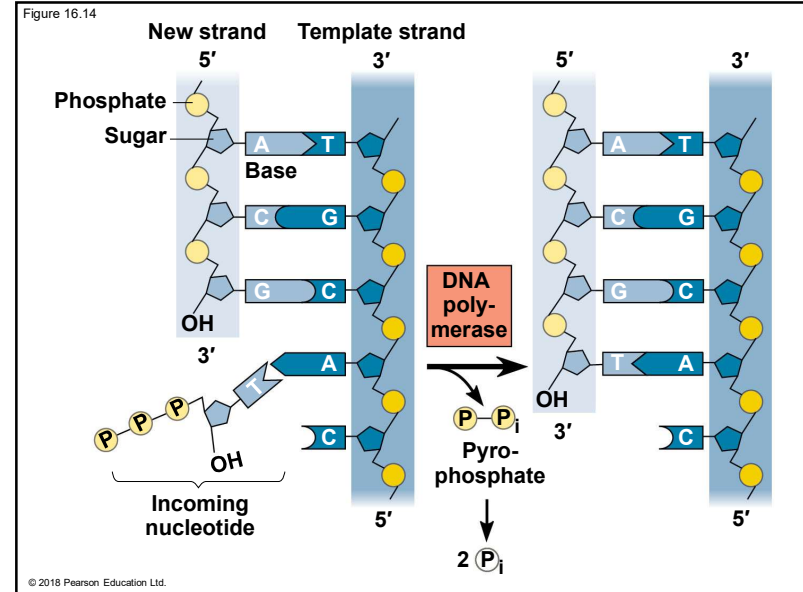
Synthesizing a New DNA Strand

- DNA polymerases require a primer to which they can add nucleotides
- The initial nucleotide strand is a short RNA **primer**
- This is synthesized by the enzyme **primase**

- 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

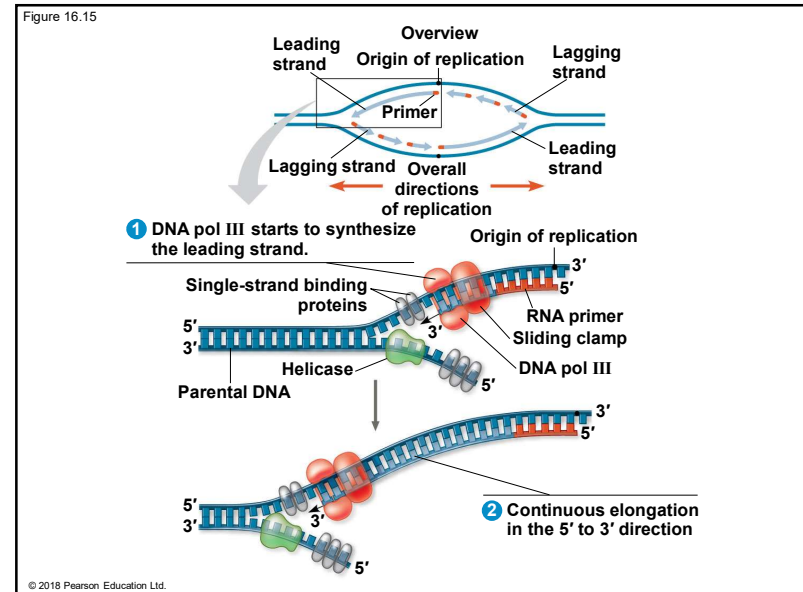
- Enzymes called **DNA polymerases** catalyze the synthesis of new DNA at a replication fork
- Most DNA polymerases require a primer and a DNA template strand
- The rate of elongation is about 500 nucleotides per second in bacteria and 50 per second in human cells

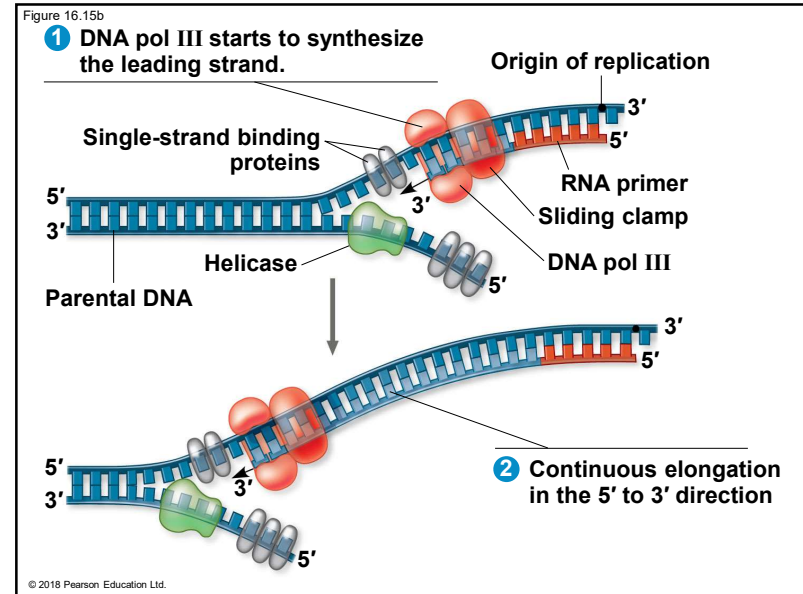
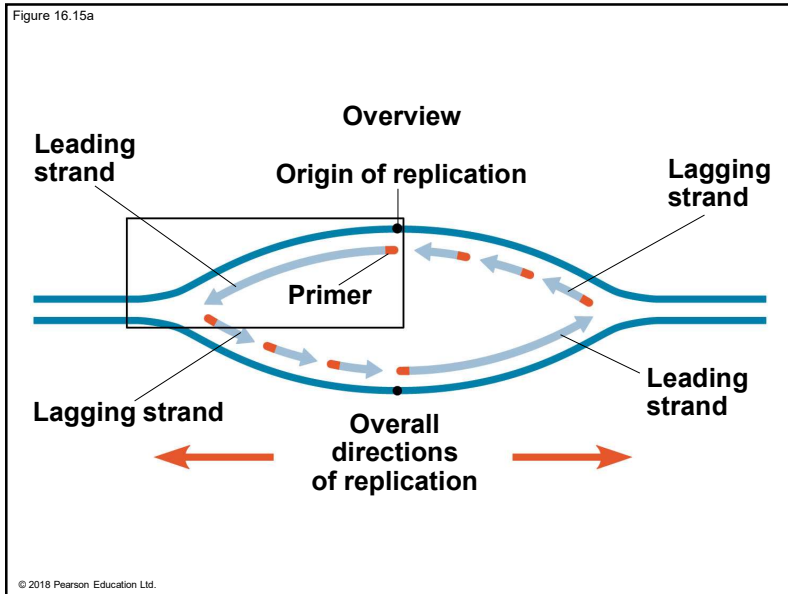
- Each nucleotide that is added to a growing DNA strand is a nucleoside triphosphate
- dATP supplies adenine to DNA and is similar to the ATP of energy metabolism
- The difference is in their sugars: dATP has deoxyribose while ATP has ribose
- As each monomer joins the DNA strand, via a dehydration reaction,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



Antiparallel Elongation

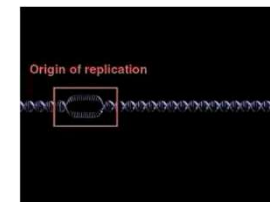
- The antiparallel structure of the double helix affects replication
- DNA polymerases add nucleotides only to the free 3' end of a growing strand; therefore, a new DNA strand can elongate only in the 5' to 3' direction





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

Animation: Leading Strand



- 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**

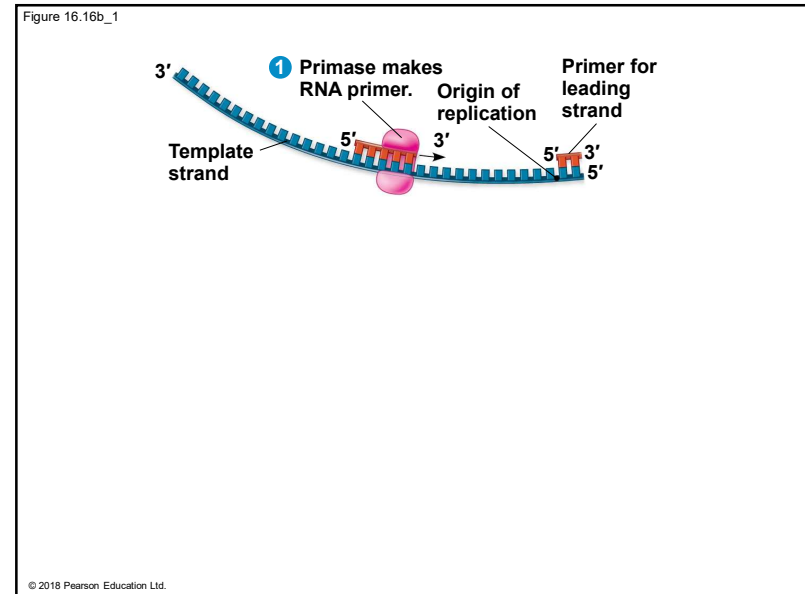
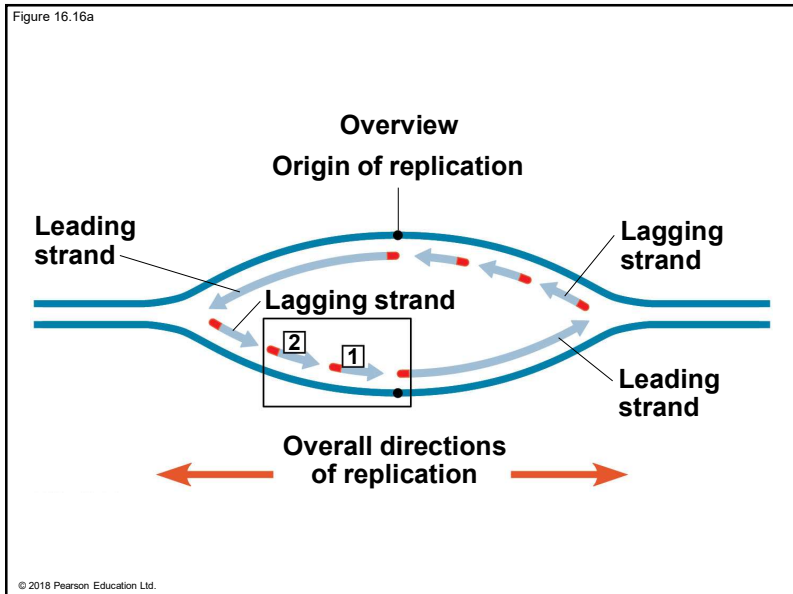
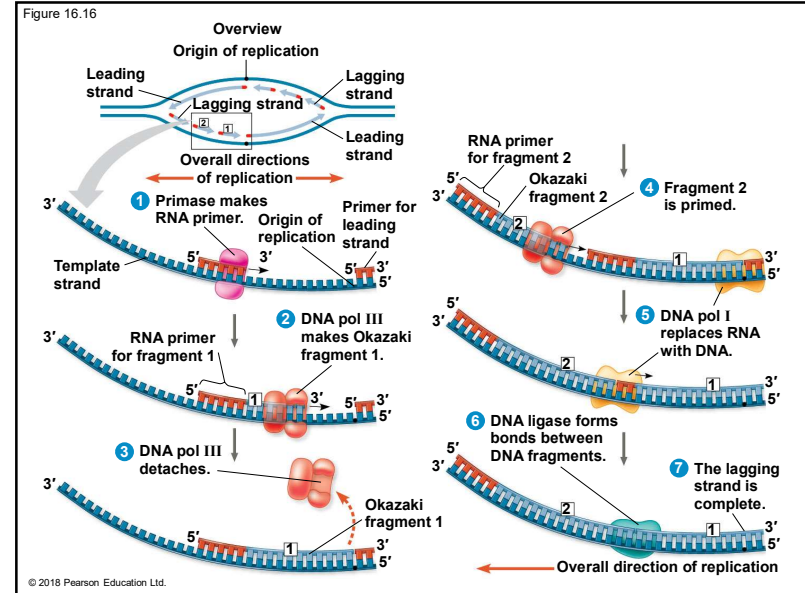
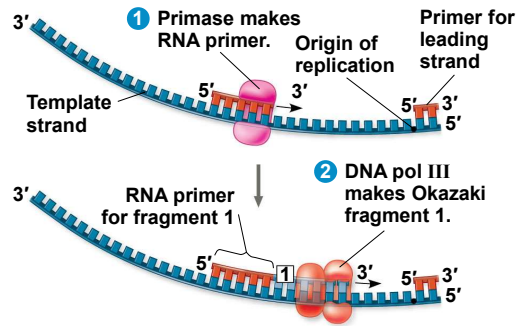
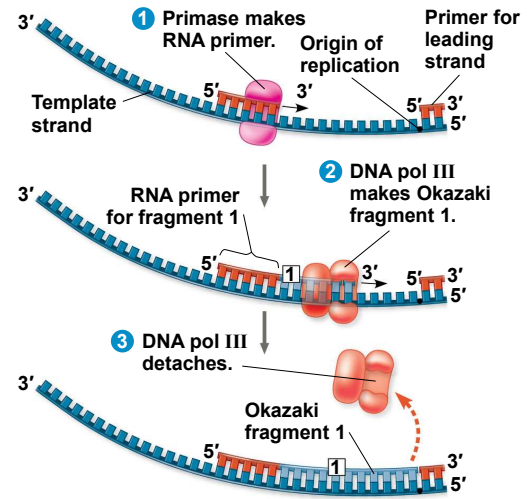


Figure 16.16b_2



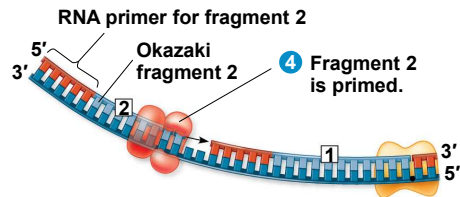
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Figure 16.16b_3



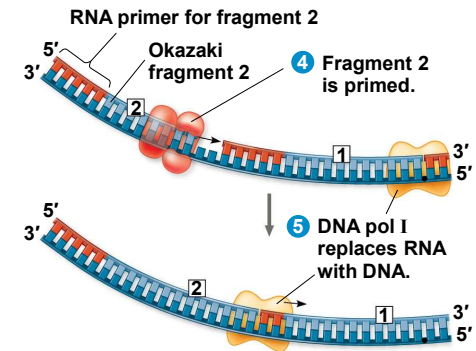
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Figure 16.16c_1



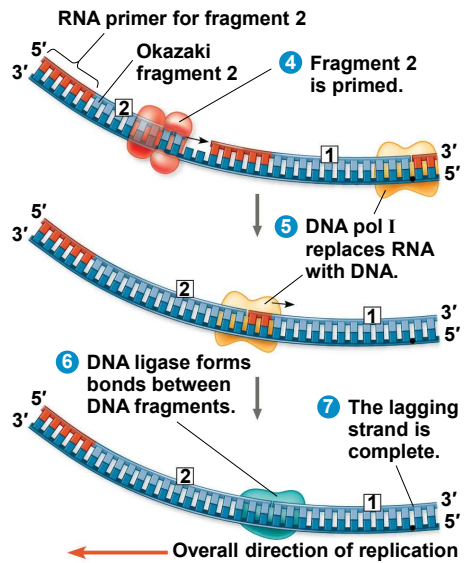
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Figure 16.16c_2



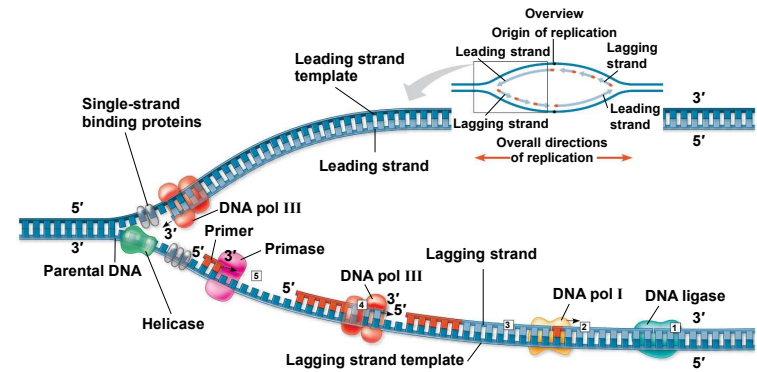
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Figure 16.16c_3



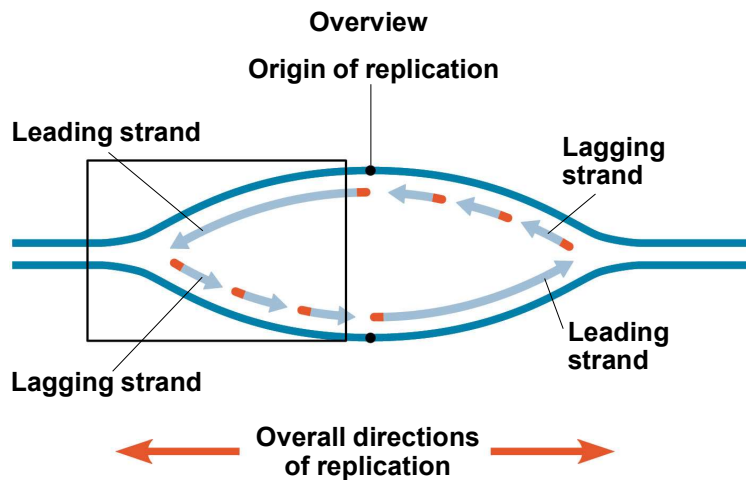
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Figure 16.17



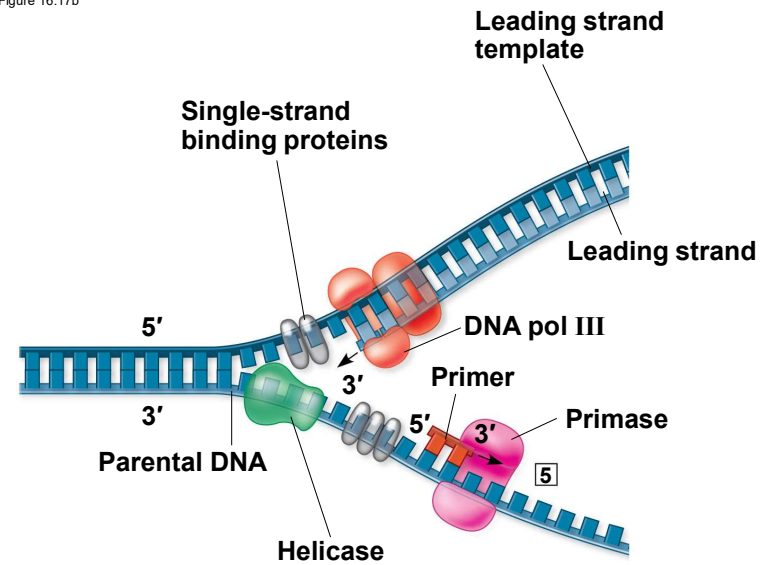
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Figure 16.17a



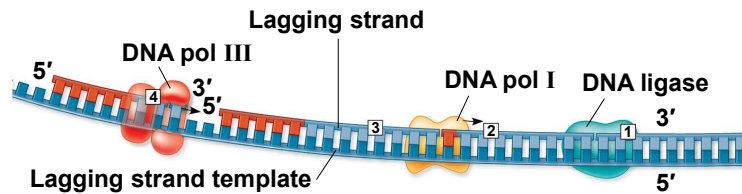
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Figure 16.17b



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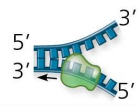



Figure 16.17c



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Table 16.1a

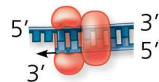


Table 16.1 Bacterial DNA Replication Proteins and Their Functions

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 3' end of leading strand and at 3' end of each Okazaki fragment of lagging strand

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Table 16.1b

Table 16.1 Bacterial DNA Replication Proteins and Their Functions

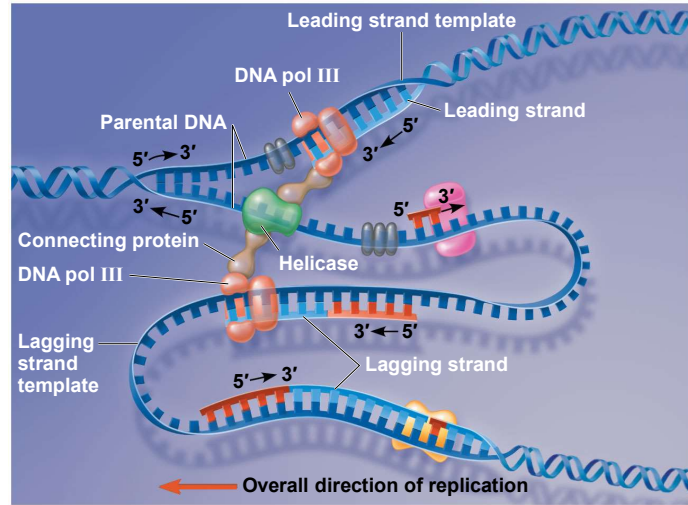
Protein	Function
DNA pol III 	Using parental DNA as a template, synthesizes new DNA strand by adding nucleotides to an RNA primer or a pre-existing DNA strand
DNA pol I 	Removes RNA nucleotides of primer from 5' end and replaces them with DNA nucleotides added to 3' end of adjacent fragment
DNA ligase 	Joins Okazaki fragments of lagging strand; on leading strand, joins 3' end of DNA that replaces primer to rest of leading strand DNA

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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
- The exact mechanism is not yet resolved

Figure 16.18

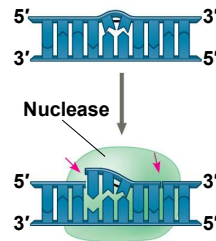


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Proofreading and Repairing DNA

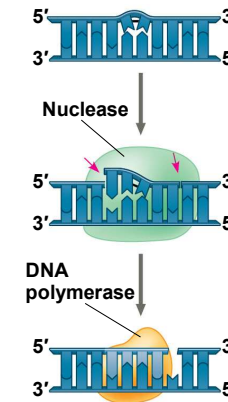
- DNA polymerases proofread newly made DNA, replacing any incorrect nucleotides
- In **mismatch repair** of DNA, repair enzymes correct errors in base pairing
- DNA can be damaged by exposure to harmful chemical or physical agents such as cigarette smoke and X-rays; it can also undergo spontaneous changes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

Figure 16.19_1



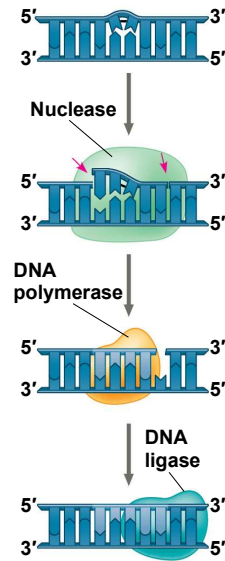
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Figure 16.19_2



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Figure 16.19_3

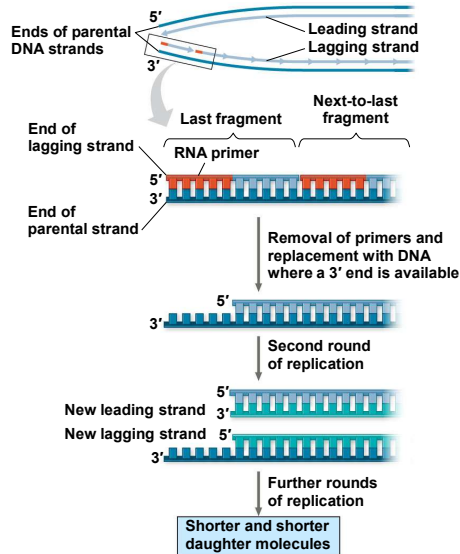


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Replicating the Ends of DNA Molecules

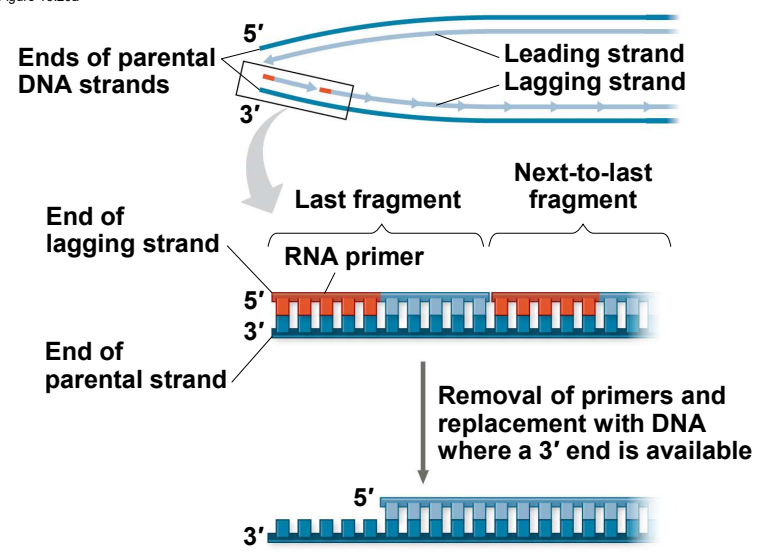
- Limitations of DNA polymerase create problems for the linear DNA of eukaryotic chromosomes
- The usual replication machinery provides no way to complete the 5' ends, so repeated rounds of replication produce shorter DNA molecules with uneven ends
- This is not a problem for prokaryotes, most of which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

Figure 16.20



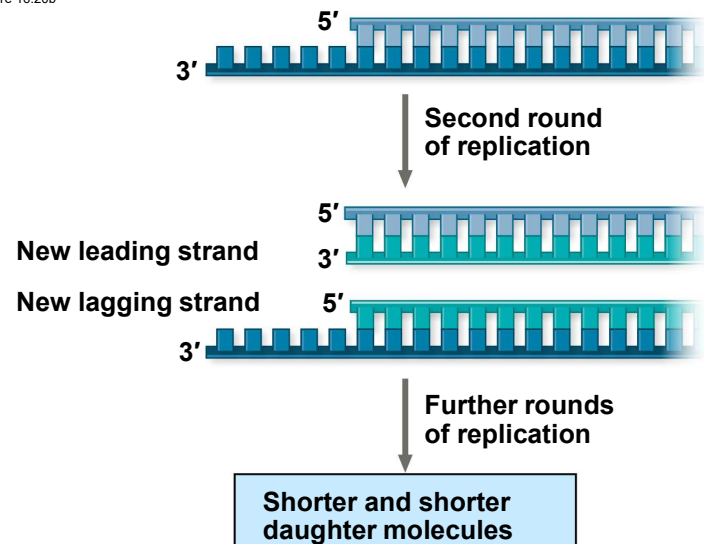
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Figure 16.20a



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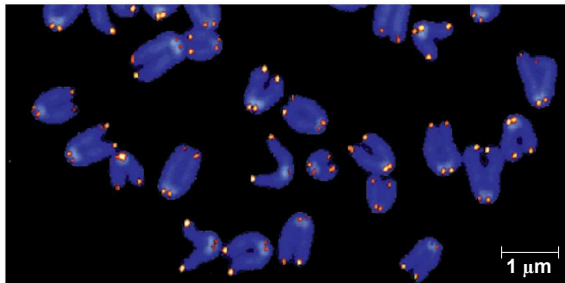
Figure 16.20b



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- 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



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- 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

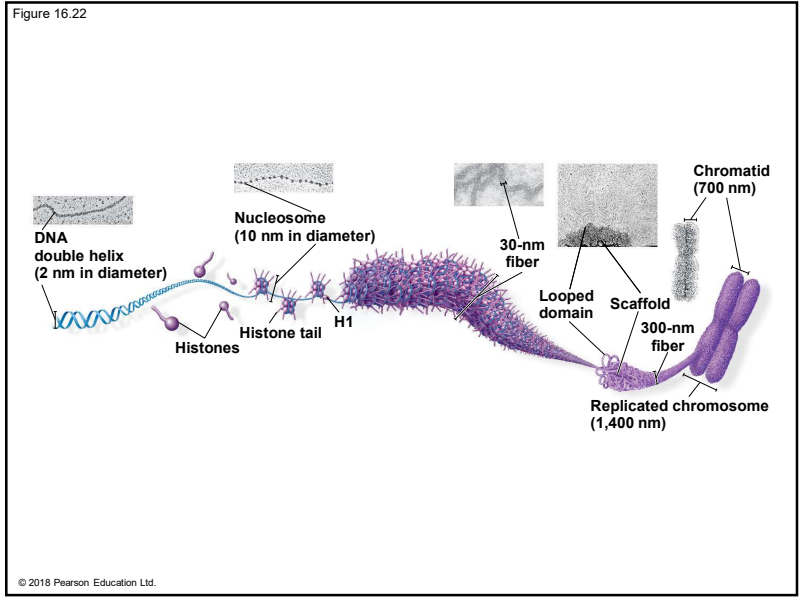
Concept 16.3: A chromosome consists of a DNA molecule packed together with proteins

- 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

- In the eukaryotic cell, DNA is precisely combined with proteins in a complex called **chromatin**
- Chromosomes fit into the nucleus through an elaborate, multilevel system of packing
- Proteins called **histones** are responsible for the first level of packing in chromatin

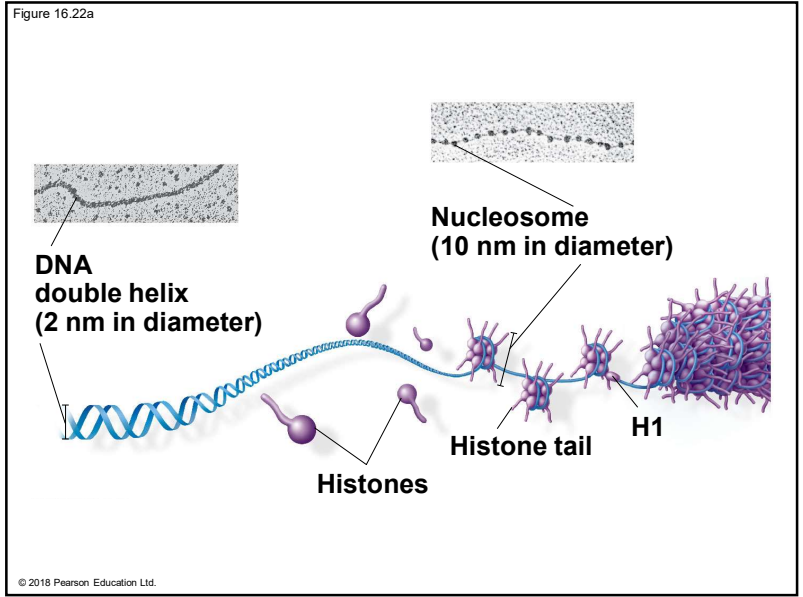
- Unfolded chromatin resembles beads on a string, with each “bead” being a **nucleosome**, the basic unit of DNA packaging
- They are composed of two each of the four basic histone types, with DNA wrapped twice around the core of the eight histones
- The N-termini (“tails”) of the histones protrude from the nucleosome
- Nucleosomes, and especially their histone tails, are involved in the regulation of gene expression

Figure 16.22



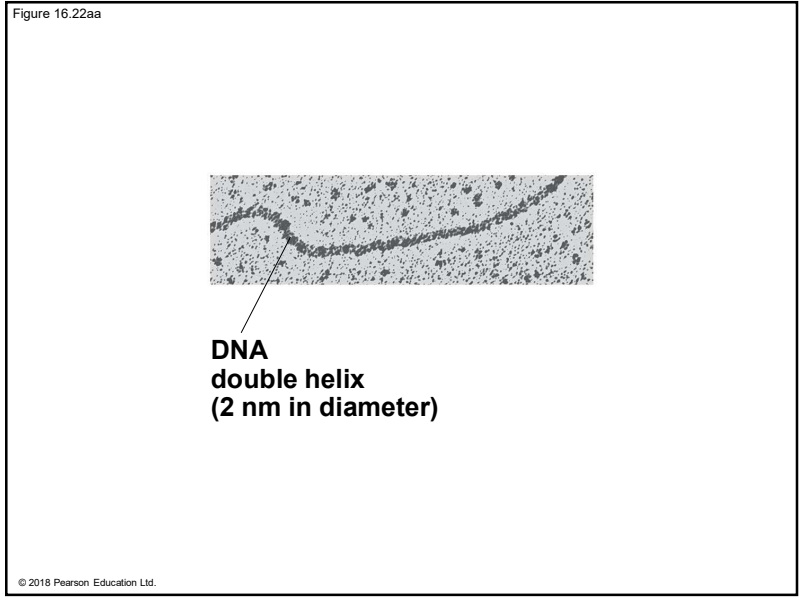
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Figure 16.22a



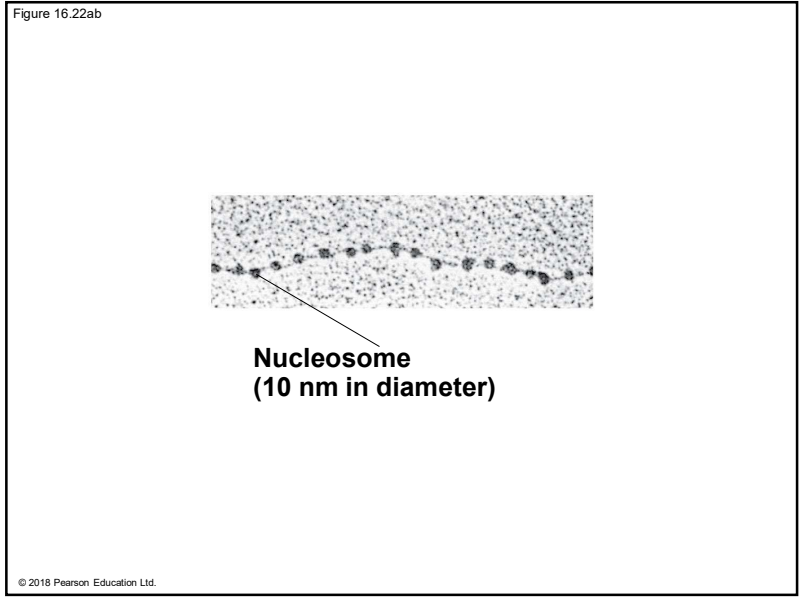
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Figure 16.22aa

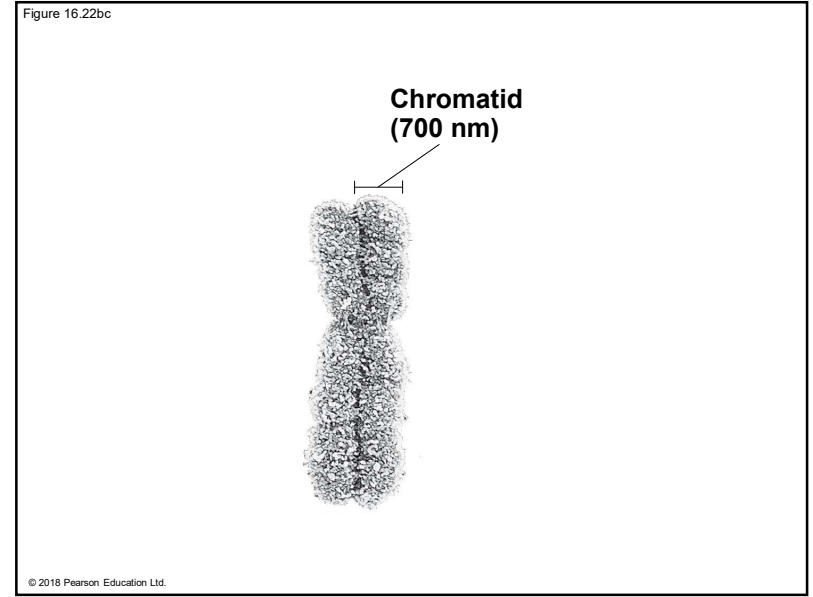
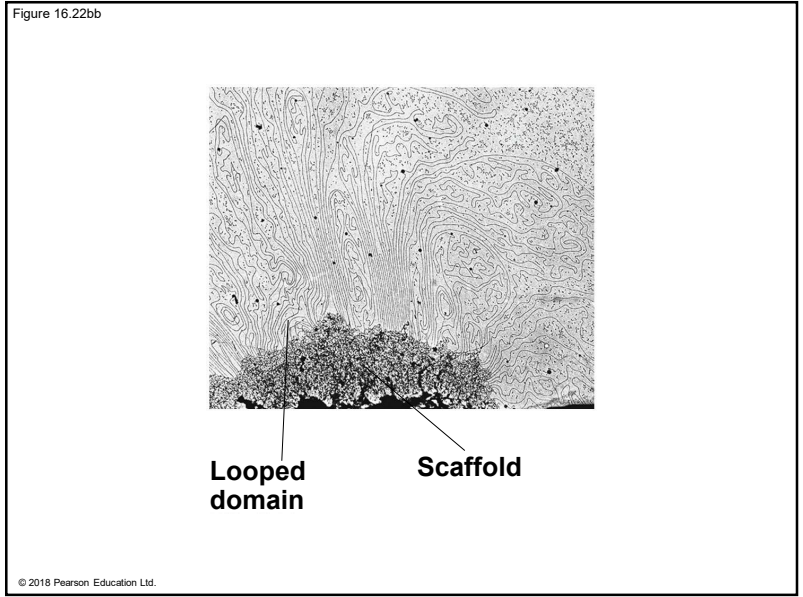
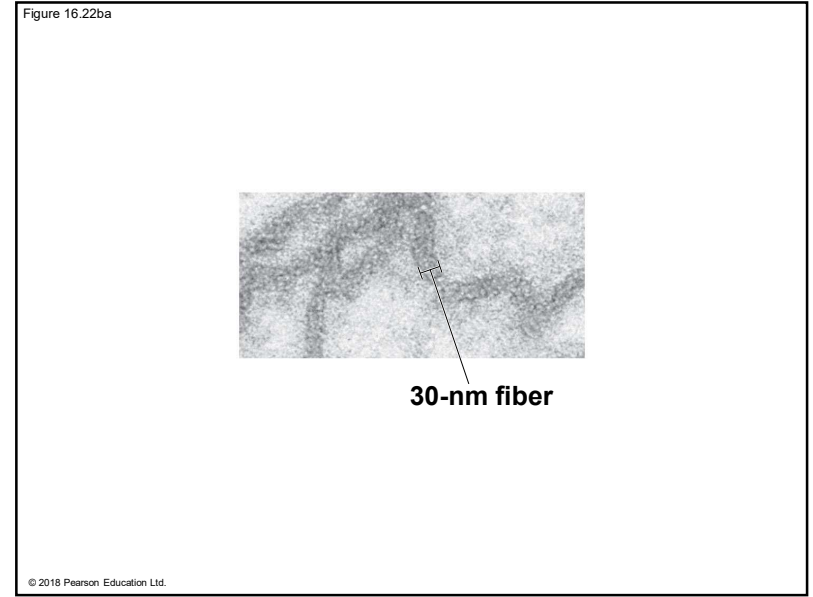
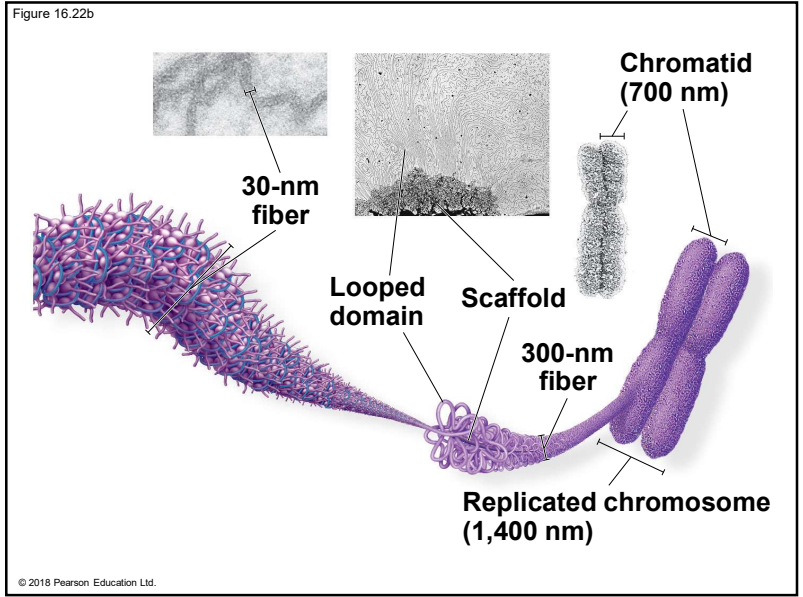


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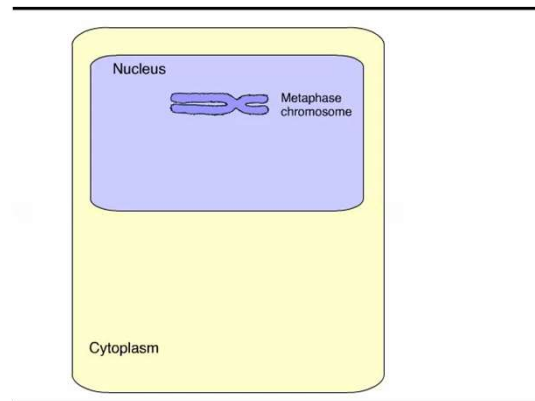
Figure 16.22ab



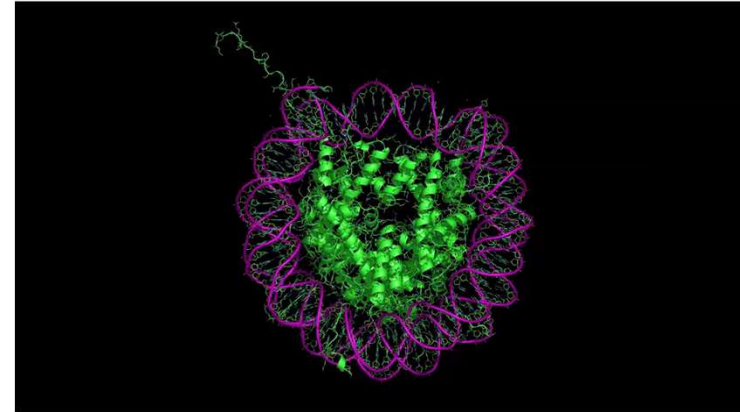
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Animation: DNA Packing

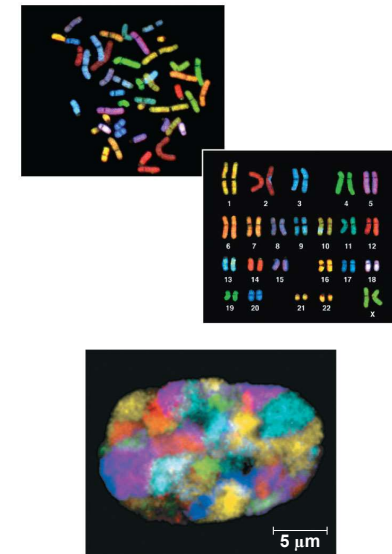


Video: Cartoon and Stick Model of a Nucleosomal Particle



- Chromatin undergoes changes in packing during the cell cycle
- At interphase, some chromatin seems to be organized into a 10-nm fiber, but much is compacted into a 30-nm fiber, through folding and looping
- Interphase chromosomes occupy specific restricted regions in the nucleus, and the fibers of different chromosomes do not become entangled

Figure 16.23



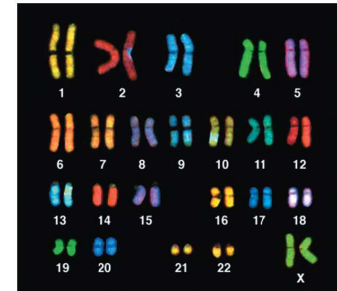
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Figure 16.23a



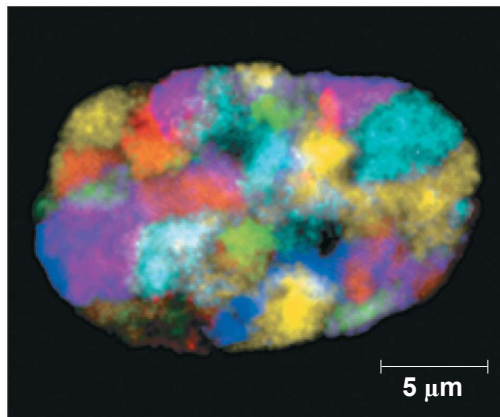
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Figure 16.23b



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Figure 16.23c



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- 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 condensation
- These changes can also have multiple effects on gene expression