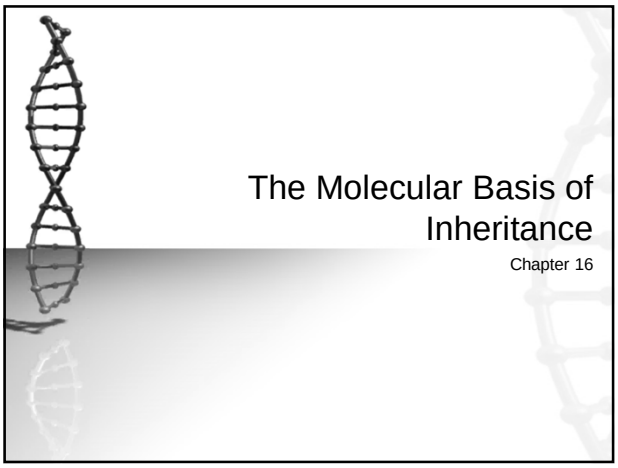

The Molecular Basis of Inheritance

Chapter 16

- Objectives
  - Describe the contributions of the following people: Griffith; Avery, McCary, and MacLeod; Hershey and Chase; Chargaff; Watson and Crick; Franklin; Meselson and Stahl
  - Describe the structure of DNA
  - Describe the process of DNA replication; include the following terms: antiparallel structure, DNA polymerase, leading strand, lagging strand, Okazaki fragments, DNA ligase, primer, primase, helicase, topoisomerase, single-strand binding proteins
  - Describe the function of telomeres

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Introduction

- In 1953, James Watson and Francis Crick shook the world with an elegant double-helical model for the structure of deoxyribonucleic acid, or DNA

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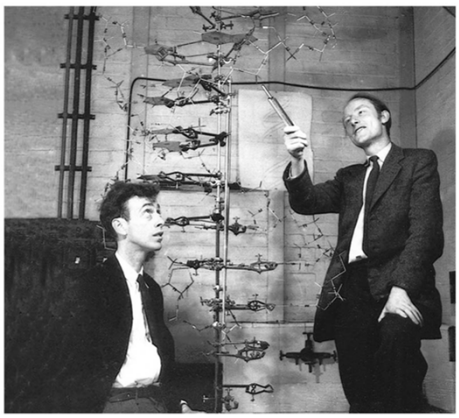

- DNA, the substance of inheritance is the most celebrated molecule of our time
- Hereditary information is encoded in the chemical language of DNA and reproduced in all the cells of your body
- It is the DNA program that directs the development of many different types of traits

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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 role of DNA in heredity was first worked out by studying bacteria and the viruses that infect them

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Evidence That DNA Can Transform Bacteria

- Frederick Griffith was studying *Streptococcus pneumoniae* a bacterium that causes pneumonia in mammals
- He worked with two strains of the bacterium, a pathogenic strain and a nonpathogenic strain
- Griffith found that when he mixed heat-killed remains of the pathogenic strain with living cells of the nonpathogenic strain, some of these living cells became pathogenic

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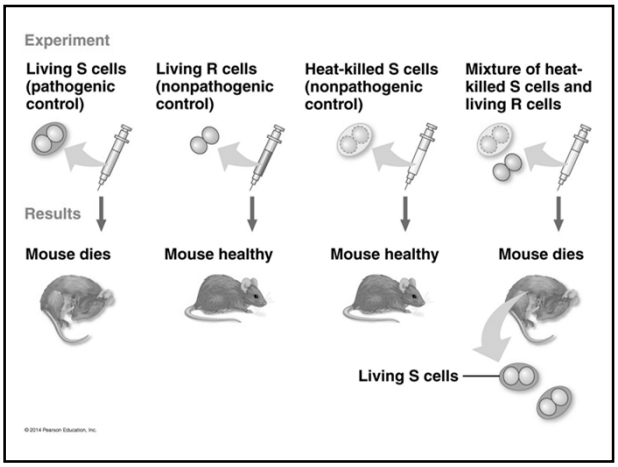

- Griffith called the phenomenon transformation
  - It is now defined as a change in genotype and phenotype due to the assimilation of external DNA by a cell
- In the early 1940's Avery, McCarty, and MacLeod extended Griffith's work
  - They demonstrated that transformation was most likely due to the transfer of DNA from one cell type to the other

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Evidence That Viral DNA Can Program Cells

- Additional evidence for DNA as the genetic material came from studies of a virus that infects bacteria
- Viruses that infect bacteria, bacteriophages, are widely used as tools by researchers in molecular genetics

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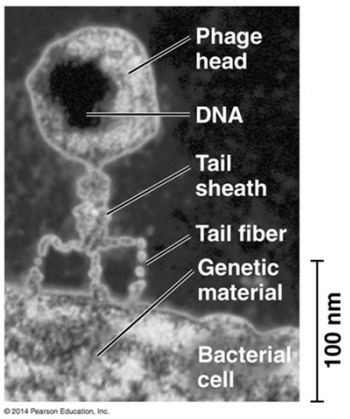

- Alfred Hershey and Martha Chase performed experiments showing that DNA is the genetic material of a phage known as T2

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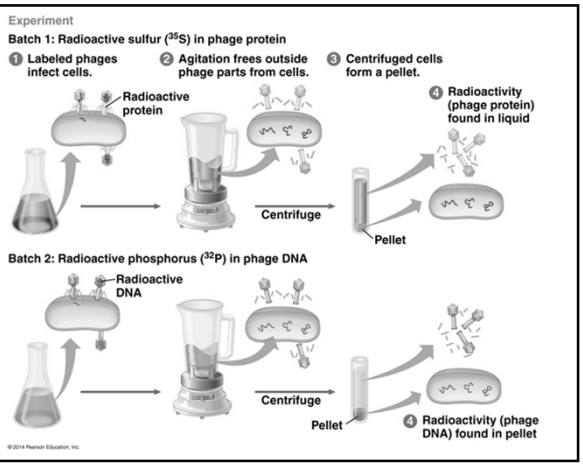

Additional Evidence That DNA Is the Genetic Material

- Prior to the 1950s, it was already known that DNA is a polymer of nucleotides, each consisting of three components: a nitrogenous base, a sugar, and a phosphate group

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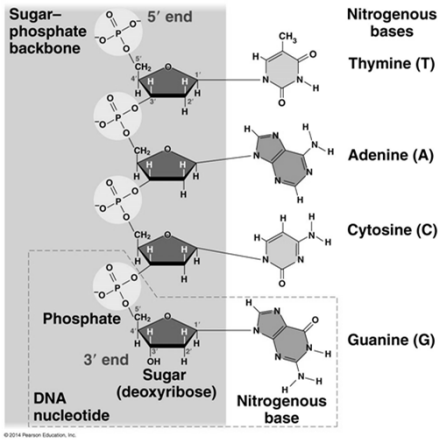

- Erwin Chargaff analyzed the base composition of DNA from a number of different organisms
- In 1947, Chargaff reported that DNA composition varies from one species to the next
- This evidence of molecular diversity among species made DNA a more credible candidate for the genetic material

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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

Building a Structural Model of DNA

- Once most biologists were convinced that DNA was the genetic material the challenge was to determine how the structure of DNA could account for its role in inheritance
- Maurice Wilkins and Rosalind Franklin were using a technique called X-ray crystallography to study molecular structure
- Rosalind Franklin produced a picture of the DNA molecule using this technique

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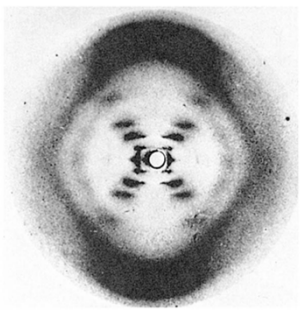
(a) Rosalind Franklin



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

- Watson and Crick deduced that DNA was a double helix through observations of the X-ray crystallographic images of DNA
- Franklin had concluded that DNA was composed of two antiparallel sugar-phosphate backbones, with the nitrogenous bases paired in the molecule's interior
  - The nitrogenous bases are paired in specific combinations: adenine with thymine, and cytosine with guanine

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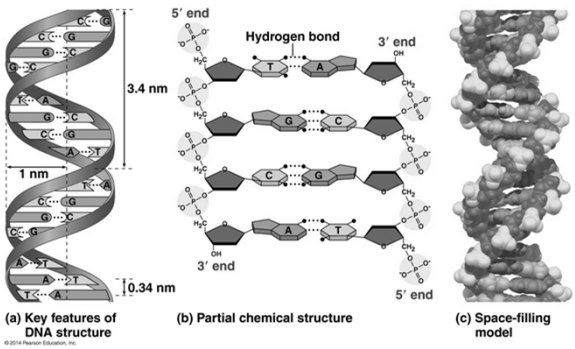

(a) Key features of DNA structure

(b) Partial chemical structure

(c) Space-filling model

- Watson and Crick reasoned that there must be additional specificity of pairing dictated by the structure of the bases
- Each base pair forms a different number of hydrogen bonds
  - Adenine and thymine form two bonds, cytosine and guanine form three bonds

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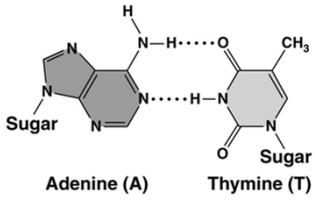

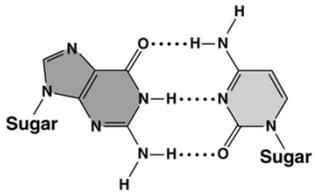

The Basic Principle of DNA Replication

- 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

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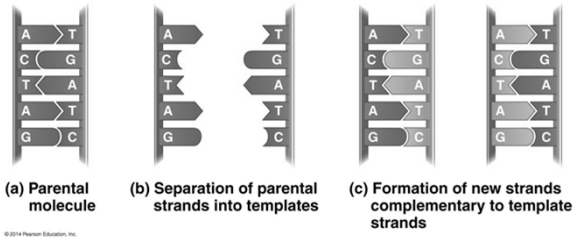

- DNA replication is semiconservative
  - Each of the two new daughter molecules will have one old strand, derived from the parent molecule, and one newly made strand
- Two other models possible
  - Conservative
  - Dispersive

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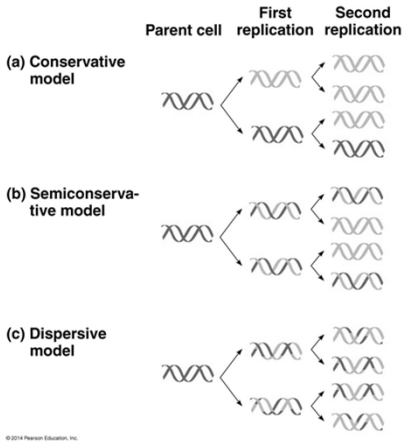

- Experiments performed by Meselson and Stahl supported the semiconservative model of DNA replication

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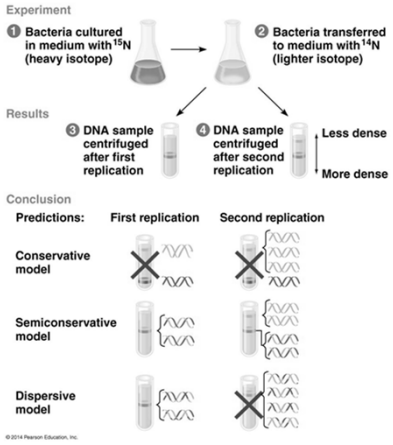

DNA Replication: A Closer Look

- The copying of DNA is remarkable in its speed and accuracy
  - Prokaryotes copy DNA at the rate of 500 nucleotides per second
  - Errors occur one in every 1 billion nucleotides added
- More than a dozen enzymes and other proteins participate in DNA replication

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Getting Started: Origins of Replication

- The replication of a DNA molecule begins at special sites called origins of replication, where the two strands are separated
- A eukaryotic chromosome may have hundreds or even thousands of replication origins

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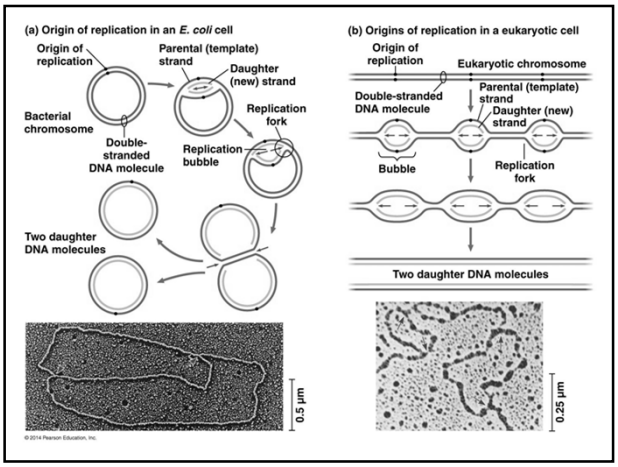

- At the end of each replication bubble is a replication fork, a Y-shaped region where new DNA strands are elongating
  - helicases are enzymes that untwist the double helix at the replication forks
  - single-strand binding proteins bind to and stabilize single-stranded DNA
  - topoisomerase corrects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

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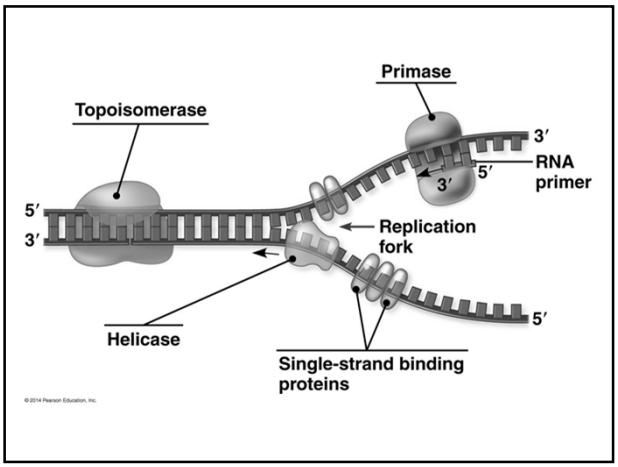

Elongating a New DNA Strand

- Elongation of new DNA at a replication fork is catalyzed by enzymes called DNA polymerases, which add nucleotides to the 3′ end of a growing strand

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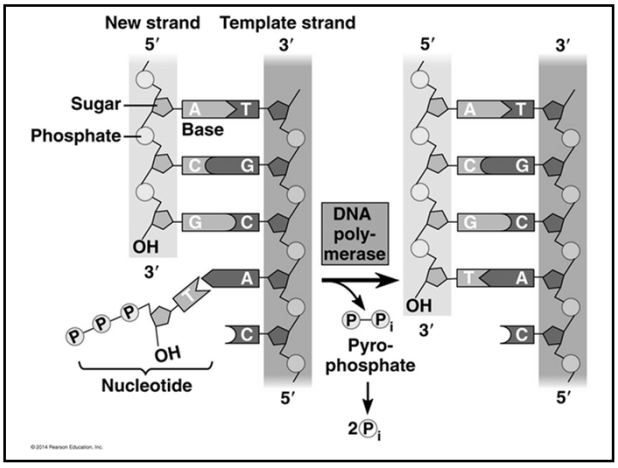

Antiparallel Elongation

- How does the antiparallel structure of the double helix affect replication?
- DNA polymerases add nucleotides only to the free 3′ end of a growing strand
- Along one template strand of DNA, the leading strand, DNA polymerase III can synthesize a complementary strand continuously, moving toward the replication fork

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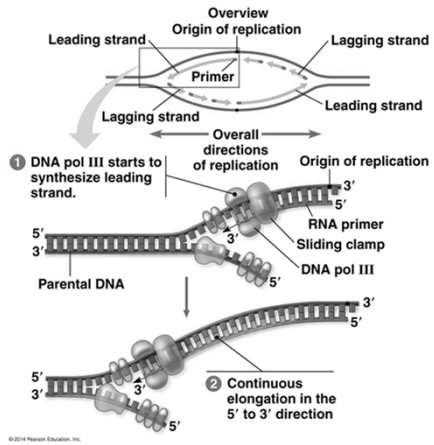

- To elongate the other new strand of DNA, the lagging strand, DNA polymerase III must work in the direction away from the replication fork
- The lagging strand is synthesized as a series of segments called Okazaki fragments, which are then joined together by DNA ligase

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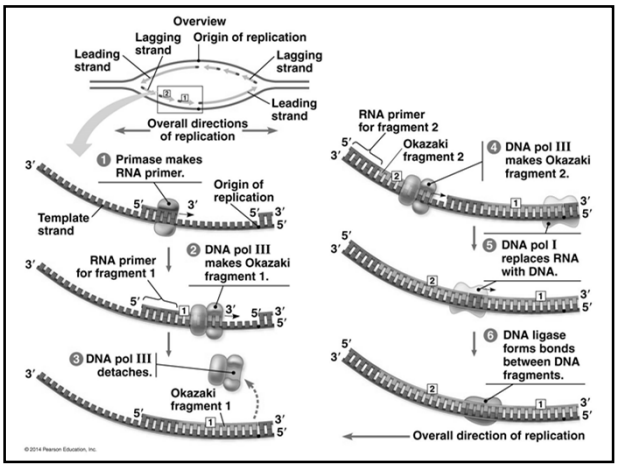

Priming DNA Synthesis

- DNA polymerases cannot initiate the synthesis of a polynucleotide, they can only add nucleotides to the 3′ end
- The initial nucleotide strand is an RNA or DNA primer
- Only one primer is needed for synthesis of the leading strand but for synthesis of the lagging strand, each Okazaki fragment must be primed separately

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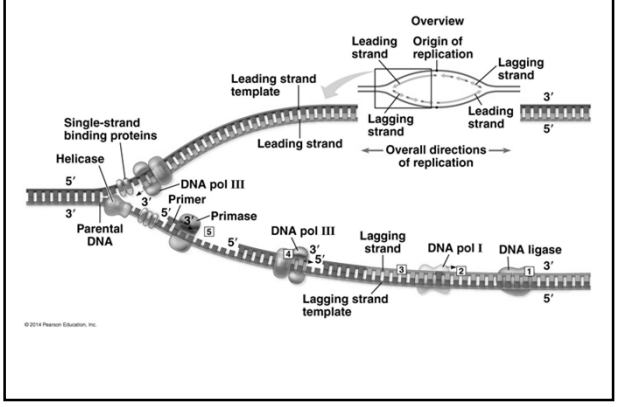

Table 16.1 Bacterial DNA Replication Proteins and Their Functions

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 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
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

The DNA Replication Machine as a Stationary Complex

- The various proteins that participate in DNA replication form a single large complex, a DNA replication "machine"
- The DNA replication machine is probably 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

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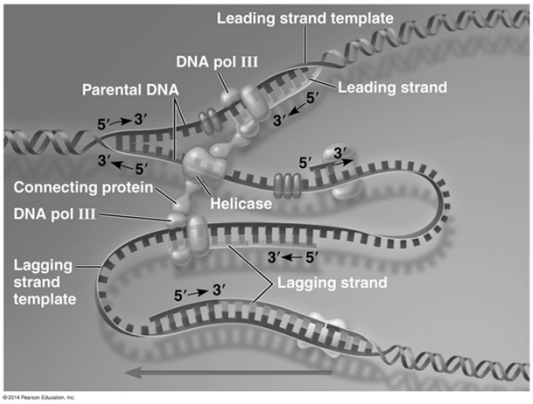

Proofreading and Repairing DNA

- DNA polymerases proofread newly made DNA replacing any incorrect nucleotides
- In mismatch repair of DNA repair enzymes correct errors in base pairing
- In nucleotide excision repair enzymes cut out and replace damaged stretches of DNA

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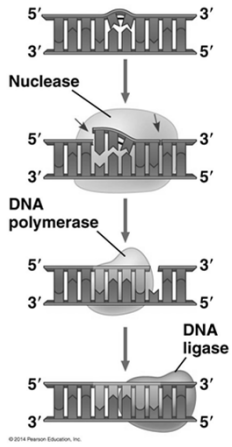

Replicating the Ends of DNA Molecules

- The ends of eukaryotic chromosomal DNA get shorter with each round of replication

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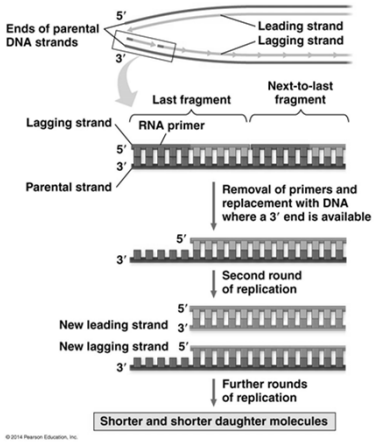

- Eukaryotic chromosomal DNA molecules have at their ends nucleotide sequences, called telomeres, that postpone the erosion of genes near the ends of DNA molecules
  - If the chromosomes of germ cells became shorter in every cell cycle essential genes would eventually be missing from the gametes they produce
  - An enzyme called telomerase catalyzes the lengthening of telomeres in germ cells

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DNA Packaging

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

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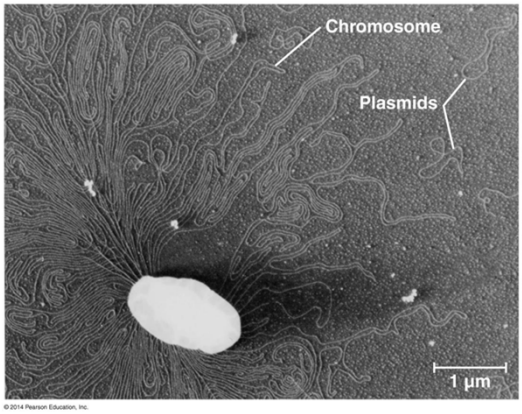

- Eukaryotic chromosomes have linear DNA molecules associated with a large amount of protein
  - DNA is precisely combined with proteins in a complex called **chromatin**
  - chromosomes fit into the nucleus through an elaborate, multilevel system of packing

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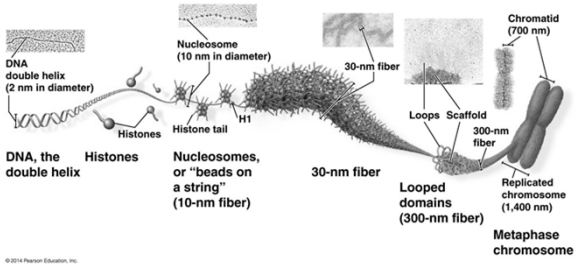

- Chromatin undergoes changes in packing during the cell cycle
  - at interphase, some chromatin is organized into a 10-nm fiber, but much is compacted into a 30-nm fiber, through folding and looping
  - interphase chromosomes occupy specific restricted regions in the nucleus and the fibers of different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

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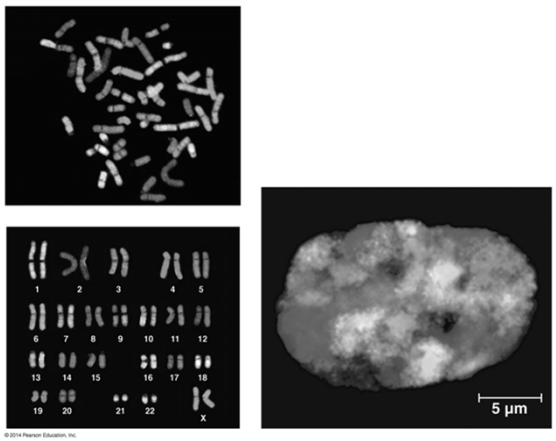

- Most chromatin is loosely packed in the nucleus during interphase and condenses prior to mitosis
  - loosely packed chromatin is called **euchromatin**
- During interphase a few regions of chromatin (centromeres and telomeres) are highly condensed into **heterochromatin**
  - dense packing of the heterochromatin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

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