Part IV

Reproduction and Heredity

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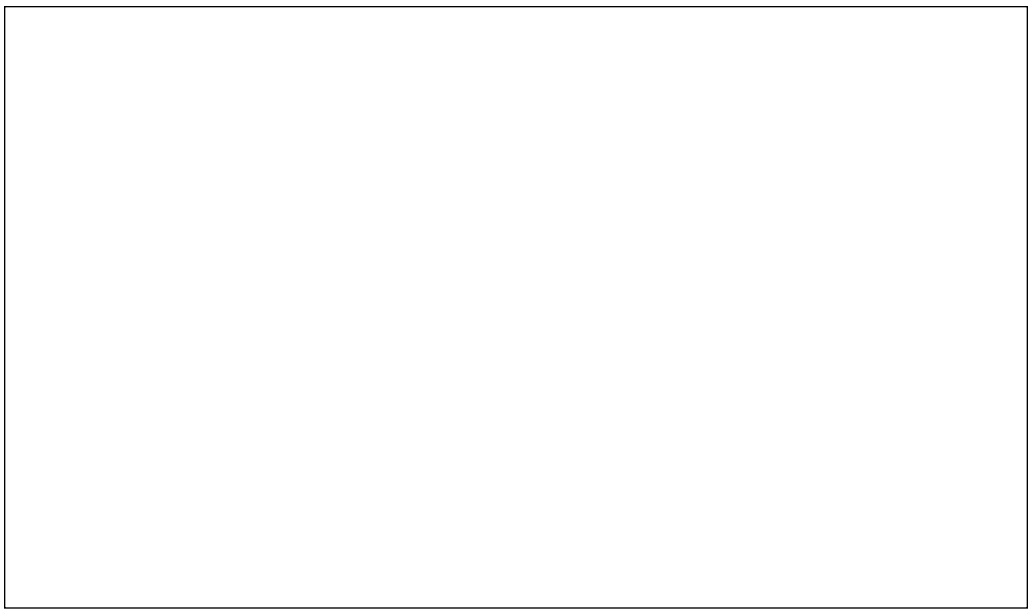

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11

How Cells Divide

Concept Outline

11.1 Bacteria divide far more simply than do eukaryotes.

Cell Division in Prokaryotes. Bacterial cells divide by splitting in two.

11.2 Chromosomes are highly ordered structures.

Discovery of Chromosomes. All eukaryotic cells contain chromosomes, but different organisms possess differing numbers of chromosomes.

The Structure of Eukaryotic Chromosomes. Proteins play an important role in packaging DNA in chromosomes.

11.3 Mitosis is a key phase of the cell cycle.

Phases of the Cell Cycle. The cell cycle consists of three growth phases, a nuclear division phase, and a cytoplasmic division stage.

Interphase: Preparing for Mitosis. In interphase, the cell grows, replicates its DNA, and prepares for cell division.

Mitosis. In prophase, the chromosomes condense and microtubules attach sister chromosomes to opposite poles of the cell. In metaphase, chromosomes align along the center of the cell. In anaphase, the chromosomes separate; in telophase the spindle dissipates and the nuclear envelope reforms.

Cytokinesis. In cytokinesis, the cytoplasm separates into two roughly equal halves.

11.4 The cell cycle is carefully controlled.

General Strategy of Cell Cycle Control. At three points in the cell cycle, feedback from the cell determines whether the cycle will continue.

Molecular Mechanisms of Cell Cycle Control. Special proteins regulate the "checkpoints" of the cell cycle.

Cancer and the Control of Cell Proliferation. Cancer results from damage to genes encoding proteins that regulate the cell division cycle.

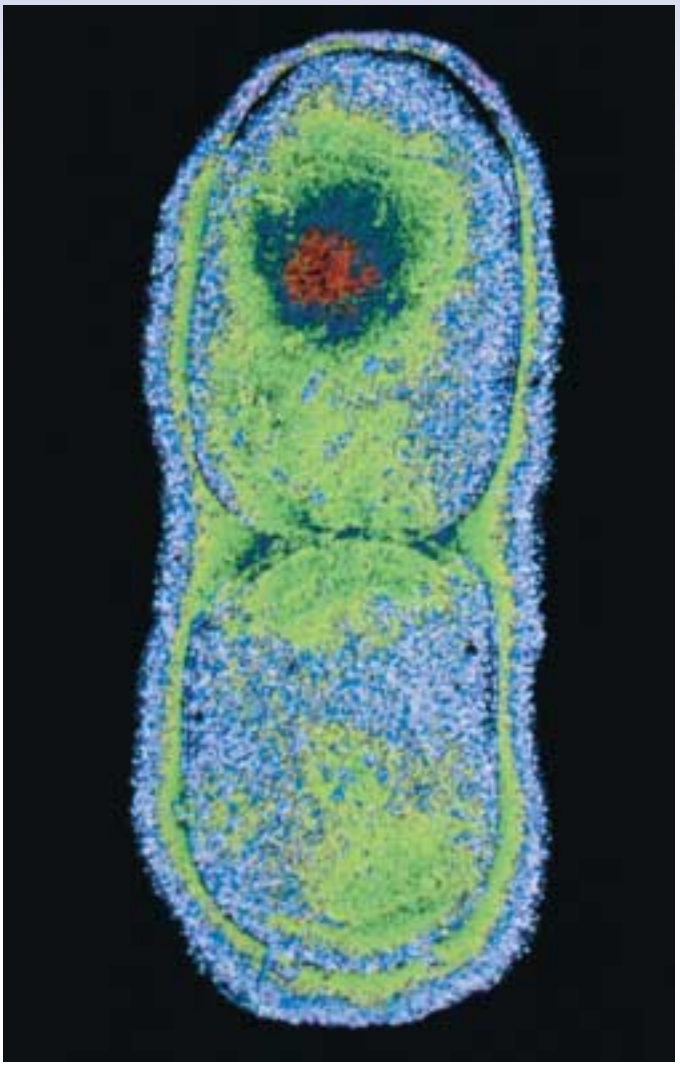


FIGURE 11.1
Cell division in bacteria. It's hard to imagine fecal coliform bacteria as beautiful, but here is *Escherichia coli*, inhabitant of the large intestine and the biotechnology lab, spectacularly caught in the act of fission.

All species of organisms—bacteria, alligators, the weeds in a lawn—grow and reproduce. From the smallest of creatures to the largest, all species produce offspring like themselves and pass on the hereditary information that makes them what they are. In this chapter, we begin our consideration of heredity with an examination of how cells reproduce (figure 11.1). The mechanism of cell reproduction and its biological consequences have changed significantly during the evolution of life on earth.

11.1 Bacteria divide far more simply than do eukaryotes.

Cell Division in Prokaryotes

In bacteria, which are prokaryotes and lack a nucleus, cell division consists of a simple procedure called **binary fission** (literally, "splitting in half"), in which the cell divides into two equal or nearly equal halves (figure 11.2). The genetic information, or *genome*, replicates early in the life of the cell. It exists as a single, circular, double-stranded DNA molecule. Fitting this DNA circle into the bacterial cell is a remarkable feat of packaging—fully stretched out, the DNA of a bacterium like *Escherichia coli* is about 500 times longer than the cell itself.

The DNA circle is attached at one point to the cytoplasmic surface of the bacterial cell's plasma membrane. At a specific site on the DNA molecule called the *replication origin*, a battery of more than 22 different proteins begins the process of copying the DNA (figure 11.3). When these enzymes have proceeded all the way around the circle of DNA, the cell possesses two copies of the genome. These "daughter" genomes are attached side-by-side to the plasma membrane.

The growth of a bacterial cell to about twice its initial size induces the onset of cell division. A wealth of recent evidence suggests that the two daughter chromosomes are actively partitioned during this process. As this process proceeds, the cell lays down new plasma membrane and cell wall materials in the zone between the attachment sites of the two daughter genomes. A new plasma membrane grows between the genomes; eventually, it reaches all the way into the center of the cell, dividing it in two. Because the membrane forms between the two genomes, each new cell is assured of retaining one of the genomes. Finally, a new cell wall forms around the new membrane.

The evolution of the eukaryotes introduced several additional factors into the process of cell division. Eukaryotic cells are much larger than bacteria, and their genomes contain much more DNA. Eukaryotic DNA is contained in a number of linear chromosomes, whose organization is much more complex than that of the single, circular DNA molecules in bacteria. In chromosomes, DNA forms a complex with packaging proteins called histones and is wound into tightly condensed coils.

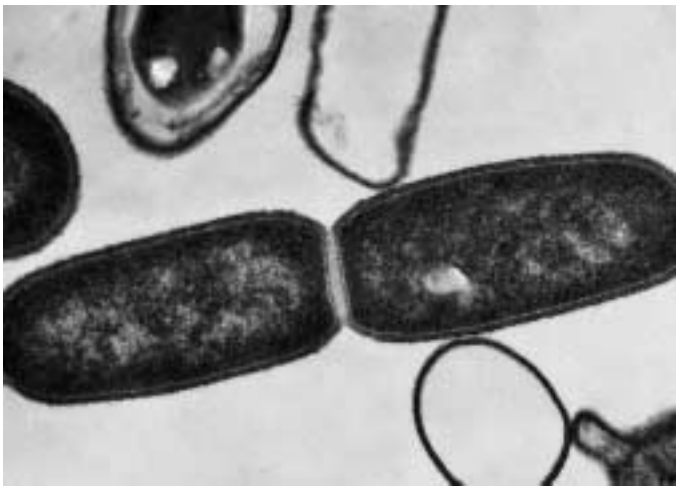


FIGURE 11.2
Fission (40,000×). Bacteria divide by a process of simple cell fission. Note the newly formed plasma membrane between the two daughter cells.

Bacteria divide by binary fission. Fission begins in the middle of the cell. An active partitioning process ensures that one genome will end up in each daughter cell.

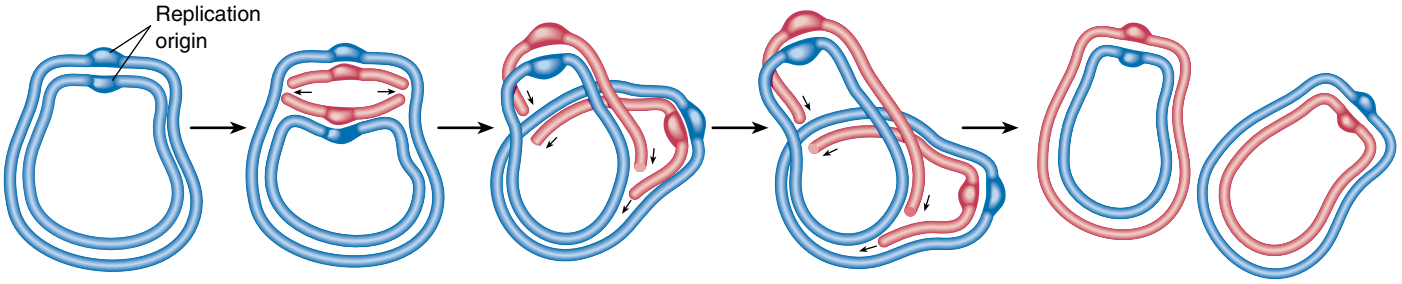


FIGURE 11.3
How bacterial DNA replicates. The replication of the circular DNA molecule (*blue*) that constitutes the genome of a bacterium begins at a single site, called the replication origin. The replication enzymes move out in both directions from that site and make copies (*red*) of each strand in the DNA duplex. When the enzymes meet on the far side of the molecule, replication is complete.

11.2 Chromosomes are highly ordered structures.

Discovery of Chromosomes

Chromosomes were first observed by the German embryologist Walther Fleming in 1882, while he was examining the rapidly dividing cells of salamander larvae. When Fleming looked at the cells through what would now be a rather primitive light microscope, he saw minute threads within their nuclei that appeared to be dividing lengthwise. Fleming called their division **mitosis,** based on the Greek word *mitos*, meaning "thread."

Chromosome Number

Since their initial discovery, chromosomes have been found in the cells of all eukaryotes examined. Their number may vary enormously from one species to another. A few kinds of organisms—such as the Australian ant *Myrmecia*, the plant *Haplopappus gracilis*, a relative of the sunflower that grows in North American deserts; and the fungus *Penicillium*—have only 1 pair of chromosomes, while some ferns have more than 500 pairs (table 11.1). Most eukaryotes have between 10 and 50 chromosomes in their body cells.

Human cells each have 46 chromosomes, consisting of 23 nearly identical pairs (figure 11.4). Each of these 46 chromosomes contains hundreds or thousands of genes that play important roles in determining how a person's body develops and functions. For this reason, possession of all the chromosomes is essential to survival. Humans missing even one chromosome, a condition called monosomy, do not survive embryonic development in most cases. Nor does the human embryo develop properly with an extra copy of any one chromosome, a condition called trisomy. For all but a few of the smallest chromosomes, trisomy is fatal, and even in those few cases, serious problems result. Individuals with an extra copy of the very small chromosome 21, for example, develop more slowly than normal and are mentally retarded, a condition called Down syndrome.

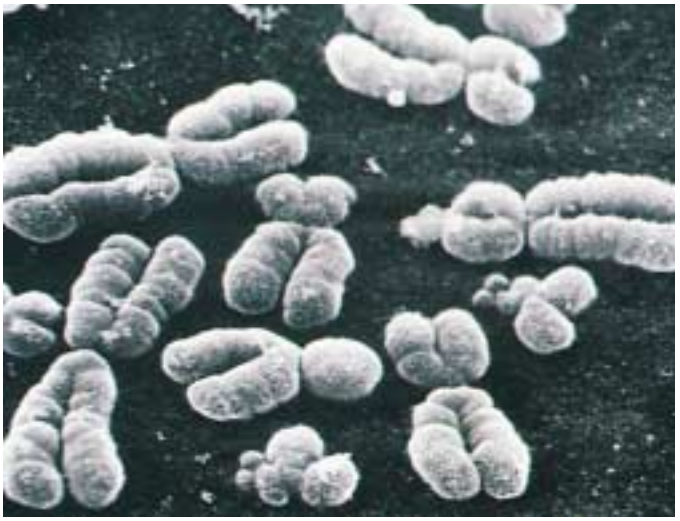


FIGURE 11.4
Human chromosomes. This photograph (950×) shows human chromosomes as they appear immediately before nuclear division. Each DNA molecule has already replicated, forming identical copies held together by a constriction called the centromere.

All eukaryotic cells store their hereditary information in chromosomes, but different kinds of organisms utilize very different numbers of chromosomes to store this information.

Table 11.1 Chromosome Number in Selected Eukaryotes

Group	Total Number of Chromosomes	Group	Total Number of Chromosomes	Group	Total Number of Chromosomes
FUNGI		**PLANTS**		**VERTEBRATES**	
Neurospora (haploid)	7	*Haplopappus gracilis*	2	Opossum	22
Saccharomyces (a yeast)	16	Garden pea	14	Frog	26
INSECTS		Corn	20	Mouse	40
Mosquito	6	Bread wheat	42	Human	46
Drosophila	8	Sugarcane	80	Chimpanzee	48
Honeybee	32	Horsetail	216	Horse	64
Silkworm	56	Adder's tongue fern	1262	Chicken	78
				Dog	78

The Structure of Eukaryotic Chromosomes

In the century since discovery of chromosomes, we have learned a great deal about their structure and composition.

Composition of Chromatin

Chromosomes are composed of **chromatin,** a complex of DNA and protein; most are about 40% DNA and 60% protein. A significant amount of RNA is also associated with chromosomes because chromosomes are the sites of RNA synthesis. The DNA of a chromosome is one very long, double-stranded fiber that extends unbroken through the entire length of the chromosome. A typical human chromosome contains about 140 million (1.4×10^8) nucleotides in its DNA. The amount of information one chromosome contains would fill about 280 printed books of 1000 pages each, if each nucleotide corresponded to a "word" and each page had about 500 words on it. Furthermore, if the strand of DNA from a single chromosome were laid out in a straight line, it would be about 5 centimeters (2 inches) long. Fitting such a strand into a nucleus is like cramming a string the length of a football field into a baseball—and that's only 1 of 46 chromosomes! In the cell, however, the DNA is coiled, allowing it to fit into a much smaller space than would otherwise be possible.

Chromosome Coiling

How can this long DNA fiber coil so tightly? If we gently disrupt a eukaryotic nucleus and examine the DNA with an electron microscope, we find that it resembles a string of beads (figure 11.5). Every 200 nucleotides, the DNA duplex is coiled around a core of eight histone proteins, forming a complex known as a **nucleosome.** Unlike most proteins, which have an overall negative charge, histones are positively charged, due to an abundance of the basic amino acids arginine and lysine. They are thus strongly attracted to the negatively charged phosphate groups of the

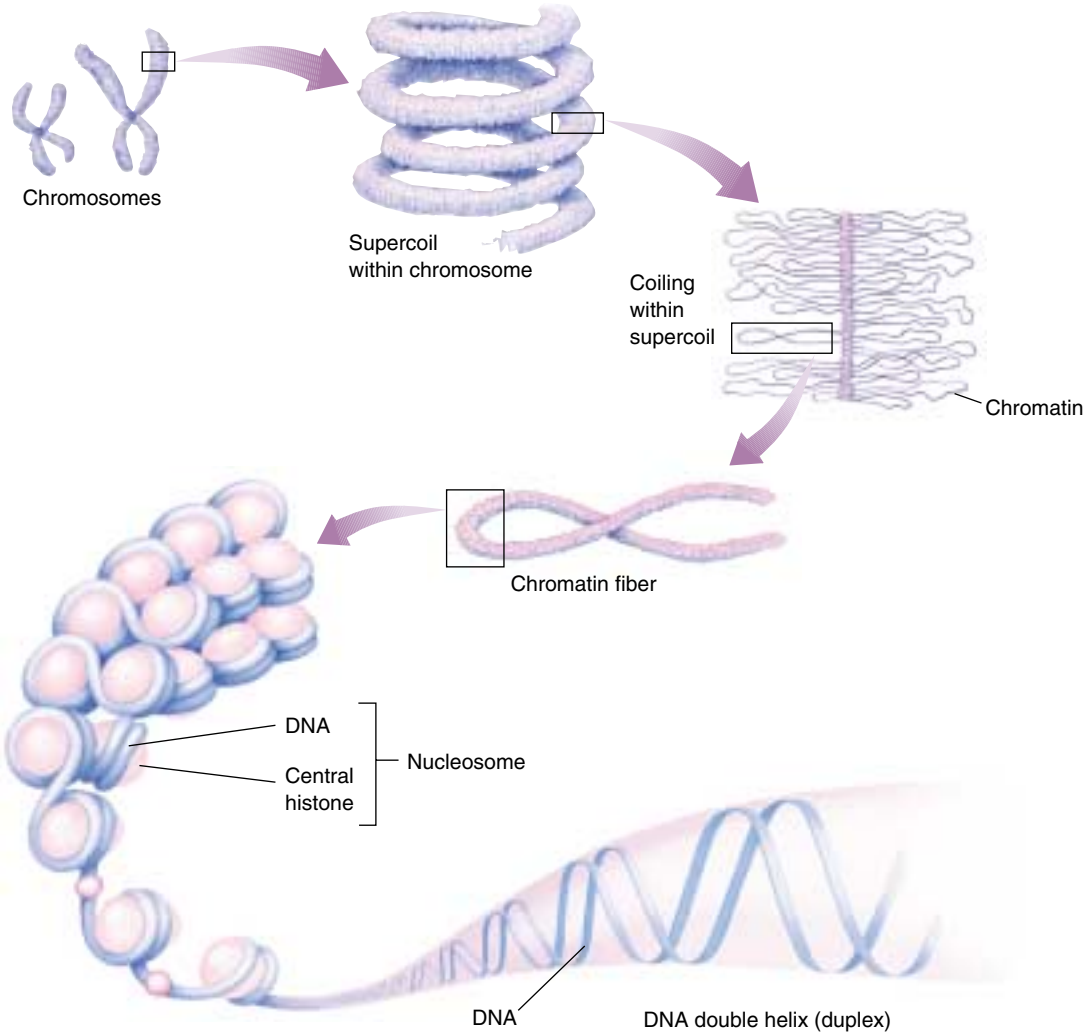


FIGURE 11.5
Levels of eukaryotic chromosomal organization.
Nucleotides assemble into long double strands of DNA molecules. These strands require further packaging to fit into the cell nucleus. The DNA duplex is tightly bound to and wound around proteins called *histones.* The DNA-wrapped histones are called *nucleosomes.* The nucleosomes then coalesce into *chromatin* fibers, ultimately coiling around into *supercoils* that make up the form of DNA recognized as a *chromosome.*

DNA. The histone cores thus act as "magnetic forms" that promote and guide the coiling of the DNA. Further coiling occurs when the string of nucleosomes wraps up into higher order coils called supercoils.

Highly condensed portions of the chromatin are called **heterochromatin.** Some of these portions remain permanently condensed, so that their DNA is never expressed. The remainder of the chromosome, called **euchromatin,** is condensed only during cell division, when compact packaging facilitates the movement of the chromosomes. At all other times, euchromatin is present in an open configuration, and its genes can be expressed. The way chromatin is packaged when the cell is not dividing is not well understood beyond the level of nucleosomes and is a topic of intensive research.

Chromosome Karyotypes

Chromosomes may differ widely in appearance. They vary in size, staining properties, the location of the *centromere* (a constriction found on all chromosomes), the relative length of the two arms on either side of the centromere, and the positions of constricted regions along the arms. The particular array of chromosomes that an individual possesses is called its **karyotype** (figure 11.6). Karyotypes show marked differences among species and sometimes even among individuals of the same species.

To examine a human karyotype, investigators collect a cell sample from blood, amniotic fluid, or other tissue and add chemicals that induce the cells in the sample to divide. Later, they add other chemicals to stop cell division at a stage when the chromosomes are most condensed and thus most easily distinguished from one another. The cells are then broken open and their contents, including the chromosomes, spread out and stained. To facilitate the examination of the karyotype, the chromosomes are usually photographed, and the outlines of the chromosomes are cut out of the photograph and arranged in order (see figure 11.6).

How Many Chromosomes Are in a Cell?

With the exception of the **gametes** (eggs or sperm) and a few specialized tissues, every cell in a human body is **diploid (2*n*).** This means that the cell contains two nearly identical copies of each of the 23 types of chromosomes, for a total of 46 chromosomes. The **haploid (1*n*)** gametes contain only one copy of each of the 23 chromosome types, while certain tissues have unusual numbers of chromosomes—many liver cells, for example, have two nuclei, while mature red blood cells have no nuclei at all. The two copies of each chromosome in body cells are called **homologous chromosomes,** or **homologues** (Greek *homologia*, "agreement"). Before cell division, each homologue replicates, producing two identical **sister chromatids** joined at the **centromere,** a condensed area found on all eukaryotic chromosomes (figure 11.7). Hence, as cell division begins, a human body cell contains a total of 46 replicated chromosomes, each composed of two sister chromatids joined by one centromere. The cell thus contains 46 centromeres and 92 chromatids (2 sister chromatids for each of 2 homologues for each of 23 chromosomes). The cell is said to contain 46 chromosomes rather than 92 because, by convention, the number of chromosomes is obtained by counting centromeres.

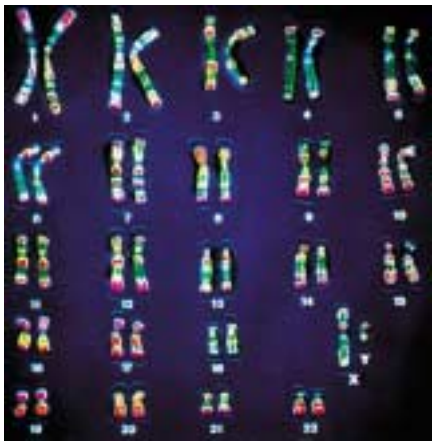


FIGURE 11.6
A human karyotype. The individual chromosomes that make up the 23 pairs differ widely in size and in centromere position. In this preparation, the chromosomes have been specifically stained to indicate further differences in their composition and to distinguish them clearly from one another.

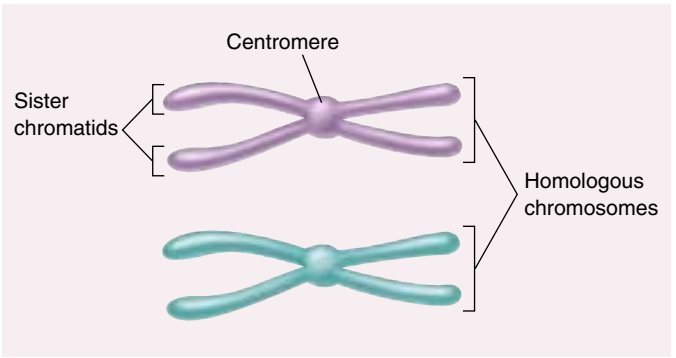


FIGURE 11.7
The difference between homologous chromosomes and sister chromatids. Homologous chromosomes are a pair of the same chromosome—say, chromosome number 16. Sister chromatids are the two replicas of a single chromosome held together by the centromeres after DNA replication.

Eukaryotic genomes are larger and more complex than those of bacteria. Eukaryotic DNA is packaged tightly into chromosomes, enabling it to fit inside cells. Haploid cells contain one set of chromosomes, while diploid cells contain two sets.

11.3 Mitosis is a key phase of the cell cycle.

Phases of the Cell Cycle

The increased size and more complex organization of eukaryotic genomes over those of bacteria required radical changes in the process by which the two replicas of the genome are partitioned into the daughter cells during cell division. This division process is diagrammed as a **cell cycle,** consisting of five phases (figure 11.8).

The Five Phases

G_1 is the primary growth phase of the cell. For many organisms, this encompasses the major portion of the cell's life span. **S** is the phase in which the cell synthesizes a replica of the genome. **G_2** is the second growth phase, in which preparations are made for genomic separation. During this phase, mitochondria and other organelles replicate, chromosomes condense, and microtubules begin to assemble at a spindle. G_1, S, and G_2 together constitute **interphase,** the portion of the cell cycle between cell divisions.

M is the phase of the cell cycle in which the microtubular apparatus assembles, binds to the chromosomes, and moves the sister chromatids apart. Called **mitosis,** this process is the essential step in the separation of the two daughter genomes. We will discuss mitosis as it occurs in animals and plants, where the process does not vary much (it is somewhat different among fungi and some protists). Although mitosis is a continuous process, it is traditionally subdivided into four stages: prophase, metaphase, anaphase, and telophase.

C is the phase of the cell cycle when the cytoplasm divides, creating two daughter cells. This phase is called **cytokinesis.** In animal cells, the microtubule spindle helps position a contracting ring of actin that constricts like a drawstring to pinch the cell in two. In cells with a cell wall, such as plant cells, a plate forms between the dividing cells.

Duration of the Cell Cycle

The time it takes to complete a cell cycle varies greatly among organisms. Cells in growing embryos can complete their cell cycle in under 20 minutes; the shortest known animal nuclear division cycles occur in fruit fly embryos (8 minutes). Cells such as these simply divide their nuclei as quickly as they can replicate their DNA, without cell growth. Half of the cycle is taken up by S, half by M, and essentially none by G_1 or G_2. Because mature cells require time to grow, most of their cycles are much longer than those of embryonic tissue. Typically, a dividing mammalian cell completes its cell cycle in about 24 hours, but some cells, like certain cells in the human liver, have cell cycles lasting more than a year. During the cycle, growth occurs throughout the G_1 and G_2 phases (referred to as "gap" phases, as they separate S from M), as well as during the S phase. The M phase takes only about an hour, a small fraction of the entire cycle.

Most of the variation in the length of the cell cycle from one organism or tissue to the next occurs in the G_1 phase. Cells often pause in G_1 before DNA replication and enter a resting state called **G_0 phase;** they may remain in this phase for days to years before resuming cell division. At any given time, most of the cells in an animal's body are in G_0 phase. Some, such as muscle and nerve cells, remain there permanently; others, such as liver cells, can resume G_1 phase in response to factors released during injury.

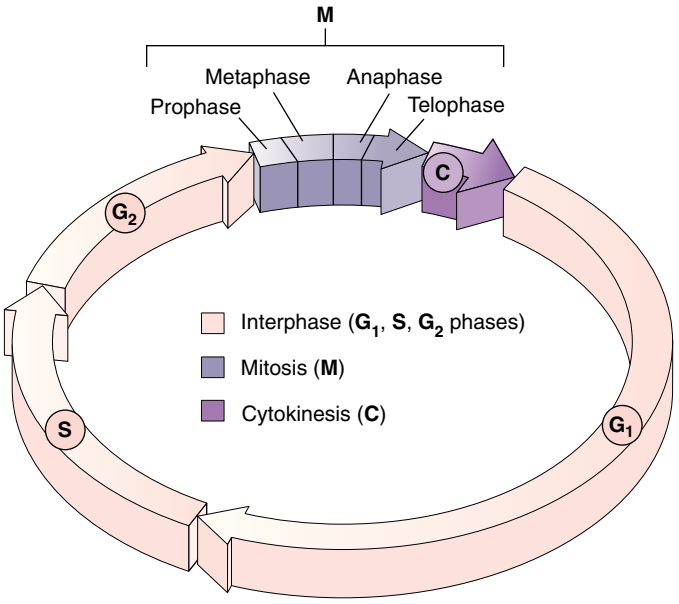


FIGURE 11.8
The cell cycle. Each wedge represents one hour of the 22-hour cell cycle in human cells growing in culture. G_1 represents the primary growth phase of the cell cycle, S the phase during which a replica of the genome is synthesized, and G_2 the second growth phase.

Most eukaryotic cells repeat a process of growth and division referred to as the cell cycle. The cycle can vary in length from a few minutes to several years.

Interphase: Preparing for Mitosis

The events that occur during interphase, made up of the G_1, S, and G_2 phases, are very important for the successful completion of mitosis. During G_1, cells undergo the major portion of their growth. During the S phase, each chromosome replicates to produce two sister chromatids, which remain attached to each other at the **centromere.** The centromere is a point of constriction on the chromosome, containing a specific DNA sequence to which is bound a disk of protein called a **kinetochore.** This disk functions as an attachment site for fibers that assist in cell division (figure 11.9). Each chromosome's centromere is located at a characteristic site.

The cell grows throughout interphase. The G_1 and G_2 segments of interphase are periods of active growth, when proteins are synthesized and cell organelles produced. The cell's DNA replicates only during the S phase of the cell cycle.

After the chromosomes have replicated in S phase, they remain fully extended and uncoiled. This makes them invisible under the light microscope. In G_2 phase, they begin the long process of **condensation,** coiling ever more tightly. Special *motor proteins* are involved in the rapid final condensation of the chromosomes that occurs early in mitosis. Also during G_2 phase, the cells begin to assemble the machinery they will later use to move the chromosomes to opposite poles of the cell. In animal cells, a pair of microtubule-organizing centers called **centrioles** replicate. All eukaryotic cells undertake an extensive synthesis of *tubulin*, the protein of which microtubules are formed.

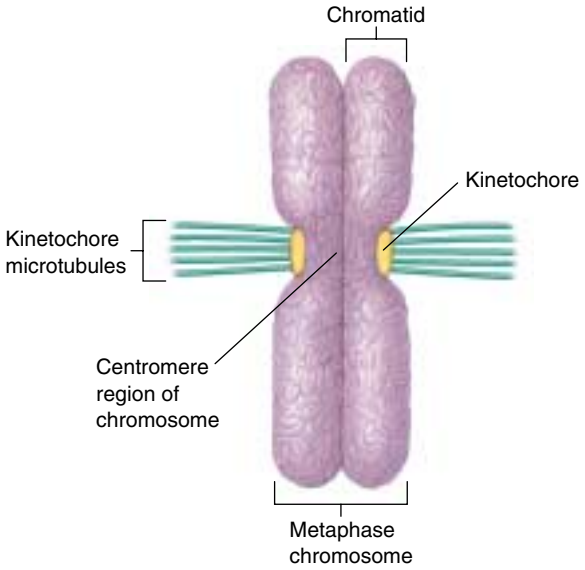


FIGURE 11.9
Kinetochores. In a metaphase chromosome, kinetochore microtubules are anchored to proteins at the centromere.

Interphase is that portion of the cell cycle in which the chromosomes are invisible under the light microscope because they are not yet condensed. It includes the G_1, S, and G_2 phases. In the G_2 phase, the cell mobilizes its resources for cell division.

A Vocabulary of Cell Division

binary fission Asexual reproduction of a cell by division into two equal or nearly equal parts. Bacteria divide by binary fission.

centromere A constricted region of a chromosome about 220 nucleotides in length, composed of highly repeated DNA sequences (satellite DNA). During mitosis, the centromere joins the two sister chromatids and is the site to which the kinetochores are attached.

chromatid One of the two copies of a replicated chromosome, joined by a single centromere to the other strand.

chromatin The complex of DNA and proteins of which eukaryotic chromosomes are composed.

chromosome The structure within cells that contains the genes. In eukaryotes, it consists of a single linear DNA molecule associated with proteins. The DNA is replicated during S phase, and the replicas separated during M phase.

cytokinesis Division of the cytoplasm of a cell after nuclear division.

euchromatin The portion of a chromosome that is extended except during cell division, and from which RNA is transcribed.

heterochromatin The portion of a chromosome that remains permanently condensed and, therefore, is not transcribed into RNA. Most centromere regions are heterochromatic.

homologues Homologous chromosomes; in diploid cells, one of a pair of chromosomes that carry equivalent genes.

kinetochore A disk of protein bound to the centromere and attached to microtubules during mitosis, linking each chromatid to the spindle apparatus.

microtubule A hollow cylinder, about 25 nanometers in diameter, composed of subunits of the protein tubulin. Microtubules lengthen by the addition of tubulin subunits to their end(s) and shorten by the removal of subunits.

mitosis Nuclear division in which replicated chromosomes separate to form two genetically identical daughter nuclei. When accompanied by cytokinesis, it produces two identical daughter cells.

nucleosome The basic packaging unit of eukaryotic chromosomes, in which the DNA molecule is wound around a cluster of histone proteins. Chromatin is composed of long strings of nucleosomes that resemble beads on a string.

Mitosis

Prophase: Formation of the Mitotic Apparatus

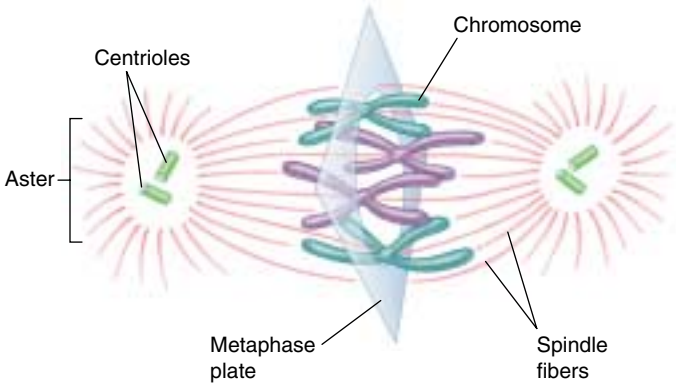
When the chromosome condensation initiated in G_2 phase reaches the point at which individual condensed chromosomes first become visible with the light microscope, the first stage of mitosis, **prophase,** has begun. The condensation process continues throughout prophase; consequently, some chromosomes that start prophase as minute threads appear quite bulky before its conclusion. Ribosomal RNA synthesis ceases when the portion of the chromosome bearing the rRNA genes is condensed.

Assembling the Spindle Apparatus. The assembly of the microtubular apparatus that will later separate the sister chromatids also continues during prophase. In animal cells, the two centriole pairs formed during G_2 phase begin to move apart early in prophase, forming between them an axis of microtubules referred to as spindle fibers. By the time the centrioles reach the opposite poles of the cell, they have established a bridge of microtubules called the spindle apparatus between them. In plant cells, a similar bridge of microtubular fibers forms between opposite poles of the cell, although centrioles are absent in plant cells.

During the formation of the spindle apparatus, the nuclear envelope breaks down and the endoplasmic reticulum reabsorbs its components. At this point, then, the microtubular spindle fibers extend completely across the cell, from one pole to the other. Their orientation determines the plane in which the cell will subsequently divide, through the center of the cell at right angles to the spindle apparatus.

In animal cell mitosis, the centrioles extend a radial array of microtubules toward the plasma membrane when they reach the poles of the cell. This arrangement of microtubules is called an **aster.** Although the aster's function is not fully understood, it probably braces the centrioles against the membrane and stiffens the point of microtubular attachment during the retraction of the spindle. Plant cells, which have rigid cell walls, do not form asters.

Linking Sister Chromatids to Opposite Poles. Each chromosome possesses two kinetochores, one attached to the centromere region of each sister chromatid (see figure 11.9). As prophase continues, a second group of microtubules appears to grow from the poles of the cell toward the centromeres. These microtubules connect the kinetochores on each pair of sister chromatids to the two poles of the spindle. Because microtubules extending from the two poles attach to opposite sides of the centromere, they attach one sister chromatid to one pole and the other sister chromatid to the other pole. This arrangement is absolutely critical to the process of mitosis; any mistakes in microtubule positioning can be disastrous. The attachment of the two sides of a centromere to the same pole, for example, leads to a failure of the sister chromatids to separate, so that they end up in the same daughter cell.



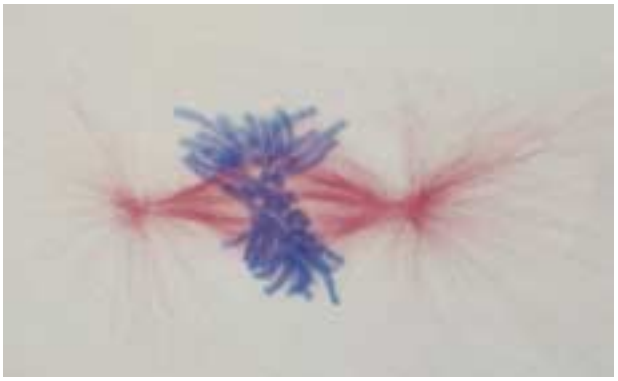


FIGURE 11.10
Metaphase. In metaphase, the chromosomes array themselves in a circle around the spindle midpoint.

Metaphase: Alignment of the Centromeres

The second stage of mitosis, **metaphase,** is the phase where the chromosomes align in the center of the cell. When viewed with a light microscope, the chromosomes appear to array themselves in a circle along the inner circumference of the cell, as the equator girdles the earth (figure 11.10). An imaginary plane perpendicular to the axis of the spindle that passes through this circle is called the *metaphase plate.* The metaphase plate is not an actual structure, but rather an indication of the future axis of cell division. Positioned by the microtubules attached to the kinetochores of their centromeres, all of the chromosomes line up on the metaphase plate (figure 11.11). At this point, which marks the end of metaphase, their centromeres are neatly arrayed in a circle, equidistant from the two poles of the cell, with microtubules extending back towards the opposite poles of the cell in an arrangement called a spindle because of its shape.

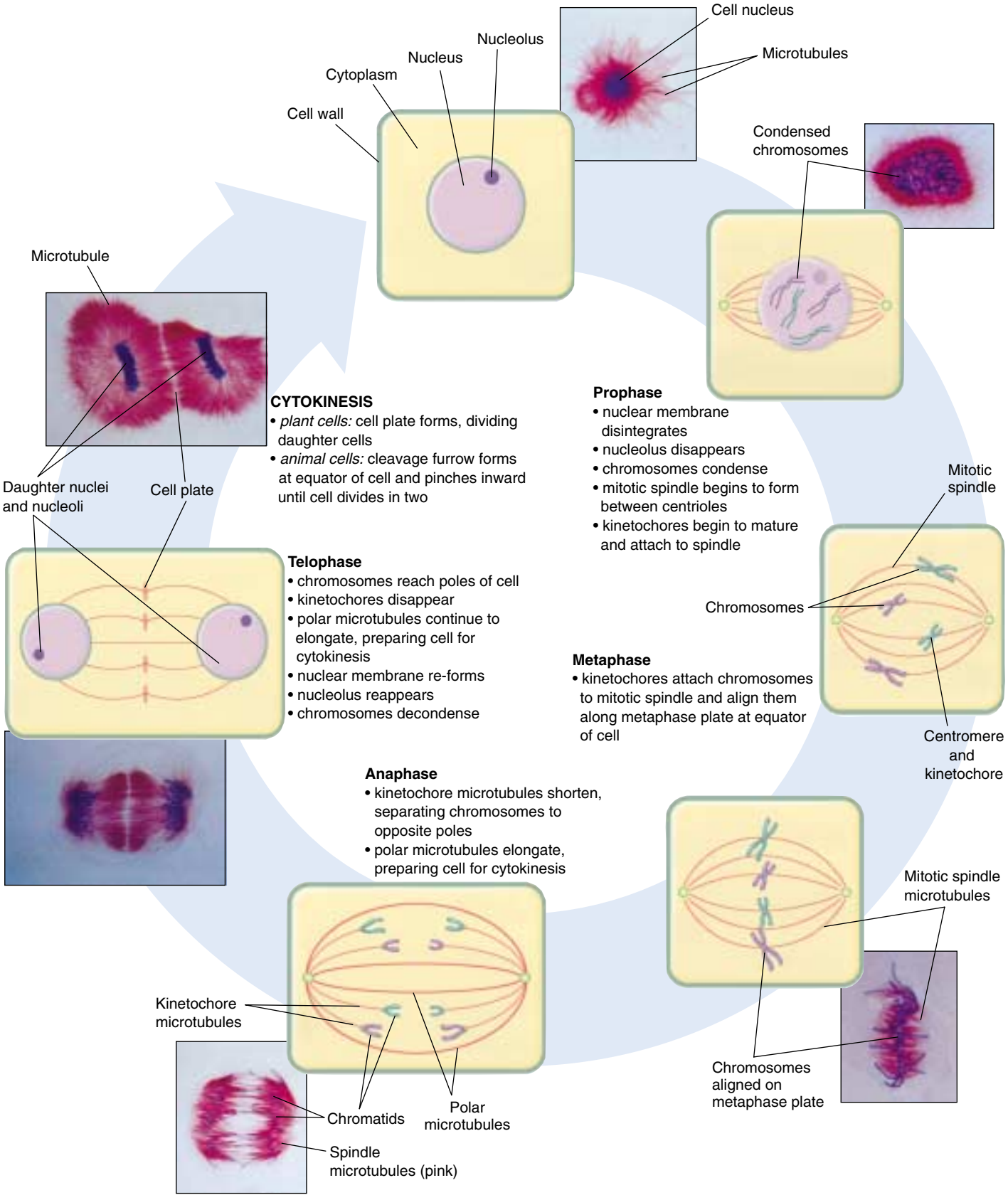


FIGURE 11.11
Mitosis and cytokinesis. Mitosis (separation of the two genomes) occurs in four stages—prophase, metaphase, anaphase, and telophase—and is followed by cytokinesis (division into two separate cells). In this depiction, the chromosomes of the African blood lily, *Haemanthus katharinae*, are stained blue, and microtubules are stained red.

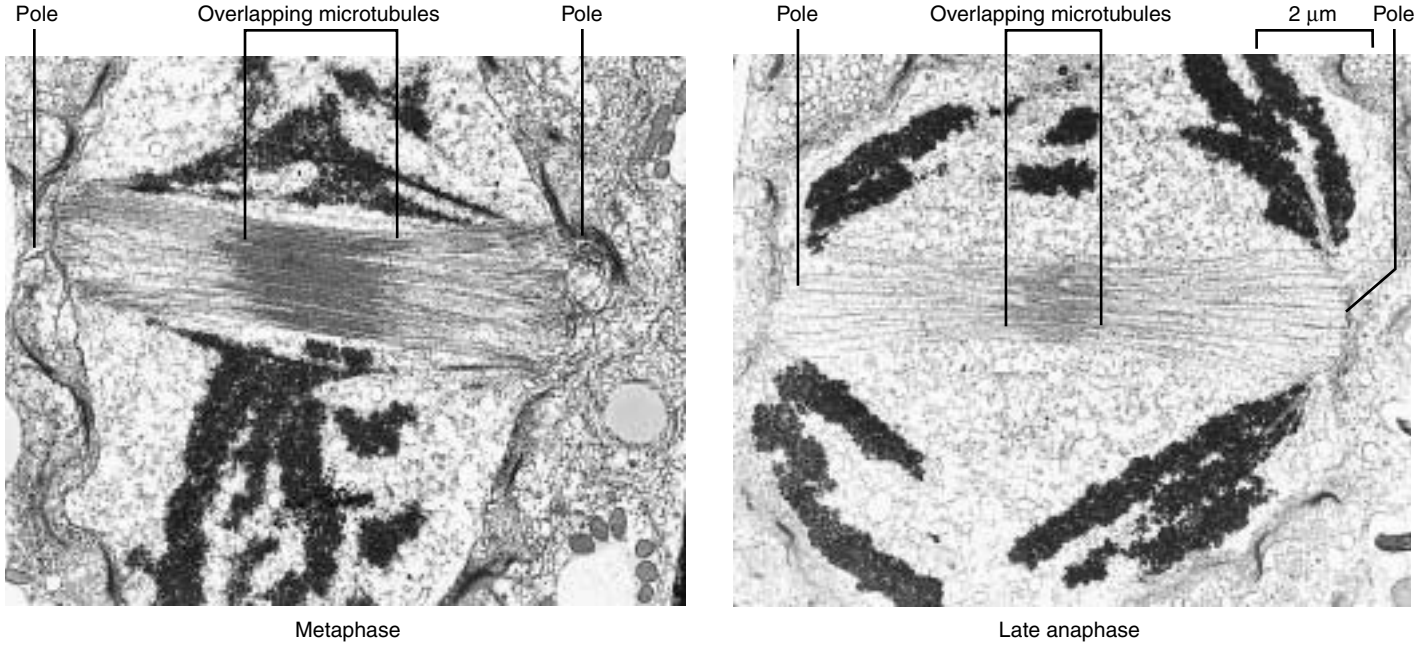


FIGURE 11.12
Microtubules slide past each other as the chromosomes separate. In these electron micrographs of dividing diatoms, the overlap of the microtubules lessens markedly during spindle elongation as the cell passes from metaphase to anaphase.

Anaphase and Telophase: Separation of the Chromatids and Reformation of the Nuclei

Of all the stages of mitosis, **anaphase** is the shortest and the most beautiful to watch. It starts when the centromeres divide. Each centromere splits in two, freeing the two sister chromatids from each other. The centromeres of all the chromosomes separate simultaneously, but the mechanism that achieves this synchrony is not known.

Freed from each other, the sister chromatids are pulled rapidly toward the poles to which their kinetochores are attached. In the process, two forms of movement take place simultaneously, each driven by microtubules.

First, *the poles move apart* as microtubular spindle fibers physically anchored to opposite poles slide past each other, away from the center of the cell (figure 11.12). Because another group of microtubules attach the chromosomes to the poles, the chromosomes move apart, too. If a flexible membrane surrounds the cell, it becomes visibly elongated.

Second, *the centromeres move toward the poles* as the microtubules that connect them to the poles shorten. This shortening process is not a contraction; the microtubules do not get any thicker. Instead, tubulin subunits are removed from the kinetochore ends of the microtubules by the organizing center. As more subunits are removed, the chromatid-bearing microtubules are progressively disassembled, and the chromatids are pulled ever closer to the poles of the cell.

When the sister chromatids separate in anaphase, the accurate partitioning of the replicated genome—the essential element of mitosis—is complete. In **telophase,** the spindle apparatus disassembles, as the microtubules are broken down into tubulin monomers that can be used to construct the cytoskeletons of the daughter cells. A nuclear envelope forms around each set of sister chromatids, which can now be called chromosomes because each has its own centromere. The chromosomes soon begin to uncoil into the more extended form that permits gene expression. One of the early group of genes expressed are the rRNA genes, resulting in the reappearance of the nucleolus.

During prophase, microtubules attach the centromeres joining pairs of sister chromatids to opposite poles of the spindle apparatus. During metaphase, each chromosome is drawn to a ring along the inner circumference of the cell by the microtubules extending from the centromere to the two poles of the spindle apparatus. During anaphase, the poles of the cell are pushed apart by microtubular sliding, and the sister chromatids are drawn to opposite poles by the shortening of the microtubules attached to them. During telophase, the spindle is disassembled, nuclear envelopes are reestablished, and the normal expression of genes present in the chromosomes is reinitiated.

Cytokinesis

Mitosis is complete at the end of telophase. The eukaryotic cell has partitioned its replicated genome into two nuclei positioned at opposite ends of the cell. While mitosis was going on, the cytoplasmic organelles, including mitochondria and chloroplasts (if present), were reassorted to areas that will separate and become the daughter cells. The replication of organelles takes place before cytokinesis, often in the S or G_2 phase. Cell division is still not complete at the end of mitosis, however, because the division of the cell proper has not yet begun. The phase of the cell cycle when the cell actually divides is called **cytokinesis.** It generally involves the cleavage of the cell into roughly equal halves.

Cytokinesis in Animal Cells

In animal cells and the cells of all other eukaryotes that lack cell walls, cytokinesis is achieved by means of a constricting belt of actin filaments. As these filaments slide past one another, the diameter of the belt decreases, pinching the cell and creating a *cleavage furrow* around the cell's circumference (figure 11.13*a*). As constriction proceeds, the furrow deepens until it eventually slices all the way into the center of the cell. At this point, the cell is divided in two (figure 11.13*b*).

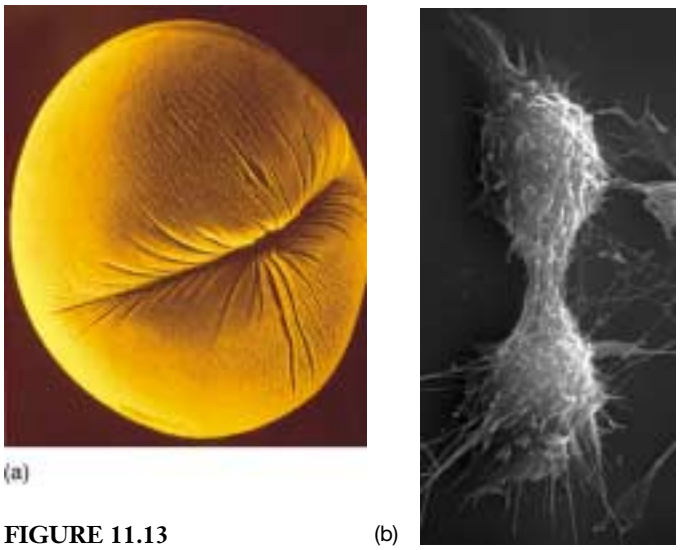


FIGURE 11.13
Cytokinesis in animal cells.
(*a*) A cleavage furrow forms around a dividing sea urchin egg (30×). (*b*) The completion of cytokinesis in an animal cell. The two daughter cells are still joined by a thin band of cytoplasm occupied largely by microtubules.

Cytokinesis in Plant Cells

Plant cells possess a cell wall far too rigid to be squeezed in two by actin filaments. Instead, these cells assemble membrane components in their interior, at right angles to the spindle apparatus (figure 11.14). This expanding membrane partition, called a **cell plate,** continues to grow outward until it reaches the interior surface of the plasma membrane and fuses with it, effectively dividing the cell in two. Cellulose is then laid down on the new membranes, creating two new cell walls. The space between the daughter cells becomes impregnated with pectins and is called a **middle lamella.**

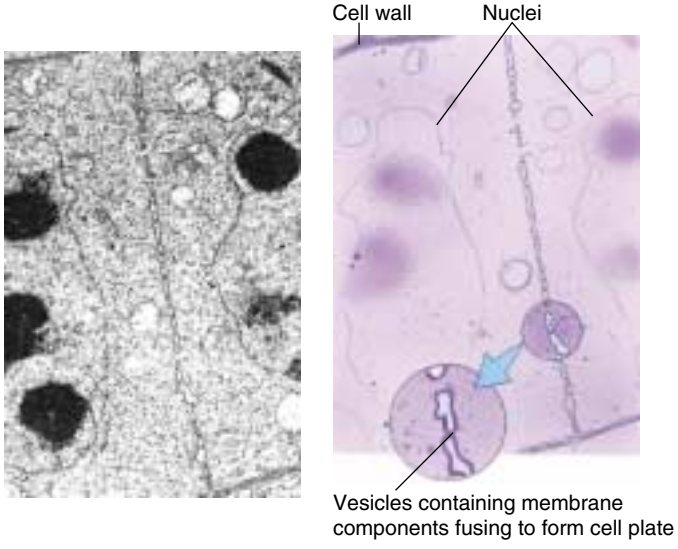


FIGURE 11.14
Cytokinesis in plant cells. In this photograph and companion drawing, a cell plate is forming between daughter nuclei. Once the plate is complete, there will be two cells.

Cytokinesis in Fungi and Protists

In fungi and some groups of protists, the nuclear membrane does not dissolve and, as a result, all the events of mitosis occurs entirely *within* the nucleus. Only after mitosis is complete in these organisms does the nucleus then divide into two daughter nuclei, and one nucleus goes to each daughter cell during cytokinesis. This separate nuclear division phase of the cell cycle does not occur in plants, animals, or most protists.

After cytokinesis in any eukaryotic cell, the two daughter cells contain all of the components of a complete cell. While mitosis ensures that both daughter cells contain a full complement of chromosomes, no similar mechanism ensures that organelles such as mitochondria and chloroplasts are distributed equally between the daughter cells. However, as long as some of each organelle are present in each cell, the organelles can replicate to reach the number appropriate for that cell.

C`ytokinesis is the physical division of the cytoplasm of a eukaryotic cell into two daughter cells.

11.4 The cell cycle is carefully controlled.

General Strategy of Cell Cycle Control

The events of the cell cycle are coordinated in much the same way in all eukaryotes. The control system human cells utilize first evolved among the protists over a billion years ago; today, it operates in essentially the same way in fungi as it does in humans.

The goal of controlling any cyclic process is to adjust the duration of the cycle to allow sufficient time for all events to occur. In principle, a variety of methods can achieve this goal. For example, an internal "clock" can be employed to allow adequate time for each phase of the cycle to be completed. This is how many organisms control their daily activity cycles. The disadvantage of using such a clock to control the cell cycle is that it is not very flexible. One way to achieve a more flexible and sensitive regulation of a cycle is simply to let the completion of each phase of the cycle trigger the beginning of the next phase, as a runner passing a baton starts the next leg in a relay race. Until recently, biologists thought this type of mechanism controlled the cell division cycle. However, we now know that eukaryotic cells employ a separate, centralized controller to regulate the process: at critical points in the cell cycle, further progress depends upon a central set of "go/no-go" switches that are regulated by feedback from the cell.

This mechanism is the same one engineers use to control many processes. For example, the furnace that heats a home in the winter typically goes through a daily heating cycle. When the daily cycle reaches the morning "turn on" checkpoint, sensors report whether the house temperature is below the set point (for example, 70°F). If it is, the thermostat triggers the furnace, which warms the house. If the house is already at least that warm, the thermostat does not start up the furnace. Similarly, the cell cycle has key checkpoints where feedback signals from the cell about its size and the condition of its chromosomes can either trigger subsequent phases of the cycle, or delay them to allow more time for the current phase to be completed.

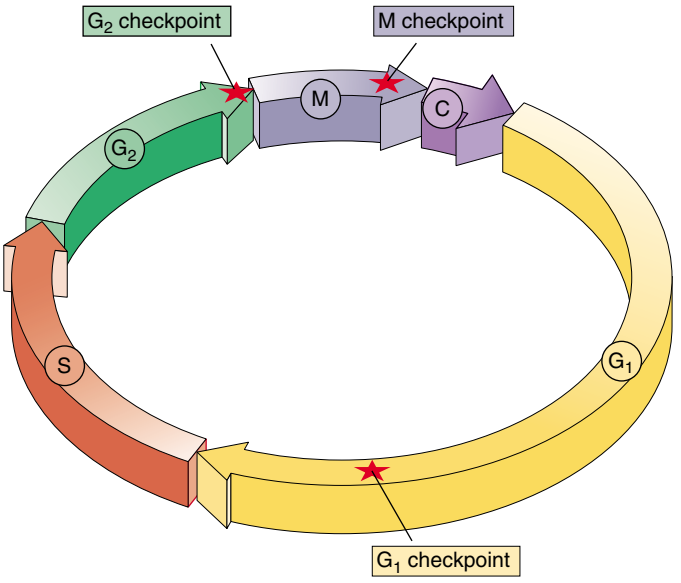


FIGURE 11.15
Control of the cell cycle. Cells use a centralized control system to check whether proper conditions have been achieved before passing three key "checkpoints" in the cell cycle.

FIGURE 11.16
The G_1 checkpoint. Feedback from the cell determines whether the cell cycle will proceed to the S phase, pause, or withdraw into G_0 for an extended rest period.

Architecture of the Control System

Three principal checkpoints control the cell cycle in eukaryotes (figure 11.15):

Cell growth is assessed at the G_1 checkpoint. Located near the end of G_1, just before entry into S phase, this checkpoint makes the key decision of whether the cell should divide, delay division, or enter a resting stage (figure 11.16). In yeasts, where researchers first studied this checkpoint, it is called START. If conditions are favorable for division, the cell begins to copy its DNA, initiating S phase. The G_1 checkpoint is where the more complex eukaryotes typically arrest the cell cycle if environmental conditions make cell division impossible, or if the cell passes into G_0 for an extended period.

The success of DNA replication is assessed at the G_2 checkpoint. The second checkpoint, which occurs at the end of G_2, triggers the start of M phase. If this checkpoint is passed, the cell initiates the many molecular processes that signal the beginning of mitosis.

Mitosis is assessed at the M checkpoint. Occurring at metaphase, the third checkpoint triggers the exit from mitosis and cytokinesis and the beginning of G_1.

The cell cycle is controlled at three checkpoints.

Molecular Mechanisms of Cell Cycle Control

Exactly how does a cell achieve central control of the division cycle? The basic mechanism is quite simple. A set of proteins sensitive to the condition of the cell interact at the checkpoints to trigger the next events in the cycle. Two key types of proteins participate in this interaction: cyclin-dependent protein kinases and cyclins (figure 11.17).

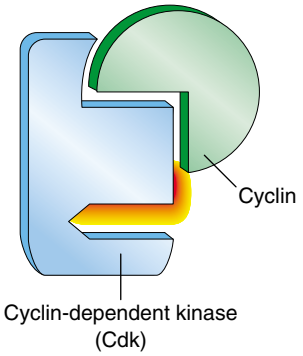


FIGURE 11.17
A complex of two proteins triggers passage through cell cycle checkpoints. Cdk is a protein kinase that activates numerous cell proteins by phosphorylating them. Cyclin is a regulatory protein required to activate Cdk; in other words, Cdk does not function unless cyclin is bound to it.

The Cyclin Control System

Cyclin-dependent protein kinases (Cdks) are enzymes that phosphorylate (add phosphate groups to) the serine and threonine amino acids of key cellular enzymes and other proteins. At the G_2 checkpoint, for example, Cdks phosphorylate histones, nuclear membrane filaments, and the microtubule-associated proteins that form the mitotic spindle. Phosphorylation of these components of the cell division machinery initiates activities that carry the cycle past the checkpoint into mitosis.

Cyclins are proteins that bind to Cdks, enabling the Cdks to function as enzymes. Cyclins are so named because they are destroyed and resynthesized during each turn of the cell cycle (figure 11.18). Different cyclins regulate the G_1 and G_2 cell cycle checkpoints.

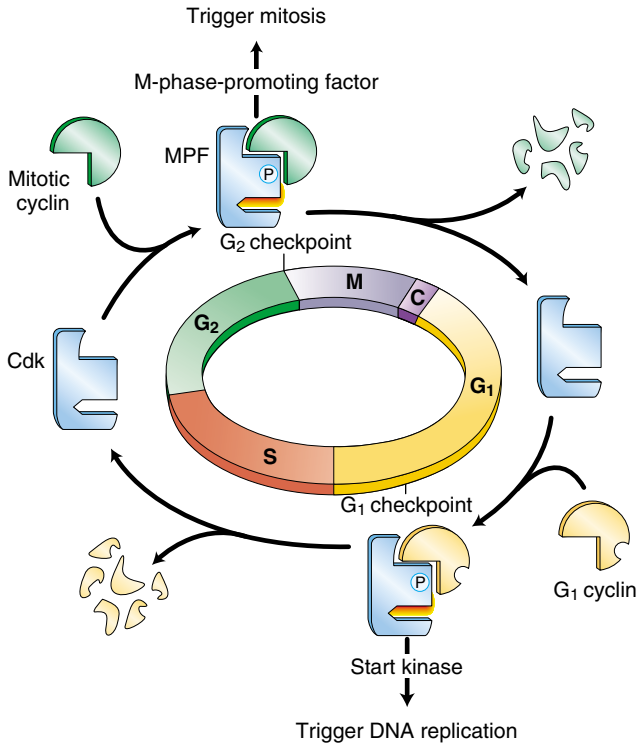


FIGURE 11.18
How cell cycle control works. As the cell cycle passes through the G_1 and G_2 checkpoints, Cdk becomes associated with different cyclins and, as a result, activates different cellular processes. At the completion of each phase, the cyclins are degraded, bringing Cdk activity to a halt until the next set of cyclins appears.

The G_2 Checkpoint. During G_2, the cell gradually accumulates G_2 cyclin (also called mitotic cyclin). This cyclin binds to Cdk to form a complex called MPF (mitosis-promoting factor). At first, MPF is not active in carrying the cycle past the G_2 checkpoint. But eventually, other cellular enzymes phosphorylate and so activate a few molecules of MPF. These activated MPFs in turn increase the activity of the enzymes that phosphorylate MPF, setting up a positive feedback that leads to a very rapid increase in the cellular concentration of activated MPF. When the level of activated MPF exceeds the threshold necessary to trigger mitosis, G_2 phase ends.

MPF sows the seeds of its own destruction. The length of time the cell spends in M phase is determined by the activity of MPF, for one of its many functions is to activate proteins that destroy cyclin. As mitosis proceeds to the end of metaphase, Cdk levels stay relatively constant, but increasing amounts of G_2 cyclin are degraded, causing progressively less MPF to be available and so initiating the events that end mitosis. After mitosis, the gradual accumulation of new cyclin starts the next turn of the cell cycle.

The G_1 Checkpoint. The G_1 checkpoint is thought to be regulated in a similar fashion. In unicellular eukaryotes such as yeasts, the main factor triggering DNA replication is cell size. Yeast cells grow and divide as rapidly as possible, and they make the START decision by comparing the volume of cytoplasm to the size of the genome. As a cell grows, its cytoplasm increases in size, while the amount of DNA remains constant. Eventually a threshold ratio is reached that promotes the production of cyclins and thus triggers the next round of DNA replication and cell division.

Controlling the Cell Cycle in Multicellular Eukaryotes

The cells of multicellular eukaryotes are not free to make individual decisions about cell division, as yeast cells are. The body's organization cannot be maintained without severely limiting cell proliferation, so that only certain cells divide, and only at appropriate times. The way that cells inhibit individual growth of other cells is apparent in mammalian cells growing in tissue culture: a single layer of cells expands over a culture plate until the growing border of cells comes into contact with neighboring cells, and then the cells stop dividing. If a sector of cells is cleared away, neighboring cells rapidly refill that sector and then stop dividing again. How are cells able to sense the density of the cell culture around them? Each growing cell apparently binds minute amounts of positive regulatory signals called **growth factors,** proteins that stimulate cell division (such as MPF). When neighboring cells have used up what little growth factor is present, not enough is left to trigger cell division in any one cell.

Growth Factors and the Cell Cycle

As you may recall from chapter 7 (cell-cell interactions), growth factors work by triggering intracellular signaling systems. Fibroblasts, for example, possess numerous receptors on their plasma membranes for one of the first growth factors to be identified: platelet-derived growth factor (PDGF). When PDGF binds to a membrane receptor, it initiates an amplifying chain of internal cell signals that stimulates cell division. PDGF was discovered when investigators found that fibroblasts would grow and divide in tissue culture only if the growth medium contained blood serum (the liquid that remains after blood clots); blood plasma (blood from which the cells have been removed without clotting) would not work. The researchers hypothesized that platelets in the blood clots were releasing into the serum one or more factors required for fibroblast growth. Eventually, they isolated such a factor and named it PDGF. Growth factors such as PDGF override cellular controls that otherwise inhibit cell division. When a tissue is injured, a blood clot forms and the release of PDGF triggers neighboring cells to divide, helping to heal the wound. Only a tiny amount of PDGF (approximately 10^{-10} M) is required to stimulate cell division.

Characteristics of Growth Factors. Over 50 different proteins that function as growth factors have been isolated (table 11.2 lists a few), and more undoubtedly exist. A specific cell surface receptor "recognizes" each growth factor, its shape fitting that growth factor precisely. When the growth factor binds with its receptor, the receptor reacts by triggering events within the cell (figure 11.19). The cellular selectivity of a particular growth factor depends upon which target cells bear its unique receptor. Some growth

Table 11.2 Growth Factors of Mammalian Cells

Growth Factor	Range of Specificity	Effects
Epidermal growth factor (EGF)	Broad	Stimulates cell proliferation in many tissues; plays a key role in regulating embryonic development
Erythropoietin	Narrow	Required for proliferation of red blood cell precursors and their maturation into erythrocytes (red blood cells)
Fibroblast growth factor (FGF)	Broad	Initiates the proliferation of many cell types; inhibits maturation of many types of stem cells; acts as a signal in embryonic development
Insulin-like growth factor	Broad	Stimulates metabolism of many cell types; potentiates the effects of other growth factors in promoting cell proliferation
Interleukin-2	Narrow	Triggers the division of activated T lymphocytes during the immune response
Mitosis-promoting factor (MPF)	Broad	Regulates entrance of the cell cycle into the M phase
Nerve growth factor (NGF)	Narrow	Stimulates the growth of neuron processes during neural development
Platelet-derived growth factor (PDGF)	Broad	Promotes the proliferation of many connective tissues and some neuroglial cells
Transforming growth factor β (TGF-β)	Broad	Accentuates or inhibits the responses of many cell types to other growth factors; often plays an important role in cell differentiation

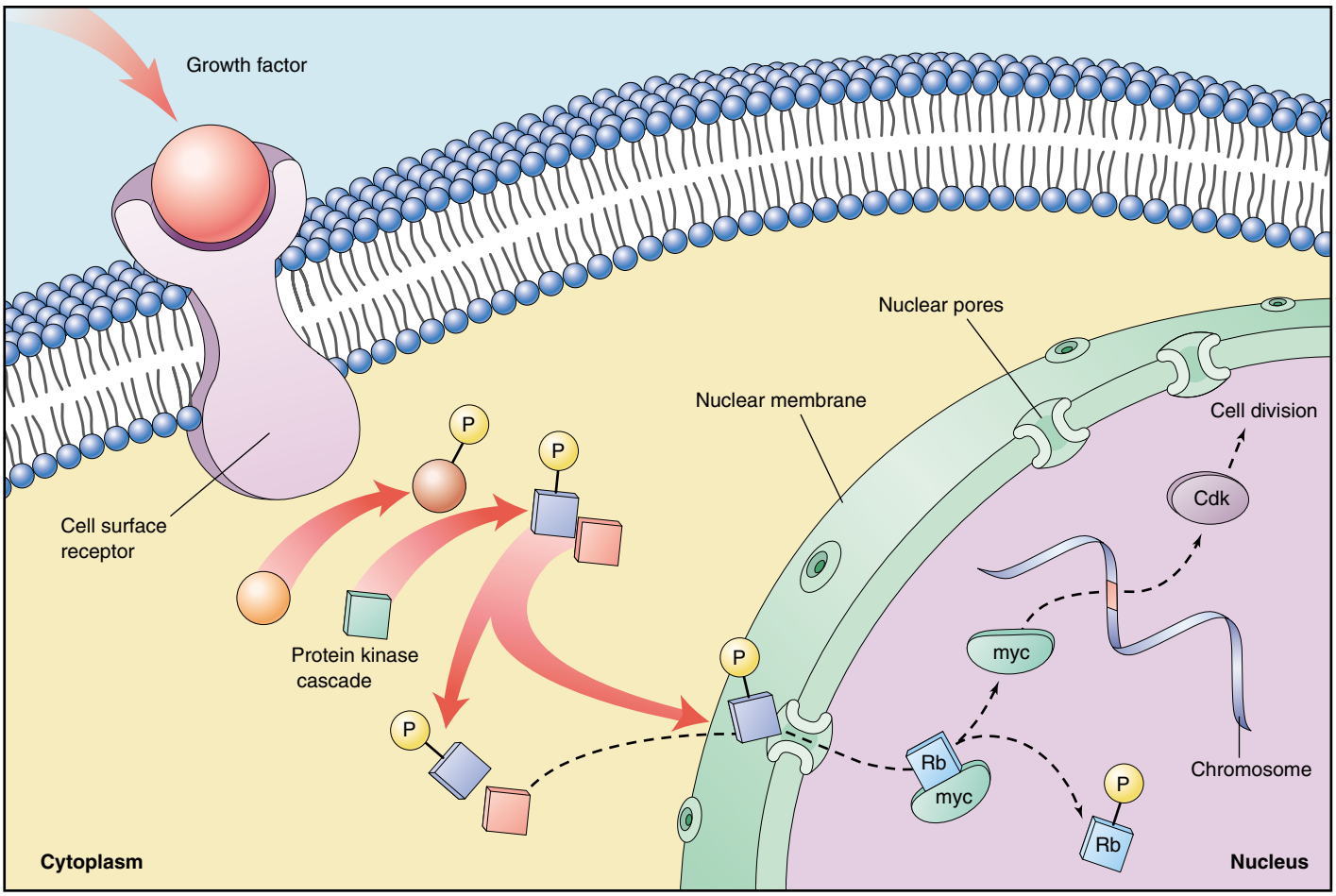


FIGURE 11.19
The cell proliferation-signaling pathway. Binding of a growth factor sets in motion a cascading intracellular signaling pathway (described in chapter 7), which activates nuclear regulatory proteins that trigger cell division. In this example, when the nuclear protein Rb is phosphorylated, another nuclear protein (myc) is released and is then able to stimulate the production of Cdk proteins.

factors, like PDGF and epidermal growth factor (EGF), affect a broad range of cell types, while others affect only specific types. For example, nerve growth factor (NGF) promotes the growth of certain classes of neurons, and erythropoietin triggers cell division in red blood cell precursors. Most animal cells need a combination of several different growth factors to overcome the various controls that inhibit cell division.

The G_0 Phase. If cells are deprived of appropriate growth factors, they stop at the G_1 checkpoint of the cell cycle. With their growth and division arrested, they remain in the G_0 phase, as we discussed earlier. This nongrowing state is distinct from the interphase stages of the cell cycle, G_1, S, and G_2.

It is the ability to enter G_0 that accounts for the incredible diversity seen in the length of the cell cycle among different tissues. Epithelial cells lining the gut divide more than twice a day, constantly renewing the lining of the digestive tract. By contrast, liver cells divide only once every year or two, spending most of their time in G_0 phase. Mature neurons and muscle cells usually never leave G_0.

Two groups of proteins, cyclins and Cdks, interact to regulate the cell cycle. Cells also receive protein signals called growth factors that affect cell division.

Cancer and the Control of Cell Proliferation

The unrestrained, uncontrolled growth of cells, called cancer, is addressed more fully in chapter 18. However, cancer certainly deserves mention in a chapter on cell division, as it is essentially a disease of cell division—a failure of cell division *control*. Recent work has identified one of the culprits. Working independently, cancer scientists have repeatedly identified what has proven to be the same gene! Officially dubbed *p53* (researchers italicize the gene symbol to differentiate it from the protein), this gene plays a key role in the G_1 checkpoint of cell division. The gene's product, the p53 protein, monitors the integrity of DNA, checking that it is undamaged. If the p53 protein detects damaged DNA, it halts cell division and stimulates the activity of special enzymes to repair the damage. Once the DNA has been repaired, *p53* allows cell division to continue. In cases where the DNA is irreparable, *p53* then directs the cell to kill itself, activating an apoptosis (cell suicide) program (see chapter 17 for a discussion of apoptosis).

By halting division in damaged cells, *p53* prevents the development of many mutated cells, and it is therefore considered a tumor-suppressor gene (even though its activities are not limited to cancer prevention). Scientists have found that *p53* is entirely absent or damaged beyond use in the majority of cancerous cells they have examined! It is precisely because *p53* is nonfunctional that these cancer cells are able to repeatedly undergo cell division without being halted at the G_1 checkpoint (figure 11.20). To test this, scientists administered healthy p53 protein to rapidly dividing cancer cells in a petri dish: the cells soon ceased dividing and died.

Scientists at Johns Hopkins University School of Medicine have further reported that cigarette smoke causes mutations in the *p53* gene. This study, published in 1995, reinforced the strong link between smoking and cancer described in chapter 18.

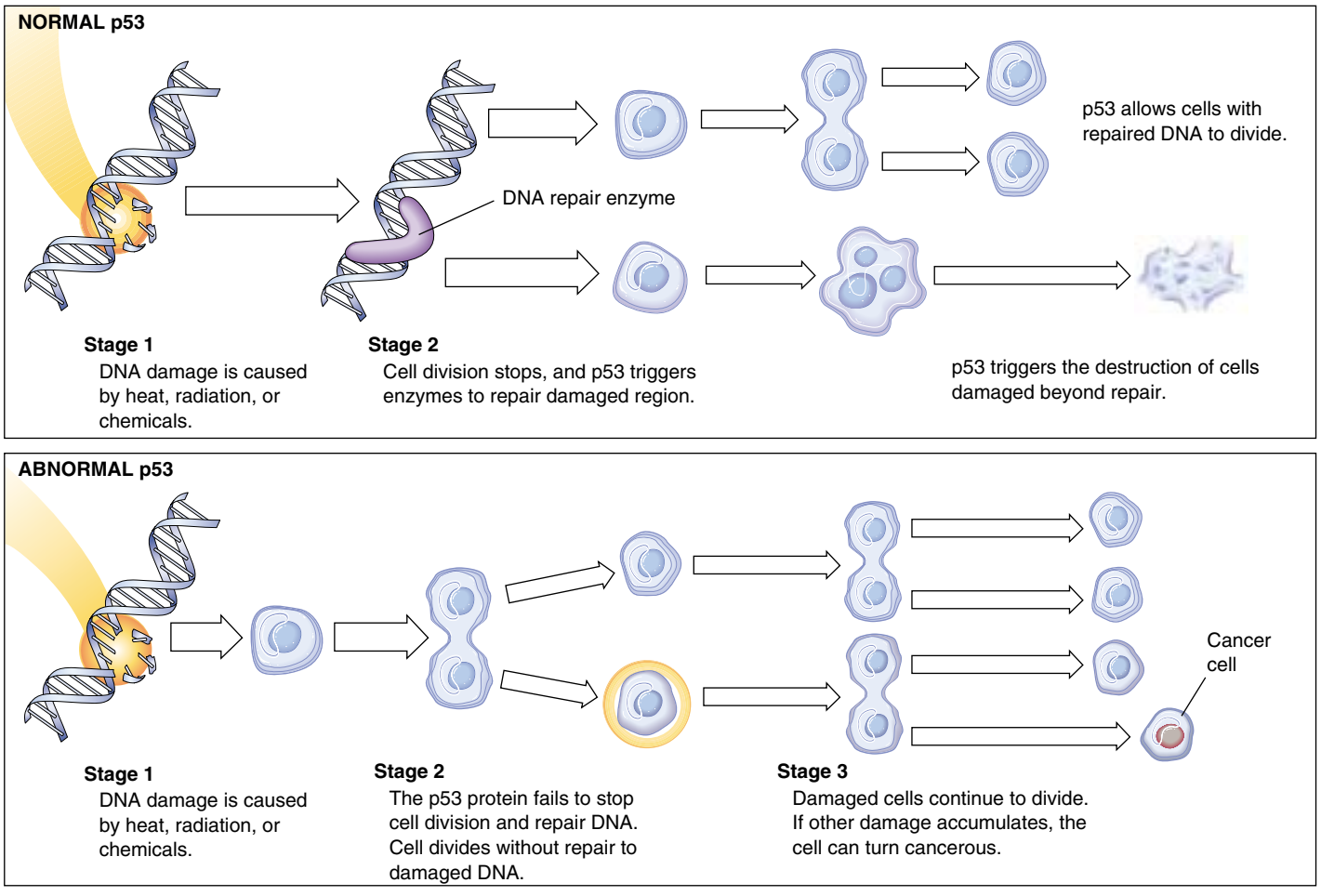


FIGURE 11.20
Cell division and p53 protein. Normal p53 protein monitors DNA, destroying cells with irreparable damage to their DNA. Abnormal p53 protein fails to stop cell division and repair DNA. As damaged cells proliferate, cancer develops.

Growth Factors and Cancer

How do growth factors influence the cell cycle? As you have seen, there are two different approaches, one positive and the other negative.

Proto-oncogenes. PDGF and many other growth factors utilize the positive approach, stimulating cell division. They trigger passage through the G_1 checkpoint by aiding the formation of cyclins and so activating genes that promote cell division. Genes that normally stimulate cell division are sometimes called *proto-oncogenes* because mutations that cause them to be overexpressed or hyperactive convert them into oncogenes (Greek *onco*, "cancer"), leading to the excessive cell proliferation that is characteristic of cancer. Even a single mutation (creating a heterozygote) can lead to cancer if the other cancer-preventing genes are nonfunctional. Geneticists, using Mendel's terms, call such mutations of proto-oncogenes *dominant*.

Some 30 different proto-oncogenes are known. Some act very quickly after stimulation by growth factors. Among the most intensively studied of these are *myc*, *fos*, and *jun*, all of which cause unrestrained cell growth and division when they are overexpressed. In a normal cell, the *myc* proto-oncogene appears to be important in regulating the G_1 checkpoint. Cells in which *myc* expression is prevented will not divide, even in the presence of growth factors. A critical activity of *myc* and other genes in this group of immediately responding proto-oncogenes is to stimulate a second group of "delayed response" genes, including those that produce cyclins and Cdk proteins (figure 11.21).

Tumor-suppressor Genes. Other growth factors utilize a negative approach to cell cycle control. They block passage through the G_1 checkpoint by preventing cyclins from binding to Cdk, thus inhibiting cell division. Genes that normally inhibit cell division are called tumor-suppressor genes. When mutated, they can also lead to unrestrained cell division, but only if both copies of the gene are mutant. Hence, these cancer-causing mutations are *recessive*.

The most thoroughly understood of the tumor-suppressor genes is the retinoblastoma (*Rb*) gene. This gene was originally cloned from children with a rare form of eye cancer inherited as a recessive trait, implying that the normal gene product was a cancer suppressor that helped keep cell division in check. The *Rb* gene encodes a protein present in ample amounts within the nucleus. This protein interacts with many key regulatory proteins of the cell cycle, but how it does so depends upon its state of phosphorylation. In G_0 phase, the Rb protein is dephosphorylated. In this state, it binds to and ties up a set of regulatory proteins, like myc and fos, needed for cell proliferation, blocking their action and so inhibiting cell division (see figure 11.19). When phosphorylated, the Rb protein releases its captive regulatory proteins, freeing them to act and so promoting cell division. Growth factors lessen the inhibition the Rb protein imposes by activating kinases that phosphorylate it. Free of Rb protein inhibition, cells begin to produce cyclins and Cdk, pass the G_1 checkpoint, and proceed through the cell cycle. Figure 11.22 summarizes the types of genes that can cause cancer when mutated.

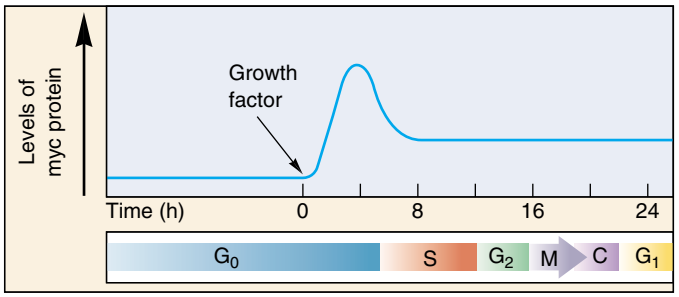
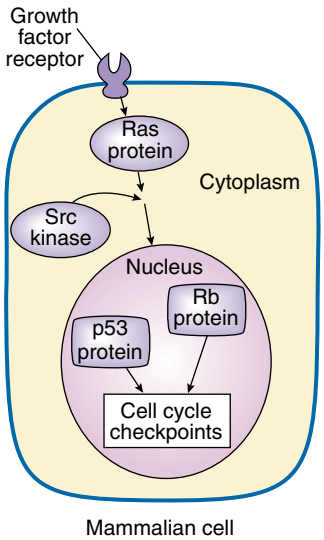


FIGURE 11.21
The role of *myc* in triggering cell division. The addition of a growth factor leads to transcription of the *myc* gene and rapidly increasing levels of the myc protein. This causes G_0 cells to enter the S phase and begin proliferating.



Key proteins associated with human cancers	
Growth factor receptor	More per cell in many breast cancers
Ras protein	Activated by mutations of *ras* in 20–30% of all cancers
Src kinase	Activated by mutations in 2–5% of all cancers
Rb protein	Mutated in 40% of all cancers
p53 protein	Mutated in 50% of all cancers

FIGURE 11.22
Mutations cause cancer. Mutations in genes encoding key components of the cell division-signaling pathway are responsible for many cancers. Among them are proto-oncogenes encoding growth factor receptors, such as ras protein, and kinase enzymes, such as src, that aid ras function. Mutations that disrupt tumor-suppressor proteins, such as Rb and p53, also foster cancer development.

The progress of mitosis is regulated by the interaction of two key classes of proteins, cyclin-dependent protein kinases and cyclins. Some growth factors accelerate the cell cycle by promoting cyclins and Cdks, others suppress it by inhibiting their action.

Chapter 11

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Summary

Questions

Media Resources

11.1 Bacteria divide far more simply than do eukaryotes.

- Bacterial cells divide by simple binary fission.
- The two replicated circular DNA molecules attach to the plasma membrane at different points, and fission is initiated between those points.

1. How is the genome replicated prior to binary fission in a bacterial cell?

- Cell Division Introduction
- Prokaryotes
- Scientists on Science: Ribozymes

11.2 Chromosomes are highly ordered structures.

- Eukaryotic DNA forms a complex with histones and other proteins and is packaged into chromosomes.
- In eukaryotic cells, DNA replication is completed during the S phase of the cell cycle, and during the G_2 phase the cell makes its final preparation for mitosis.
- Along with G^1, these two phases constitute the portion of the cell cycle called interphase, which alternates with mitosis and cytokinesis.

2. What are nucleosomes composed of, and how do they participate in the coiling of DNA?

3. What are the differences between heterochromatin and euchromatin?

4. What is a karyotype? How are chromosomes distinguished from one another in a karyotype?

- Chromosomes

11.3 Mitosis is a key phase of the cell cycle.

- The first stage of mitosis is prophase, during which the mitotic spindle apparatus forms.
- In the second stage of mitosis, metaphase, the chromosomes are arranged in a circle around the periphery of the cell.
- At the beginning of the third stage of mitosis, anaphase, the centromeres joining each pair of sister chromatids separate, freeing the sister chromatids from each other.
- After the chromatids physically separate, they are pulled to opposite poles of the cell by the microtubules attached to their centromeres.
- In the fourth and final stage of mitosis, telophase, the mitotic apparatus is disassembled, the nuclear envelope re-forms, and the chromosomes uncoil.
- When mitosis is complete, the cell divides in two, so that the two sets of chromosomes separated by mitosis end up in different daughter cells.

5. Which phases of the cell cycle is generally the longest in the cells of a mature eukaryote?

6. What happens to the chromosomes during S phase?

7. What changes with respect to ribosomal RNA occur during prophase?

8. What event signals the initiation of metaphase?

9. What molecular mechanism seems to be responsible for the movement of the poles during anaphase?

10. Describe three events that occur during telophase.

11. How is cytokinesis in animal cells different from that in plant cells?

- Art Activity: Mitosis Overview
- Art Activity: Plant Cell Mitosis
- Mitosis
- Mitosis
- Student Research: Nuclear Division in Drosophila

11.4 The cell cycle is carefully controlled.

- The cell cycle is regulated by two types of proteins, cyclins and cyclin-dependent protein kinases, which permit progress past key "checkpoints" in the cell cycle only if the cell is ready to proceed further.
- Failures of cell cycle regulation can lead to uncontrolled cell growth and lie at the root of cancer.

12. What aspects of the cell cycle are controlled by the G_1, G_2, and M checkpoints? How are cyclins and cyclin-dependent protein kinases involved in cell cycle regulation at checkpoints?

- Exploration: Regulating the cell cycle