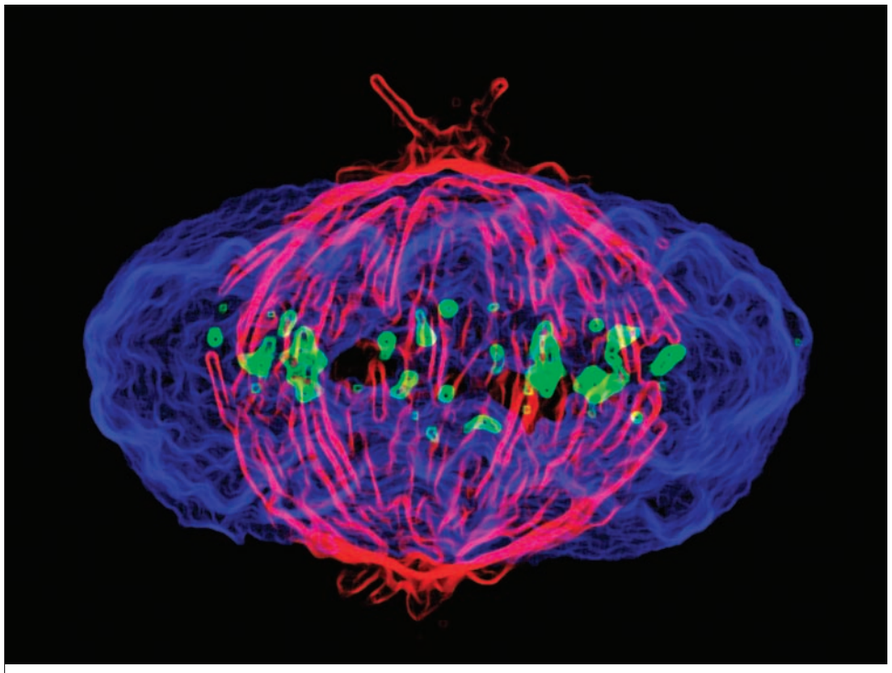
A cell in mitosis (fluorescence micrograph). The spindle (red) is separating copies of the cell's chromosomes (green) prior to cell division.



Dr. Paul Andrews, University of Dundee/Science Photo Library/Photo Researchers, Inc.

Study Plan

10 Cell Division and Mitosis

Why It Matters

The first rays of the sun dance over the wild Alagnak River of the Alaskan tundra. This September morning, life is both beginning and ending in the clear, cold waters. By the thousands, mature silver salmon have returned from the open ocean to spawn in their native freshwater stream. The salmon rest briefly in quiet eddies, then continue upstream **(Figure 10.1).** They are tinged with red, the color of spawning.

A female salmon pauses, then hollows out a shallow nest in the gravel riverbed. Now scores of translucent pink eggs emerge from her body (see Figure 10.1, inset). Within moments, a male salmon appears and sheds a cloud of sperm over the eggs. Trout and other predators will consume most of the eggs; but a few fertilized eggs will survive and give rise to a new generation of salmon.

The female lingers for some hours, but depleted of eggs and with vital organs failing, she soon dies and floats to the surface. A bald eagle loses no time in retrieving her carcass and consuming it on the riverbank. Yet, her remains speak of a remarkable journey. That female silver salmon started life as a pea-sized egg that was fertilized in the Alagnak's gravel riverbed. She hatched in the

Chris Huss

Figure 10.1
The end of one generation of silver salmon *(Oncorhynchus kisutch)* and the beginning of the next in the Alagnak River in Alaska. The inset shows eggs being laid by a female salmon.

stream, fed, and grew for a time, then migrated to the sea; within 3 years in the ocean, she became a fully grown adult salmon, fashioned from billions of cells. Early in her development, some of her cells were destined for reproduction, and in time, they gave rise to eggs that, after her return to the stream of her birth, were laid as part of an ongoing story of birth and reproduction.

For humans, as for the silver salmon and all other organisms, reproduction depends on the capacity of individual cells to grow and then to divide. Starting with a fertilized egg in your mother's body, a single cell divided into two, the two into four, and so on, until billions of cells were growing, developing along genetically determined pathways, and dividing further to produce the tissues and organs. Cell divisions still continue in many parts of the body. For example, constant cell divisions produce enough cells to replace the lining of the small intestine every 5 days; more than 2 million cells divide *each second* to maintain the supply of red blood cells. Cell divisions also underlie the development of egg or sperm cells in your body. All human cell divisions proceed almost without error despite the complexities of the mechanism.

The high accuracy of eukaryotic cell division depends on three elegantly interrelated systems. One system is DNA replication, which duplicates a DNA molecule into two copies with almost perfect fidelity. The second system is a mechanical system of microtubules, which divides the DNA copies precisely between the daughter cells. The third mechanism is an elaborate system of molecular controls that regulates when and where division occurs and corrects random mistakes. This chapter focuses on the mechanical and regulatory systems of cell division.

10.1 The Cycle of Cell Growth and Division: An Overview

As a prelude to dividing, most eukaryotic cells enter a period of growth, in which they synthesize proteins, lipids, and carbohydrates and at one stage replicate the nuclear DNA. After the growth period, the nuclei divide and, usually, *cytokinesis* (*cyto* = cell, derived from "hollow vessel"; *kinesis* = movement)—the division of the cytoplasm—follows, partitioning nuclei to daughter cells. Each daughter nucleus contains one copy of the replicated DNA. The sequence of events—a period of growth followed by nuclear division and cytokinesis—is known as the **cell cycle.**

The Products of Mitosis Are Genetic Duplicates of the Dividing Cell

In eukaryotic cell cycles, nuclear division after the growth period occurs by one of two mechanisms: *mitosis* or *meiosis*. **Mitosis** divides the replicated DNA equally and with great precision, producing daughter nuclei that are exact genetic copies of the parental nucleus. Cytokinesis segregates the daughter nuclei into separate cells. This version of the cell cycle—growth and mitosis followed by cytokinesis—is the mechanism by which multicellular eukaryotes increase into size and maintain their body mass. It is also the mechanism by which many single-celled eukaryotes such as yeast and protozoa reproduce. Another cell division process, meiosis, produces daughter nuclei that differ genetically from the parental nuclei entering the process. Meiosis occurs as part of the developmental changes that produce gametes in animals and spores in plants and many fungi.

This chapter concentrates on mitosis; meiosis and its role in generating genetic diversity are covered in Chapter 11. How prokaryotic organisms grow and divide also is explored in this chapter. We begin our discussion with **chromosomes,** the nuclear units of genetic information divided and distributed by mitotic cell division.

Chromosomes Are the Genetic Units Divided by Mitosis

In all eukaryotes, the hereditary information of the nucleus is distributed among individual, linear DNA molecules. These DNA molecules are combined with proteins, which stabilize the DNA molecules, maintain their structure, and control the activity of individual genes, the segments of DNA that code for proteins. Each linear DNA molecule, with its associated proteins, is known as a *chromosome* (*chroma* = color, referring to the strong colors the chromosomes of dividing cells take on when stained with dyes used to

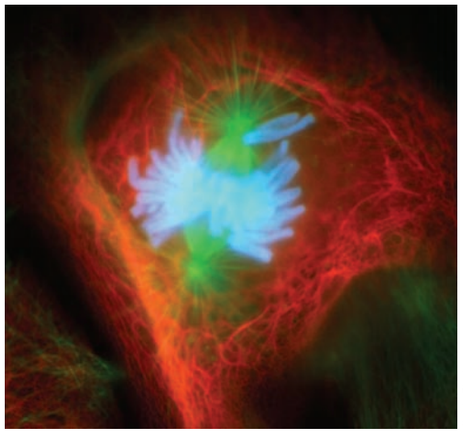


Figure 10.2
Eukaryotic chromosomes (blue) in a dividing animal cell.

prepare cells for light microscopy, and *soma* = body; **Figure 10.2**).

Many eukaryotes have two copies of each type of chromosome in their nuclei, so their chromosome complement is said to be **diploid**, or 2*n*. For example, humans have 23 pairs of chromosomes for a diploid number of 46 chromosomes. Other eukaryotes, mostly microorganisms, have only one copy of each type of chromosome in their nuclei, so their chromosome complement is said to be **haploid**, or *n*. For example, yeast is a haploid organism with16 different chromosomes. Still others, such as many plant species, have three, four, or even more complete sets of chromosomes in each cell. The number of chromosome sets is called the **ploidy** of a cell or species.

During replication, each chromosome is duplicated into two exact copies called **sister chromatids.** Mitosis separates the sister chromatids and places one in each of the two daughter nuclei produced by the division. *As a result of this precise division, each daughter nucleus receives exactly the same number and types of chromosomes and contains the same genetic information as the parent cell entering the division.* The equal distribution of daughter chromosomes to each of the two cells that result from cell division is **chromosome segregation.**

The precision of chromosome replication and segregation in the mitotic cell cycle underlies the growth of all multicellular eukaryotes. Each person's development from a fertilized egg, through billions of mitotic divisions, reflects the precision of mitotic division.

Study Break

Compare the DNA content of daughter cells with that of the parent cell.

10.2 The Mitotic Cell Cycle

Growth and division of both diploid and haploid cells occurs by the mitotic cell cycle. The first stage of the mitotic cell cycle is **interphase.** During this stage, the cell grows and replicates its DNA before undergoing mitosis (also called *M phase*) and cytokinesis **(Figure 10.3).** Internal regulatory controls trigger each phase, ensuring that the processes of one phase are completed successfully before the next phase can begin. In multicellular eukaryotes, the internal controls are modified by external signal molecules such as hormones, which coordinate the division of individual cells with the overall developmental and metabolic processes of the organism.

Interphase Extends from the End of One Mitosis to the Beginning of the Next Mitosis

Interphase begins as a daughter cell from a previous division cycle enters an initial period of cytoplasmic growth. During this initial growth stage, called the **G_1 phase** of the cell cycle, the cell makes proteins and other types of cellular molecules but not nuclear DNA (the *G* in G_1 stands for *gap,* referring to the absence of DNA synthesis). Then, if the cell is going to divide,

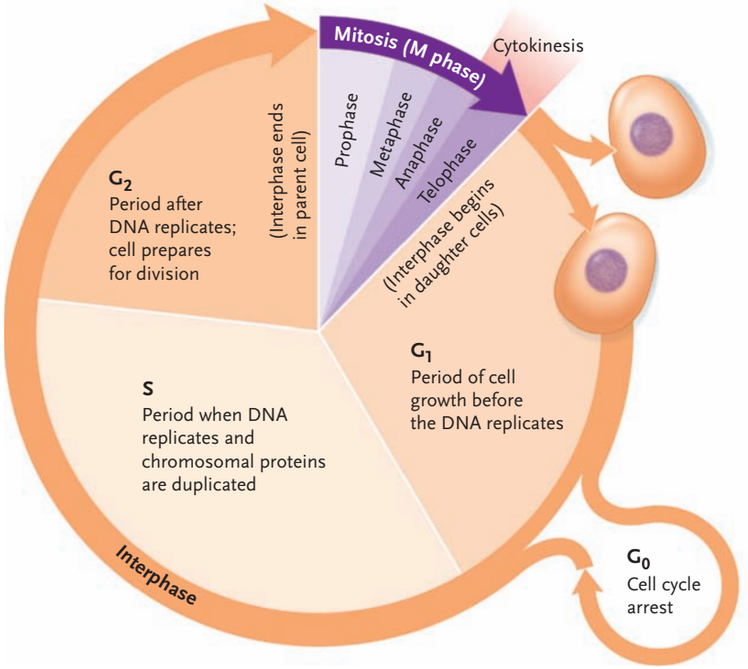


Figure 10.3
The cell cycle. The length of G_1 varies, but for a given cell type, the timing of S, G_2, and mitosis is usually relatively uniform. Cytokinesis (segment at 2 o'clock) usually begins while mitosis is in progress and reaches completion as mitosis ends. Cells in a state of division arrest are considered to enter a side loop or shunt from G_1 called G_0.

DNA replication begins, initiating the **S phase** of the cell cycle (S stands for *synthesis,* meaning DNA synthesis).

During the S phase, the cell duplicates the chromosomal proteins, as well as the DNA, and continues the synthesis of other cellular molecules. As the S phase is completed, the cell enters the **G_2 phase** of the cell cycle (G_2 refers to the second gap during which there is no DNA synthesis). During G_2, the cell continues to synthesize proteins, including those required for mitosis, and the cell continues to grow. At the end of G_2, which marks the end of interphase, mitosis begins. During all the steps of interphase, the chromosomes are in their extended form, making them invisible under a light microscope.

Usually, G_1 is the only phase of the cell cycle that varies in length. The other phases are typically uniform in length within a species. Thus, whether cells divide rapidly or slowly primarily depends on the length of G_1. Once DNA replication begins, most mammalian cells take about 10 to 12 hours to proceed through the S phase, about 4 to 6 hours to go through G_2, and about 1 hour or less to complete mitosis.

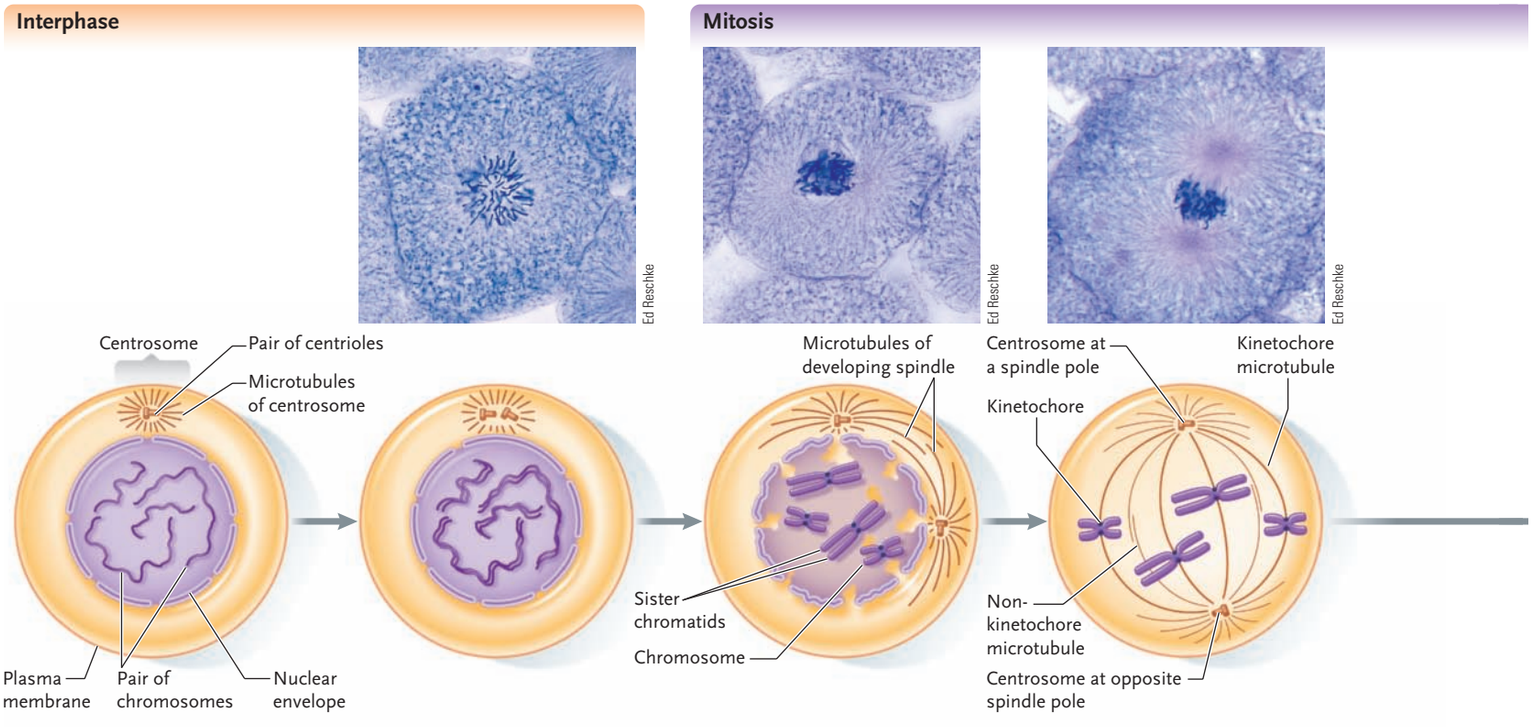
G_1 is also the stage in which many cell types stop dividing. This state of division arrest is often designated the **G_0 phase** (see Figure 10.3). For example, in humans, most cells of the nervous system stop dividing once they are fully mature.

The events of interphase are an important focus of research, particularly the regulatory controls for the transition from the G_1 phase to the S phase, and with it, the commitment to cell division. Understanding the molecular events that regulate the G_1/S phase transition is important because one of the hallmarks of cancer is loss of the normal control of that transition.

After Interphase, Mitosis Proceeds in Five Stages

Once it begins, mitosis proceeds continuously, without significant pauses or breaks. However, for convenience in study, biologists separate mitosis into five sequential stages: *prophase* (*pro* = before), *prometaphase* (meta = between), *metaphase, anaphase* (*ana* = back), and *telophase* (*telo* = end). Mitosis in an animal cell and a plant cell is shown in **Figures 10.4** and **10.5,** respectively. The entire process takes from 1 to 4 hours in most eukaryotes.

Prophase. During **prophase**, the duplicated chromosomes within the nucleus *condense* from the greatly



The chromosomes are unreplicated and extend throughout the nucleus. For simplicity we show only two pairs of chromosomes. One of each pair was inherited from one parent, and the other was inherited from the other parent.

After replication during the S phase of interphase, each chromosome is double at all points and now consists of two sister chromatids. The centrioles within the centrosome have also doubled into pairs.

The chromosomes condense into threads that become visible under the light microscope. Each chromosome is double as a result of replication. The centrosome has divided into two parts, which are generating the spindle as they separate.

The nuclear envelope has disappeared and the spindle enters the former nuclear area. Microtubules from opposite spindle poles attach to the two kinetochores of each chromosome.

Figure 10.4
The stages of mitosis. Light micrographs show mitosis in an animal cell (whitefish embryo). Diagrams show mitosis in an animal cell with two pairs of chromosomes.

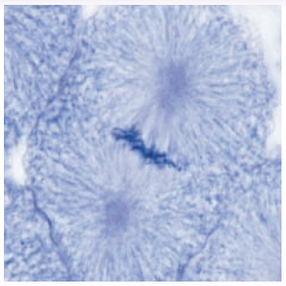
extended state typical of interphase into compact, rodlike structures. As they condense, the chromosomes appear as thin threads under the light microscope. (The word *mitosis* [*mitos* = thread] is derived from this threadlike appearance.) At this point, each chromosome is a double structure made up of two identical sister chromatids. While condensation is in progress, the nucleolus becomes smaller and eventually disappears in most species. The disappearance reflects a shutdown of all types of RNA synthesis, including the ribosomal RNA made in the nucleolus.

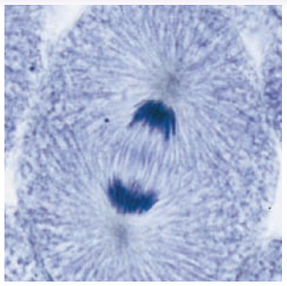
Why is condensation necessary? Each diploid human cell, although on average only 40 to 50 nm in diameter, contains *2 meters* of DNA distributed among 23 pairs of chromosomes. Condensation during prophase packs these long DNA molecules into units small enough to be divided successfully during mitosis.

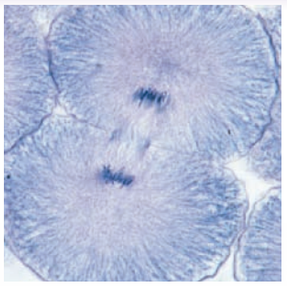
In the cytoplasm, the mitotic **spindle** (**Figure 10.6;** see also Figure 10.11), the structure that actually separates chromatids, begins to form between the two centrosomes as they start migrating toward the opposite ends of the cell, where they will form the **spindle poles.** The spindle develops as two bundles of microtubules that radiate from the two spindle poles.

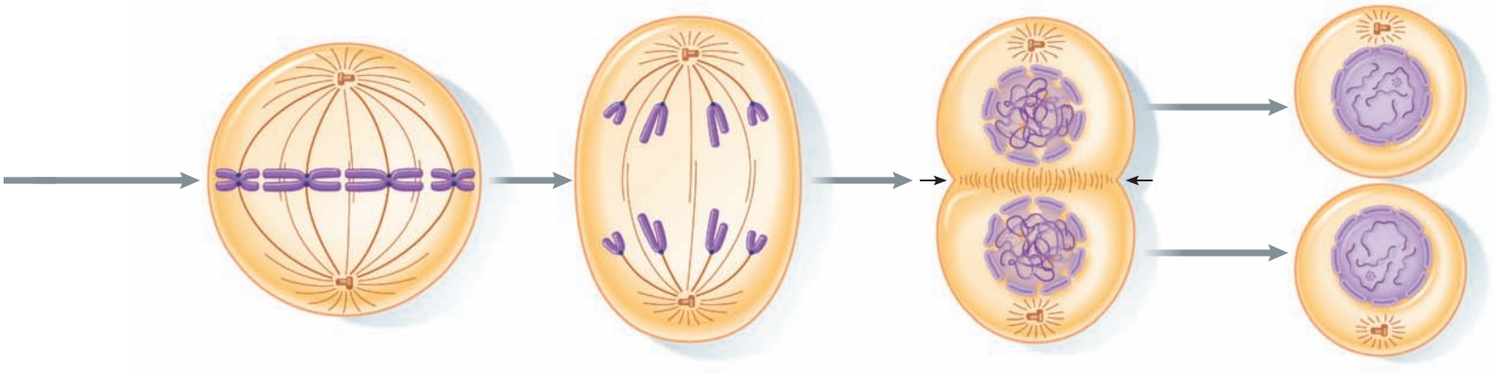
Prometaphase. At the end of prophase, the nuclear envelope breaks down, heralding the beginning of **prometaphase.** The developing spindle now enters the former nuclear area. Bundles of spindle microtubules grow from centrosomes at the *opposite spindle poles* toward the center of the cell. By this time, a complex of several proteins, a **kinetochore,** has formed on each chromatid at the **centromere,** a region named because it lies centrally in many chromosomes and because it forms a segment that is often narrower than the rest of the chromosome. *Kinetochore microtubules* bind to the kinetochores. These connections determine the outcome of mitosis, because they attach the sister chromatids of each chromosome to microtubules leading to the opposite spindle poles (see Figure 10.6). Nonkinetochore microtubules overlap those from the opposite spindle pole.

Metaphase. During **metaphase,** the spindle reaches its final form and the spindle microtubules move the chromosomes into alignment at the spindle midpoint, also called the *metaphase plate*. The chromosomes complete their condensation in this stage. The pattern of condensation gives each chromosome a characteristic shape, determined by the location of the centromere


Ed Reschke


Ed Reschke


Ed Reschke



Metaphase
The chromosomes become aligned at the spindle midpoint.

Anaphase
The spindle separates the two sister chromatids of each chromosome and moves them to opposite spindle poles.

Telophase
The chromosomes unfold and return to the interphase state, and new nuclear envelopes form around the daughter nuclei. The cytoplasm is beginning to divide by furrowing at the points marked by arrows.

G_1 of the following interphase
The two daughter cells are genetic duplicates of the parental cell that entered mitotic division.

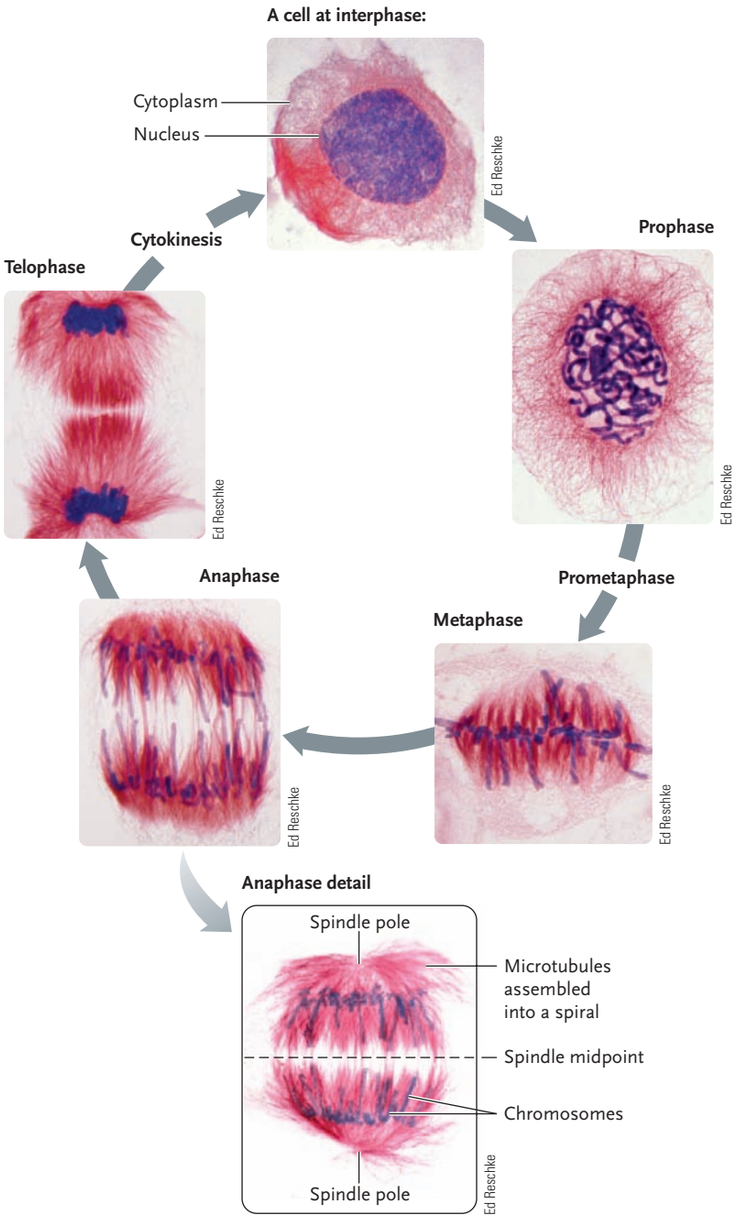


Figure 10.5
Mitosis in the blood lily *Haemanthus*. The chromosomes are stained blue; the spindle microtubules are stained red.

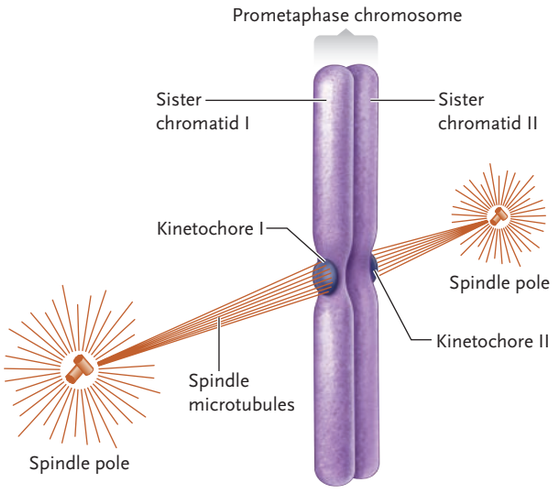


Figure 10.6
Spindle connections made by chromosomes at mitotic prometaphase. The two kinetochores of the chromosome connect to opposite spindle poles, ensuring that the chromatids are separated and moved to opposite spindle poles during anaphase.

and the length and thickness of the arms that extend from the centromere. The shapes and sizes of all the chromosomes at metaphase form the **karyotype** of the species. In many cases, the karyotype is so distinctive that a species can be identified from this characteristic alone. How human chromosomes are prepared for analysis as a karyotype is shown in **Figure 10.7.**

Once the chromosomes are assembled at the spindle midpoint, with the sister chromatids of each chromosome attached to microtubules leading to opposite spindle poles, metaphase is complete.

Anaphase. During **anaphase**, the spindle separates sister chromatids and pulls them to opposite spindle poles. The first signs of chromosome movement can be seen at the centromeres, where tension developed by the spindle pulls the kinetochores toward opposite poles. The movement continues until the separated chromatids, now called *daughter chromosomes,* have reached the two poles. At this point, chromosome segregation has been completed.

Telophase. During **telophase**, the spindle disassembles and the chromosomes at each spindle pole decondense and return to the extended state typical of interphase. As decondensation proceeds, the nucleolus reappears, RNA transcription resumes, and a new nuclear envelope forms around the chromosomes at each pole producing the two daughter nuclei. At this point, nuclear division is complete, and the cell has two nuclei.

Cytokinesis Completes Cell Division by Dividing the Cytoplasm between Daughter Cells

Cytokinesis, the division of the cytoplasm, usually follows the nuclear division stage of mitosis and produces two daughter cells, each containing one of the daughter nuclei. In most cells, cytokinesis begins during telophase or even late anaphase. By the time cytokinesis is completed, the daughter nuclei have progressed to the interphase stage and entered the G_1 phase of the next cell cycle.

Cytokinesis proceeds by different pathways in the various kingdoms of eukaryotic organisms. In animals, protists, and many fungi, a groove, the **furrow**, girdles the cell and gradually deepens until it cuts the cytoplasm into two parts. In plants, a new cell wall, called the **cell plate**, forms between the daughter nuclei and grows laterally until it divides the cytoplasm. In both

Figure 10.7 Research Method

Preparing a Human Karyotype

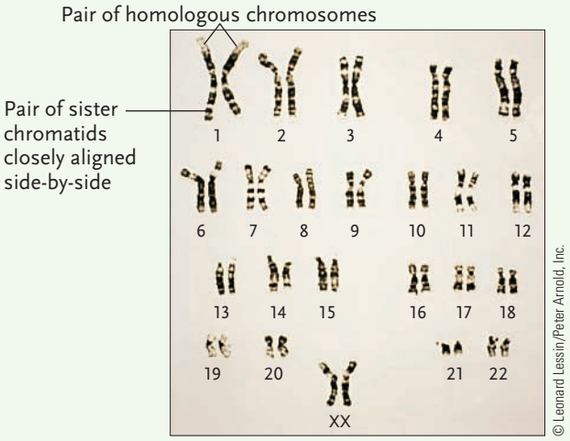
PURPOSE: A karyotype is a display of chromosomes of an organism arranged in pairs. A normal karyotype has a characteristic appearance for each species. Examination of the karyotype of the chromosomes from a particular individual indicates whether the individual has a normal set of chromosomes or whether there are abnormalities in number or appearance of individual chromosomes, and also indicates the species.

PROTOCOL:

1. Add sample (for example, blood) to culture medium that has stimulator for growth and division of white blood cells. Incubate at 37°C. Add colchicine, which causes spindle to disassemble, to arrest mitosis at metaphase.

2. Stain the cells so that the chromosomes are distinguished. Some stains produce chromosome-specific banding patterns, as shown in the photograph below.

3. View the stained cells under a microscope equipped with a digital imaging system and take a digital photograph. A computer processes the photograph to arrange the chromosomes in pairs and number them according to size and shape.



INTERPRETING THE RESULTS: The karyotype is evaluated with respect to the scientific question being asked. For example, it may identify a particular species, or it may indicate whether or not the chromosome set of a human (fetus, child, or adult) is normal or aberrant.

cases, the plane of cytoplasmic division is determined by the layer of microtubules that persist at the former spindle midpoint.

Furrowing. In furrowing, the layer of microtubules that remains at the former spindle midpoint expands laterally until it stretches entirely across the dividing cell **(Figure 10.8).** As the layer develops, a band of microfilaments forms just inside the plasma membrane, forming a belt that follows the inside boundary of the cell in the plane of the microtubule layer (microfilaments are discussed in Section 5.3). Powered by motor proteins, the microfilaments slide together, tightening the band and constricting the cell. The constriction forms a groove—the furrow—in the plasma membrane. The furrow gradually deepens, much like the tightening of a drawstring, until the daughter cells are completely separated. The cytoplasmic division separates the daughter nuclei into the two cells and, at the same time, distributes the organelles and other structures (which also have doubled) approximately equally between the cells.

Cell Plate Formation. In cell plate formation, the layer of microtubules that persists at the former spindle midpoint serves as an organizing site for vesicles produced by the endoplasmic reticulum (ER) and Golgi complex **(Figure 10.9).** As the vesicles collect, the layer expands until it spreads entirely across the dividing cell. During this expansion, the vesicles fuse together and their contents assemble into a new cell wall, the cell plate, that stretches completely across the former spindle midpoint. The junction separates the cytoplasm and its organelles into two parts and isolates the daughter nuclei in separate cells. The plasma membranes that line the two sur-

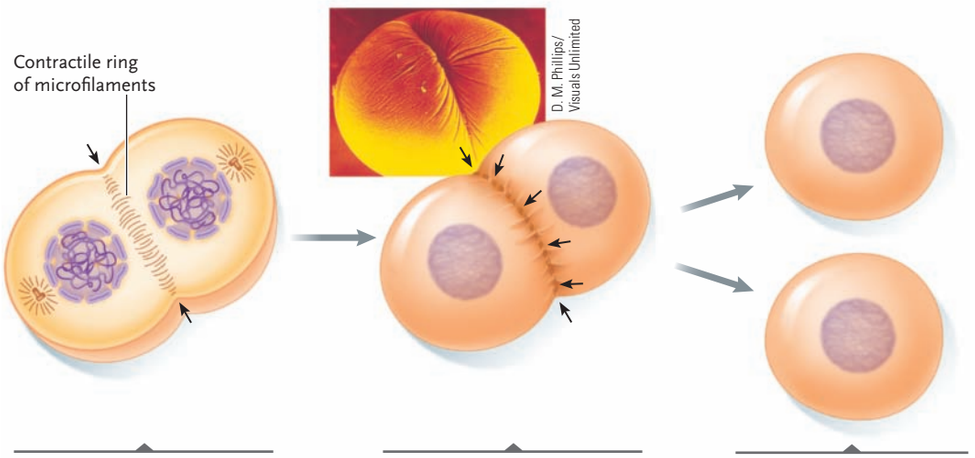


Figure 10.8
Cytokinesis by furrowing. The micrograph shows a furrow developing in the first division of a fertilized egg cell.

faces of the cell plate are derived from the vesicle membranes.

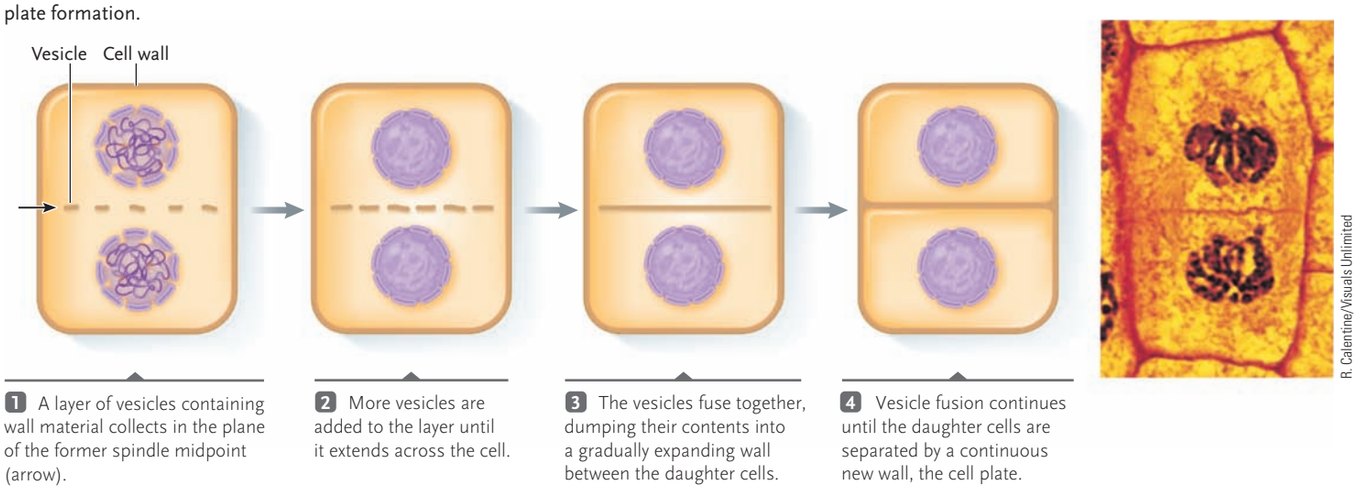
Microscopic pores, lined with plasma membrane, remain open in the cell plate. These openings, called *plasmodesmata* (singular, *plasmodesma*), form membrane-lined channels that directly connect the cytoplasm of the daughter cells. Molecules and ions that flow through the channels create direct avenues of communication between the daughter cells (see Section 5.4).

The Mitotic Cell Cycle Is Significant for Both Development and Reproduction

The mitotic cycle of interphase, nuclear division, and cytokinesis accounts for the growth of multicellular eukaryotes from single initial cells, such as a fertilized egg, to fully developed adults. Mitosis also serves as a method of reproduction called **vegetative** or **asexual reproduction**, which occurs in many kinds of plants and protists and in some animals. In asexual reproduction, daughter cells produced by mitotic cell division are released from the parent and grow separately by further mitosis into complete individuals. For example, asexual reproduction occurs when a single-celled protozoan such as an amoeba divides by mitosis to produce two separate individuals or when a leaf cutting is used to generate an entire new plant.

A group of cells produced by mitotic division of a single cell is known as a *clone*. Except for chance DNA mutations, all the cells of a clone are genetically identical because they are produced by mitosis. A clone may consist either of two or more individual cells or two or more entire multicellular organisms. (The *Focus on Research* explains how cells are grown as clones for biological experimentation.)

Figure 10.9
Cytokinesis by cell plate formation.



Focus on Research

Basic Research: Growing Cell Clones in Culture

How can investigators safely test whether a particular substance is toxic to human cells or whether it can cure or cause cancer? One widely used approach is to work with **cell cultures**—living cells grown in laboratory vessels. Many types of prokaryotic and eukaryotic cells can be grown in this way.

When cell cultures are started from single cells, they form **clones:** barring mutations, all the individuals descending from the original cell are genetically identical. Clones are ideal for experiments in genetics, biochemistry, molecular biology, and medicine because the cells lack genetic differences that could affect the experimental results.

Microorganisms such as yeasts and many bacteria are easy to grow in laboratory cultures. For example, the human intestinal bacterium *Escherichia coli* can be grown in solutions (growth media) that contain only an organic carbon source such as glucose, a nitrogen source, and inorganic salts. Under optimal conditions, the cycle of cell growth and division of *E. coli* cells takes 20 minutes. As a result, large numbers of cells are produced in a short time. The cells may be grown in liquid suspensions or on the surface of a solid growth medium such as an agar gel (agar is a polysaccharide extracted from an alga). Many thousands of bacterial strains are used in a wide variety of experimental studies.

Many types of plant cells can also be cultured as clones in specific growth media. With the addition of plant growth hormones, complete plants can often be grown from single cultured cells. Growing plants from cultured cells is particularly valuable in genetic engineering, in which genes introduced into cultured cells can be tracked in fully developed plants. Plants that have been engineered successfully can then be grown simply by planting their seeds.

Animal cells vary in what is needed to culture them. For many types, the culture medium must contain essential amino acids—that is, the amino acids that the cells cannot make for themselves. In addition, mammalian cells require specific growth factors provided by adding blood serum, the fluid part of the blood left after red and white blood cells are removed.

Even with added serum, many types of normal mammalian cells cannot be grown in long-term cultures. Eventually, the cells stop dividing and die. By contrast, tumor cells often form cultures that grow and divide indefinitely.

The first successful culturing of cancer cells was performed in 1951 in the laboratory of George and Margaret Gey (Johns Hopkins University, Baltimore, MD). Gey and Gey's cultures of normal cells died after a few weeks, but the researchers achieved success with a culture of tumor cells from a cancer patient. The cells in culture continued to grow and divide; in fact, descendants of those cells are still being cultured and used for research today. The cells were given the code name *HeLa,* from the first two letters of the patient's first and last names—Henrietta Lacks. Unfortunately, the tumor cells in Henrietta's body also continued to grow, and she died within 2 months of her cancer diagnosis.

Other types of human cells have since been grown successfully in culture, derived either from tumor cells or normal cells that have been "immortalized" by inducing genetic changes that transformed them into tumorlike cells.

Mitosis Varies in Detail But Always Produces Duplicate Nuclei

Although variations occur in the details of mitosis, particularly among protists, fungi, and primitive plants, its function is to duplicate nuclei each with the same set of chromosomes as the nucleus of the parent cell. The process is the same no matter what the chromosome number of the cell is. That is, the number of chromosome sets does not affect the outcome of mitosis because each chromosome attaches individually to spindle microtubules and proceeds independently through the division process.

Study Break

1. What is the order of the stages of mitosis?
2. What is the importance of centromeres to mitosis?
3. Colchicine, an alkaloid extracted from plants, prevents the formation of spindle microtubules. What would happen if a cell enters mitosis when colchicine is present?

10.3 Formation and Action of the Mitotic Spindle

The mitotic spindle is central to both mitosis and cytokinesis. The spindle is made up of microtubules and their motor proteins, and its activities depend on their changing patterns of organization during the cell cycle.

Microtubules form a major part of the interphase cytoskeleton of eukaryotic cells. (Section 5.3 outlines the patterns of microtubule organization in the cytoskeleton.) As mitosis approaches, the microtubules disassemble from their interphase arrangement and

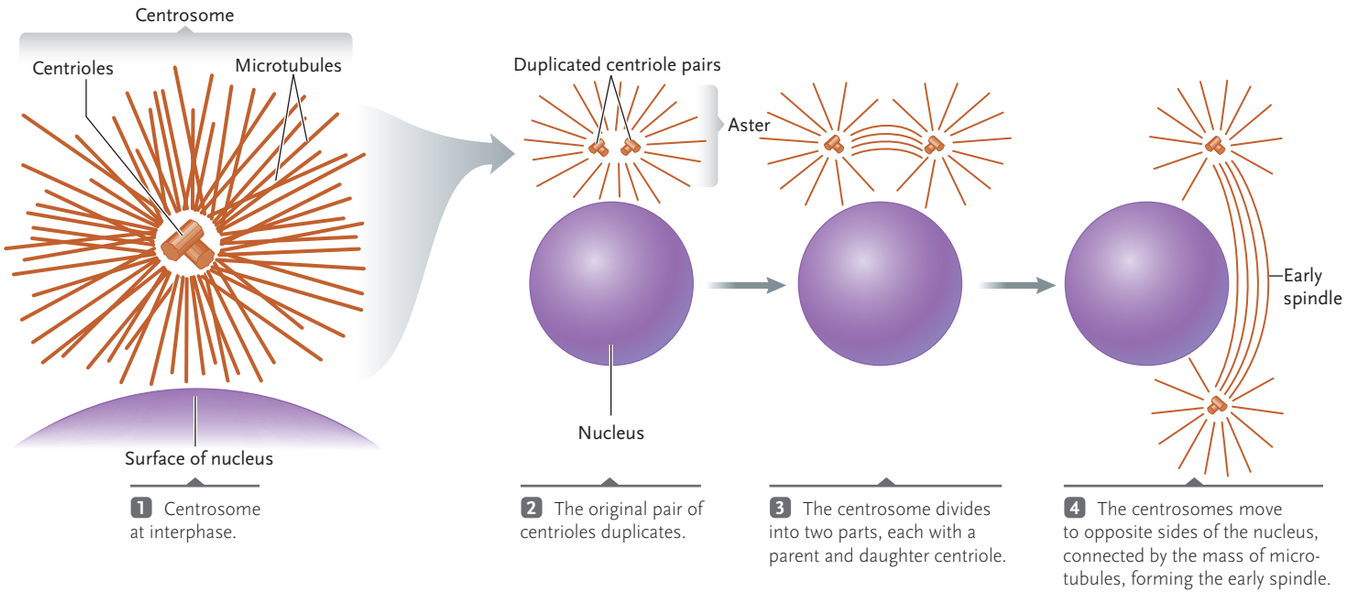


Figure 10.10
The centrosome and its role in spindle formation.

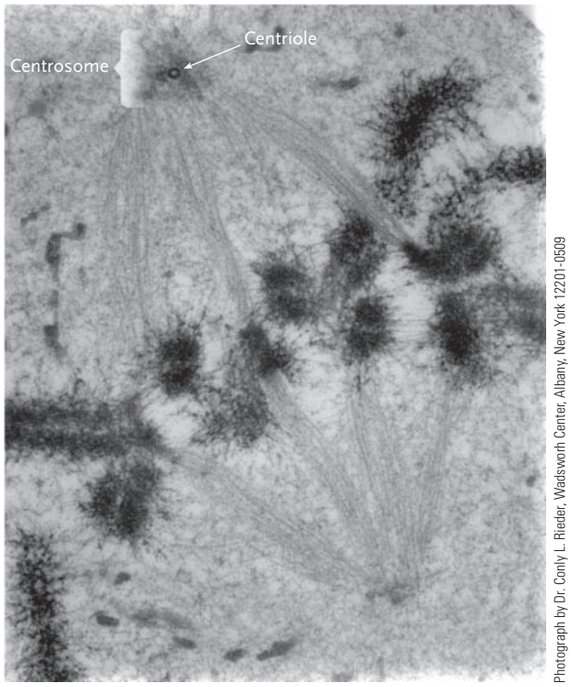
reorganize into the spindle, which grows until it fills almost the entire cell. This reorganization follows one of two pathways in different organisms, depending on the presence or absence of a *centrosome* during interphase. However, once organized, the basic function of the spindle is the same, regardless of whether a centrosome is present.

Animals and Plants Form Spindles in Different Ways

Animal cells and many protists have a **centrosome**, a site near the nucleus from which microtubules radiate outward in all directions (**Figure 10.10,** step 1). The centrosome organizes the microtubule cytoskeleton during interphase and positions many of the cytoplasmic organelles (see Section 5.3). In fact, the centrosome is the main **microtubule organizing center (MTOC)** of the cell. The centrosome contains a pair of **centrioles**, usually arranged at right angles to each other. The radiating microtubules of the centrosome surround the centrioles. These microtubules, rather than the centrioles, generate the spindle. That is, if experimenters remove the centrioles, the spindle still forms by essentially the same pattern.

At the time that DNA replicates during the S phase of the cell cycle, the centrioles within the centrosome also duplicate, producing two pairs of centrioles (Figure 10.10, step 2). As *prophase* begins in the M phase, the centrosome separates into two parts, each containing one "old" and one "new" centriole—one centriole of the original pair and its copy (step 3). The duplicated centrosomes, with the centrioles inside them, continue to separate until they reach opposite ends of the nucleus (step 4). As they move apart, the microtubules between the centrosomes lengthen and increase in number.

By *late prophase,* when the centrosomes are fully separated, the microtubules that extend between them form a large mass around one side of the nucleus called the *early spindle*. When the nuclear envelope subsequently breaks down at the end of prophase, the spindle moves into the region formerly occupied by the



Photograph by Dr. Conly L. Rieder, Wadsworth Center, Albany, New York 12201-0509

Figure 10.11
A fully developed spindle in a mammalian cell. Only microtubules connected to chromosomes have been caught in the plane of this section. One of the centrioles is visible in cross section in the centrosome at the top of the micrograph. Original magnification ×14,000.

nucleus and continues growing until it fills the cytoplasm. The microtubules that extend from the centrosomes also grow in length and extent, producing radiating arrays called **asters** that appear starlike under the light microscope.

By dividing the duplicated centrioles, the spindle ensures that when the cytoplasm divides during cytokinesis, the daughter cells each receive a pair of centrioles and that centrioles are maintained in the cell line. In the cell and its descendents, centrioles carry out their primary function: they generate flagella or cilia, the whiplike extensions that provide cell motility, at one or more stages of the life cycle of a species (see Section 5.5).

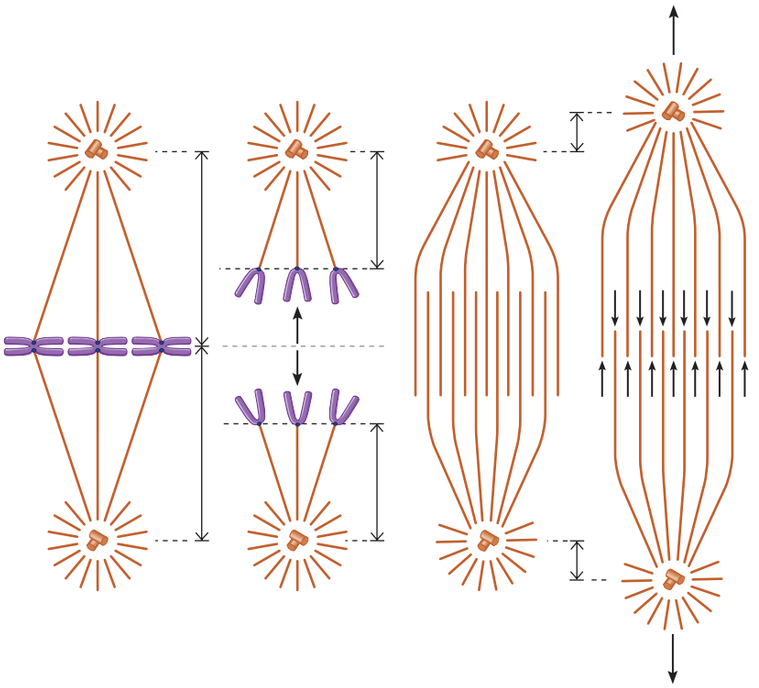
No centrosome or centrioles are present in angiosperms (flowering plants) or in most gymnosperms, such as conifers. Instead, the spindle forms from microtubules that assemble in all directions from multiple MTOCs surrounding the entire nucleus (see Figure 10.5). When the nuclear envelope breaks down at the end of prophase, the spindle moves into the former nuclear region, as in animals.

Mitotic Spindles Move Chromosomes by a Combination of Two Mechanisms

When fully formed at metaphase, the spindle may contain from hundreds to many thousands of microtubules, depending on the species **(Figure 10.11).** In almost all eukaryotes, these microtubules are divided into two groups. *Kinetochore microtubules* connect the chromosomes to the spindle poles **(Figure 10.12a).** *Nonkinetochore microtubules* extend between the spindle poles without connecting to chromosomes; at the spindle midpoint, these microtubules from one pole overlap with microtubules from the opposite pole **(Figure 10.12b).** The separation of the chromosomes at anaphase results from a combination of separate but coordinated movements produced by the two types of microtubules.

In kinetochore microtubule–based movement, the motor proteins in the kinetochores of the chromosomes "walk" along the kinetochore microtubules, pulling the chromosomes with them until they reach the poles **(Figure 10.13).** The kinetochore microtubules disassemble as the kinetochores pass along them; thus, the microtubules become shorter as the movement progresses (see Figure 10.12a). The movement is similar to a locomotive traveling over a railroad track, except that the track is disassembled as the locomotive passes by.

In nonkinetochore microtubule–based movement, the entire spindle is lengthened, pushing the poles farther apart (see Figure 10.12b). The pushing movement is produced by microtubules sliding over one another in the zone of overlap, powered by proteins acting as microtubule motors. In many species, the nonkinetochore microtubules also push the poles apart by growing in length as they slide.



a. The kinetochore microtubules connected to the kinetochores of the chromosomes become shorter, lessening the distance from the chromosomes to the poles.

b. Sliding of the nonkinetochore microtubules in the zone of overlap at the spindle midpoint pushes poles farther apart and increases the total length of the spindle.

Figure 10.12
The two microtubule-based movements of the anaphase spindle.

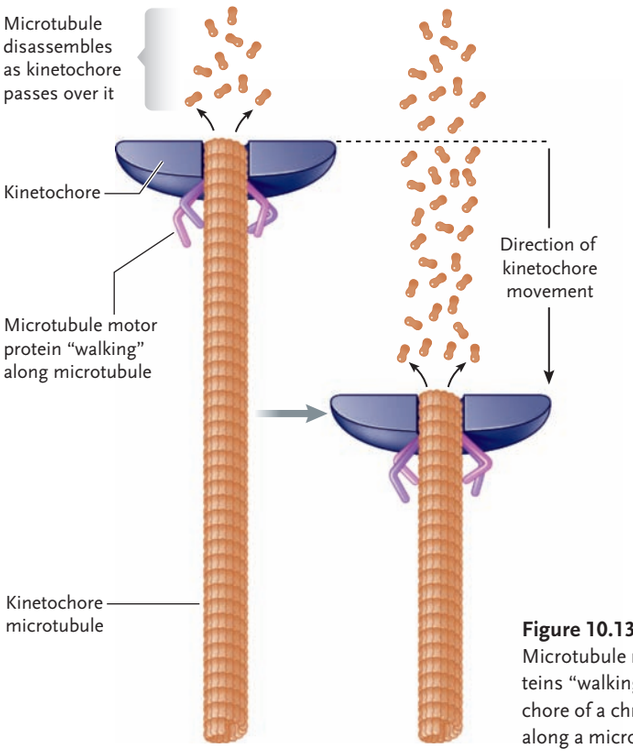


Figure 10.13
Microtubule motor proteins "walking" the kinetochore of a chromosome along a microtubule.

Figure 10.14 Experimental Research

How Do Chromosomes Move during Anaphase of Mitosis?

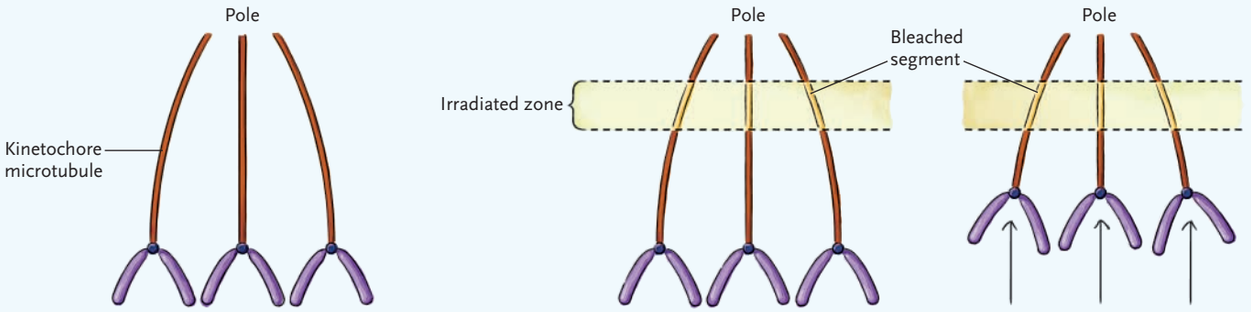
HYPOTHESIS: One hypothesis was that kinetochore microtubules move during anaphase, pulling chromosomes to the poles. An alternative hypothesis was that chromosomes move by sliding over or along kinetochore microtubules.

EXPERIMENT: G. J. Gorbsky and his colleagues made regions of the kinetochore microtubules visibly distinct to test the hypotheses.

1. Kinetochore microtubules were combined with a dye molecule that bleaches when it is exposed to light.

2. The region of the spindle between the kinetochores and the poles was exposed to a microscopic beam of light that bleached a narrow stripe across the microtubules. The bleached region could be seen with a light microscope and analyzed as anaphase proceeded.

RESULTS: The bleached region remained at the same distance from the pole as the chromosomes moved toward the pole.



CONCLUSION: The results support the hypothesis that chromosomes move by sliding over or along kinetochore microtubules.

Researchers discovered kinetochore-based movement by tagging kinetochore microtubules at points with a microscopic beam of ultraviolet light, producing bleached sites that could be seen in the light microscope **(Figure 10.14).** As the chromosomes were pulled to the spindle poles, the bleached sites stayed in the same place. This result showed that the kinetochore microtubules do not move with respect to the poles during the anaphase movement; it is the basis for our understanding of chromosomes' movement along the microtubules.

Study Break

1. How does spindle formation differ in animals and plants?
2. How do mitotic spindles move chromosomes?

10.4 Cell Cycle Regulation

We have noted that a number of internal and external regulatory mechanisms control the mitotic cell cycle. As part of the internal controls, the cell cycle has built-in **checkpoints** to prevent critical phases from beginning until the previous phases are completed. Hormones, growth factors, and other external controls coordinate the cell cycle with the needs of an organism by stimulating or inhibiting division. Some key research contributing to our understanding of cell cycle regulation, particularly defining the genes involved and their protein products, was done using yeast. The *Focus on Research: Model Research Organisms* describes yeast and its role in research in more detail.

Cyclins and Cyclin-Dependent Kinases Are the Internal Controls That Directly Regulate Cell Division

A major factor that regulates cell division is the complex of a protein called **cyclin** with an enzyme called **cyclin-dependent kinase (CDK).** The CDK is a *protein kinase,* which adds phosphate groups to target proteins. The activity of the CDK directly affects the cell cycle, whereas cyclin turns CDK "on" or "off." R. Timothy Hunt, Imperial Cancer Research Fund, London, UK, received a Nobel Prize in 2001 for discovering cyclins.

Focus on Research

Model Research Organisms: The Yeast *Saccharomyces cerevisiae*

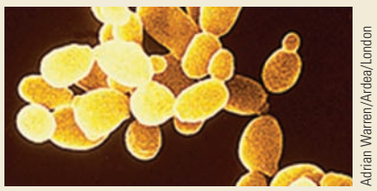
Saccharomyces cerevisiae, commonly known as baker's yeast or brewer's yeast, was probably the first microorganism to have been grown and kept in cultures—a beer-brewing vessel is basically a *Saccharomyces* culture. Favorite strains of baker's and brewer's yeast have been kept in continuous cultures for centuries. The yeast has also been widely used in scientific research; its microscopic size and relatively short generation time make it easy and inexpensive to culture in large numbers in the laboratory.

The cells growing in *Saccharomyces* cultures are haploids. If the culture conditions are kept at optimal levels (which requires only a source of a fermentable sugar such as glucose, a nitrogen source, and minerals), the cells reproduce asexually by budding. *Saccharomyces* has two mating types (that is, sexes). If two yeast cells of different mating types contact one another, they fuse—mate—producing a diploid cell. Diploid cells can also reproduce asexually by budding. Diploid yeast can be induced to reproduce sexually by adjusting cultures to less favorable conditions, such as a reduced nitrogen supply. The cells then undergo meiosis, producing haploid spores. When conditions again become favorable, the spores germinate into haploid cells, which reproduce asexually.

Sexual reproduction allows *Saccharomyces* to be used for genetic crosses. Its large number of offspring makes it possible to detect relatively rare genetic events, as can be done with bacteria. Genetic studies with *Saccharomyces* led to the discovery of some of the genes that control the eukaryotic cell cycle, including those for the entry into DNA replication and both mitotic and meiotic cell division. (Leland Hartwell, Fred Hutchinson Cancer Research Center, Seattle, Washington, and Paul Nurse, Imperial Cancer Research Fund, London, UK, received a Nobel Prize for their work in this area.) Many of these genes, after their first discovery in yeast cells, were found to have counterparts in animals and plants. Genetic studies with *Saccharomyces* were also the first to show the genes carried in the DNA of mitochondria and their patterns of inheritance. The complete DNA sequence of *S. cerevisiae,* which includes more than 12 million base pairs that encode about 6000 genes, was the first eukaryotic genome to be obtained.

Another advantage of yeast for genetic studies is that plasmids, extrachromosomal segments of DNA, have been produced that can be used for introducing genes into yeast cells. Using the plasmids, researchers can alter essentially any of the yeast genes experimentally to test their functions and can introduce genes or DNA samples from other organisms for testing or cloning. These genetic engineering studies have demonstrated that many mammalian genes can replace yeast genes when introduced into the fungi, confirming their close relationships, even though mammals and fungi are separated by millions of years of evolution.

Saccharomyces has been so important to genetic studies in eukaryotes that it is often called the eukaryotic *E. coli.* Research with another yeast, *Schizosaccharomyces pombe,* has been similarly productive, particularly in studies of genes that control the cell cycle.



Adrian Warren/Ardea/London

CDK enzymes are "cyclin-dependent" because they are active only when combined with a cyclin molecule. The levels of the CDKs are the same throughout the cell cycle, but the levels of the cyclins fluctuate, reaching amounts capable of activating CDKs only at particular points of the cell cycle. The name *cyclin* reflects these cyclic changes in its concentration.

Several different cyclin/CDK combinations regulate cell cycle transitions at checkpoints. For example, the two cyclin/CDK combinations that control the cell cycle at the G_1-to-S and the G_2-to-M checkpoints are shown in **Figure 10.15.** At the G_1-to-S checkpoint, cyclin E has reached a concentration high enough to form a complex with CDK2 and activate it. The CDK2 of the complex then phosphorylates a number of cell cycle control proteins, which trigger the cell to make the transition into the S phase. After the transition is made, the level of cyclin E decreases by degradation of the protein. CDK2 then becomes activated again only when cyclin E levels are high at the next G_1-to-S checkpoint.

Similar events occur at the G_2-to-M checkpoint. Cyclin B reaches a sufficient level to complex with CDK1. When the cell is ready to enter mitosis, the CDK1 of the complex phosphorylates a number of target proteins that move the cell from the G_2-to-M phase and promote the stages of mitosis. The activity of the CDK1/cyclin B complex is highest during metaphase; during anaphase, the cyclin B component is degraded and the transition from mitosis to G_1 soon occurs.

Internal Checkpoints Stop the Cell Cycle if Stages Are Incomplete

The cyclin/CDK combinations directly control the cell cycle, but other factors within the cell act as indirect controls by altering the activity of the cyclin/CDK com-

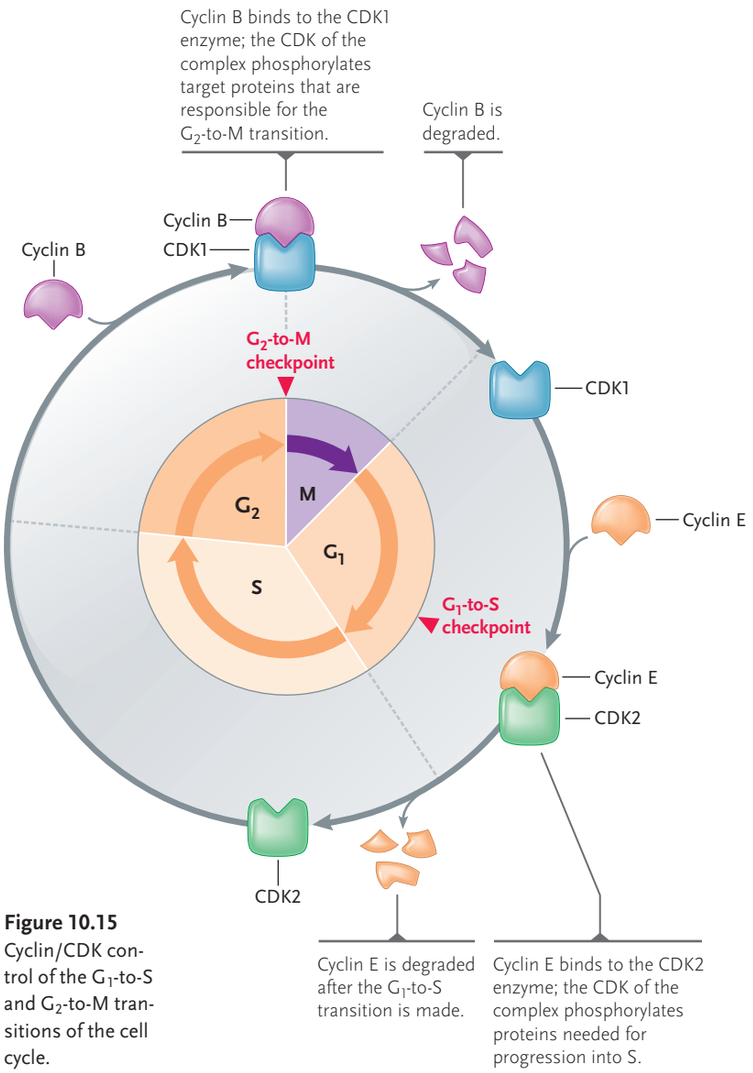


Figure 10.15
Cyclin/CDK control of the G_1-to-S and G_2-to-M transitions of the cell cycle.

plexes. Among the most critical controls are the checkpoints that keep the cycle from progressing to the next phase unless the actions of a previous phase are successfully completed. At each key checkpoint, regulatory events block the cyclin/CDK complex from triggering the associated cell cycle transition until the cell is ready and able to undergo that transition.

For example, as we just described, the cyclin B/CDK1 complex stimulates the cell to enter the M phase. Until the cell is ready to enter mitosis, phosphorylation of a site on CDK1 in the complex by another kinase keeps the CDK inactive. When the cell is ready, a phosphatase removes the inhibitory phosphate, the CDK becomes active, and the cell is moved into mitosis. Control at checkpoints is exerted in many types of circumstances. For instance, if not all of the DNA is replicated during the S phase, the cell slows its progress during G_2 to allow more time for replication to be completed. Similarly, if radiation or chemicals damage DNA, inhibitory events at checkpoints around the cell cycle will slow the cycle to give the cell time to potentially repair the damage.

External Controls Coordinate the Mitotic Cell Cycle of Individual Cells with the Overall Activities of the Organism

The internal controls that regulate the cell cycle are modified by signal molecules that originate from outside the dividing cells. In animals, these signal molecules include the peptide hormones and similar proteins called *growth factors*.

Many of the external factors bind to receptors at the cell surface, which respond by triggering reactions inside the cell. These reactions often include steps that add inhibiting or stimulating phosphate groups to the cyclin/CDK complexes, particularly to the CDKs. The reactions triggered by the activated receptor may also directly affect the same proteins regulated by the cyclin/CDK complexes. The overall effect is to speed, slow, or stop the progress of cell division, depending on the particular hormone or growth factor and the internal pathway that is stimulated. Some growth factors are even able to break the arrest of cells shunted into the G_0 stage and return them to active division. (Hormones, growth factors, and other signal molecules are part of the cell communication system, as discussed in Chapter 7.)

Cell-surface receptors in animals also recognize contact with other cells or with molecules of the extracellular matrix (see Section 5.5). The contact triggers internal reaction pathways that inhibit division by arresting the cell cycle, usually in the G_1 phase. The response, called **contact inhibition**, stabilizes cell growth in fully developed organs and tissues. As long as the cells of most tissues are in contact with one another or the extracellular matrix, they are shunted into the G_0 phase and prevented from dividing. If the contacts are broken, the freed cells often enter rounds of division.

Contact inhibition is easily observed in cultured mammalian cells grown on a glass or plastic surface. In such cultures, division proceeds until all the cells are in contact with their neighbors in a continuous, unbroken, single layer. At this point, division stops. If a researcher then scrapes some of the cells from the surface, cells at the edges of the "wound" are released from inhibition and divide until they form a continuous layer and all the cells are again in contact with their neighbors.

Cell Cycle Controls Are Lost in Cancer

Cancer occurs when cells lose the normal controls that determine when and how often they will divide. Cancer cells divide continuously and uncontrollably, producing a rapidly growing mass called a *tumor* **(Figure 10.16).** Cancer cells also typically lose their adhesions to other cells and often become actively mobile. As a result, in a process called *metastasis,* they tend to break loose from an original tumor, spread throughout the body,

Insights from the Molecular Revolution

Herpesviruses and Uncontrolled Cell Division

Almost all of us harbor one or more herpesviruses as more or less permanent residents in our cells. Fortunately, most of the herpesviruses are relatively benign—one group is responsible for the bothersome but nonlethal oral and genital ulcers known commonly as cold sores or "herpes." But another virus, *herpesvirus 8,* has been implicated as the cause of two kinds of cancer: Kaposi's sarcoma and lymphomas of the body cavity. How does herpesvirus 8 cause the uncontrolled cell division characteristic of malignant tumors? To answer this question, investigators in London and at the Friedrich-Alexander University in Germany decided to examine the effects of herpesvirus 8 on the primary transition point that leads to cell division, the change from G_1 to S. The investigators focused on how the virus might interfere with regulatory mechanisms that regulate the rate of cell division.

One way that cells slow their rate of division is to use regulatory proteins that inhibit cyclin D/CDK complexes. Cylin D combined with either CDK4 or CDK6 contributes to the G_1/S transition and thus stimulates cell division. Three important regulatory proteins, p16, p21, and p27, can slow cell division by binding to cyclin D/CDK complexes. These proteins prevent normal cells from becoming transformed into cancer cells (*p* stands for protein; the number indicates the molecular weight in thousands). Because these proteins have that ability, they are called *tumor suppressor proteins.*

The investigators knew that the DNA of herpesvirus 8 encodes a protein that acts as a cyclin. Could this viral cyclin, *K-cyclin,* be the means by which the herpesvirus bypasses normal controls and triggers the rapid cell division characteristic of cancer? To answer this question, researchers first inserted the DNA coding for K-cyclin into a benign virus. When they infected cultured human cells with this virus, the virus produced K-cyclin, which bound to the human CDK6. These K-cyclin/CDK6 complexes stimulated the initiation of the S phase much faster than the normal cyclin D/CDK6 complexes. In addition, the tumor suppressor proteins that normally regulate cell division by binding to cyclin D/CDK6 complexes were unable to bind to the K-cyclin complexes, resulting in uncontrolled division.

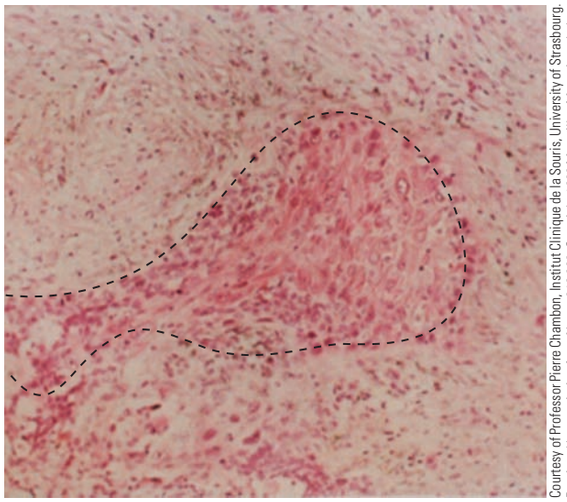
Thus, herpesvirus 8 has evolved as a mechanism that overrides normal cellular controls and triggers cell division. At some point in its evolution, the virus may have picked up a copy of a cyclin gene, which through mutation and selection became the K-cyclin that is unaffected by the inhibitors. Researchers hope that their findings may lead to treatments that can switch off K-cyclin and stop the virally induced tumor growth.

and grow into new tumors in other body regions. Metastasis is promoted by changes that defeat contact inhibition and alter the cell-surface molecules that link cells together or to the extracellular matrix.

Enlarging tumors damage surrounding normal tissues by compressing them and interfering with blood supply and nerve function. Tumors may also break through barriers such as the outer skin, internal cell layers, or the gut wall. The breakthroughs cause bleeding, open the body to infection by microorganisms, and destroy the separation of body compartments necessary for normal function. Both compression and breakthroughs can cause pain that, in advanced cases, may become extreme. As tumors increase in mass, the actively growing and dividing cancer cells may deprive normal cells of their required nutrients, leading to generally impaired body functions, muscular weakness, fatigue, and weight loss.

Cancer cells typically have a number of genes of different types with functions that have been altered in some way to promote uncontrolled cell division or metastasis. One type of altered gene, called an **oncogene**, has a normal, unaltered counterpart in nontumor cells in the same organism. Some of the genes that become oncogenes encode components of the cyclin/CDK system that regulates cell division; others encode proteins that regulate gene activity, form cell surface receptors, or make up elements of the systems controlled by the receptors.

For example, one oncogene encodes a faulty surface receptor that is constantly active, even without binding an extracellular signal molecule. As a result, the internal



Courtesy of Professor Pierre Chambon, Institut Clinique de la Souris, University of Strasbourg. Reprinted by permission from *Nature* 348:699. Copyright 1990 Macmillan Magazines, Ltd.

Figure 10.16
A mass of tumor cells (dashed line) embedded in normal tissue. As is typical, the tumor cells appear more densely packed because they have less cytoplasmic volume than normal cells. Original magnification ×270.

reaction pathways triggered by the receptor, which induce cell division, are continually turned on. Another oncogene encodes a faulty cyclin that constantly activates its CDK and triggers DNA replication and the rest of the cell cycle. (*Insights from the Molecular Revolution* describes an experiment testing the effects of a viral system that induces cancer by overriding normal controls of the cyclin/CDK system.) Cancer, oncogenes, and the alterations that convert normal genes to oncogenes are discussed in further detail in Chapter 16.

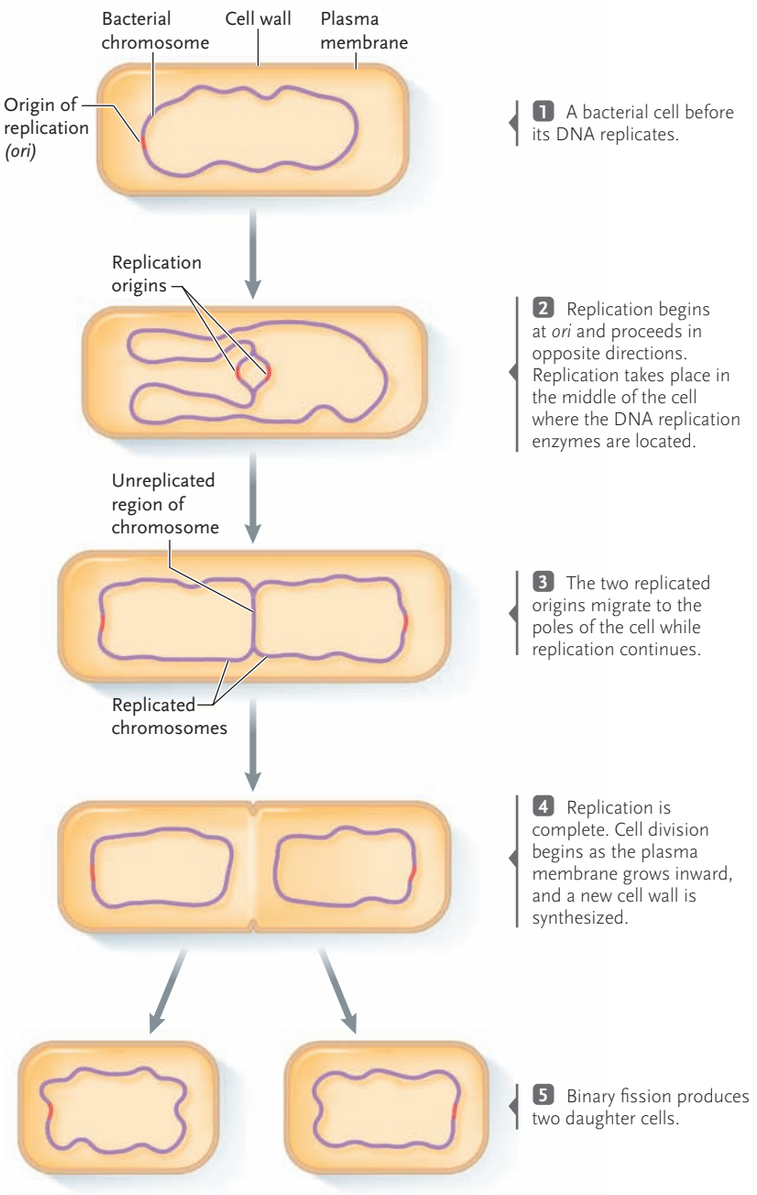


Figure 10.17
Model for the segregation of replicated bacterial chromosomes to daughter cells.

The overview of the mitotic cell cycle and its regulation presented in this chapter only hints at the complexity of cell growth and division. The greatest wonder of the processes is that, despite the complexity of the events, the cell cycle functions almost without error in every multicellular organism. For example, the 2 million per second mitotic divisions that produce red blood cells proceed with few or no detectable errors throughout the lifetimes of most humans.

Study Break

1. Why is a CDK not active throughout the entire cell cycle?
2. How do cyclin/CDK complexes typically trigger transitions in the cell cycle?
3. What is an oncogene? How might an oncogene affect the cell cycle?

10.5 Cell Division in Prokaryotes

Prokaryotes undergo a cycle of cytoplasmic growth, DNA replication, and cell division, producing two daughter cells from an original parent cell. The entire mechanism of prokaryotic cell division is called **binary fission**—that is, splitting or dividing into two parts. There is no known prokaryotic equivalent of mitosis, nor are there prokaryotic equivalents of microtubules, a spindle apparatus, or the cyclin/CDK control proteins.

Replication Occupies Most of the Cell Cycle in Rapidly Dividing Prokaryotic Cells

In most prokaryotes, hereditary information is encoded in a single, circular DNA molecule known as a **bacterial chromosome** (**Figure 10.17,** step 1). In prokaryotic cells dividing at the maximum rate, DNA replication occupies most of the period between cytoplasmic divisions. As soon as replication is complete, the cytoplasm divides to complete the cell cycle. For example, in *Escherichia coli* cells, which divide every 20 minutes, DNA replication occupies all but 1 minute of the entire division cycle.

Replicated Chromosomes Are Distributed Actively to the Halves of the Prokaryotic Cell

In the 1960s, François Jacob of The Pasteur Institute, Paris, France, proposed a model for the segregation of bacterial chromosomes to the daughter cells in which the two chromosomes attach to the plasma membrane near the middle of the cell and separate as a new plasma membrane is added between the two sites during cell

elongation. The essence of this model is that chromosome separation is passive. However, current research indicates that bacterial chromosomes rapidly separate in an active way that is linked to DNA replication events and is independent of cell elongation. The new model is shown in Figure 10.17.

Replication of a bacterial chromosome commences at a specific region called the **origin of replication** (ori). The ori is in the middle of the cell where the enzymes for DNA replication are located. Once the ori has been duplicated, the two origins migrate toward the two ends (poles) of the cell as replication continues for the rest of the chromosome. This active movement distributes the two replicated chromosomes to the two ends of the cell. How this movement occurs is unknown.

Next, cytoplasmic division in prokaryotes occurs through an inward growth of the plasma membrane, along which new cell wall material is assembled to cut the cell into two parts (Figure 10.17, step 5). The new wall divides the replicated DNA molecules and the cytoplasmic structures and molecules equally between the daughter cells.

Mitosis Has Evolved from Binary Fission

The prokaryotic mechanism works effectively because most prokaryotic cells have only a single chromosome; so, if a daughter cell receives at least one copy of the chromosome, its genetic information is complete. By contrast, the genetic information of eukaryotes is divided among several to many chromosomes, with each chromosome containing a much greater length of DNA than a bacterial chromosome. If a daughter cell fails to receive a copy of even one chromosome, the effects are usually lethal. The evolution of mitosis solved the mechanical problems associated with distributing long DNA molecules without breakage. Mitosis provided the level of precision required to ensure that each daughter cell receives a complete complement of the chromosomes, together with a complete copy of the genetic information for the parental cell.

Scientists believe that the ancestral division process was binary fission and that mitosis evolved from that process. Variations in the mitotic apparatus in modern-day organisms illuminate possible intermediates in this evolutionary pathway. For example, in

Unanswered Questions

Disrupted or defective control of cell growth and division can lead to diseases such as cancer. Complex, interacting molecular networks within the cell fine tune the division of each cell in both unicellular and multicellular organisms. Identifying the genes and proteins involved in these networks is crucial both for a complete understanding of cell growth and division and for developing models for diseases caused by cell cycle defects. Many researchers are working in this area worldwide.

How are transitions between phases of the cell cycle regulated?

Research in many labs has shown that transitions are important control points for progression through the cell cycle. If a cell in G_1 phase has damaged DNA, for instance, the cell pauses to repair the DNA before entering S phase, to ensure that any mutations are not passed on to progeny cells. More specifically, one researcher, Raymond Deshaies of Caltech, is using mammalian cells in tissue culture and the yeast *Saccharomyces cerevisiae* as model organisms to characterize the molecular events involved in two cell cycle transitions, G_1 to S and mitosis to G_1. At the G_1-to-S transition, DNA replication enzymes become active. At the mitosis-to-G_1 transition, the mitotic spindle breaks down, allowing the cell to return to G_1 phase. In yeast, both of these transitions are controlled by a specific cellular process for breaking down proteins. Deshaies's research group is performing experiments to determine how the proteins involved in the G_1-to-S and mitosis-to-G_1 transitions work at the molecular and cellular levels and how their activities are controlled.

Can targeting p53 be an effective anticancer therapy?

The factors that trigger uncontrolled cell division to convert normal cells into cancer cells is one of the most relevant areas of current research to humankind in general. The hope is that by working out the molecular events that regulate the cell cycle, the factors that cause cancer can be identified and the progression to cancer can be reversed or at least controlled, thus stopping tumor growth. Investigations of tumor suppressor proteins have developed some of the most promising leads. In their normal role in cells, these factors stop or slow cell division. For example, p53, so named for its molecular weight of 53,000 daltons, is one of the factors that normally prevent cells from progressing from S to G_2 and mitosis when DNA is damaged in some way. Investigators have found that loss of function of p53 is involved in more than 50% of all human cancers. The mutant proteins build up to abnormally high levels in cancer cells.

Clearly, p53 represents a major target for developing new anticancer therapies. Rainer Brachmann at the University of California, Irvine, who is doing research in this direction, has studied many common p53 mutant proteins found in cancers. He has found that by changing particular amino acids at certain positions in the p53 mutant proteins, tumor suppressor function is restored. His lab group is determining the structures of a number of the p53 mutant proteins by X-ray crystallography, and they hope to be able to design small molecules that can stabilize the mutant proteins and perhaps be an effective anticancer therapy.

Peter J. Russell

many primitive eukaryotes, such as dinoflagellates (a type of single-celled alga), the nuclear envelope remains intact during mitosis, and the chromosomes bind to the inner membrane of the nuclear membrane. When the nucleus divides, the chromosomes are segregated.

A more advanced form of the mitotic apparatus is seen in yeasts and diatoms (another type of single-celled alga). In these organisms, the mitotic spindle forms and chromosomes segregate to daughter nuclei without the disassembly and reassembly of the nuclear envelope. Currently, scientists think that the types of mitosis seen in yeasts and diatoms, as well as in animals and higher plants, evolved separately from a common ancestral type. Mitotic cell division, the subject of this chapter, produces two cells that have the same genetic information as the parental cell entering division. In the next chapter, you will learn about meiosis, a specialized form of cell division that produces gametes, which have half the number of chromosomes as that present in diploid cells.

Study Break

1. How do prokaryotes divide?
2. What processes involved in eukaryotic cell division are absent from prokaryotic cell division?

Review

Go to ThomsonNOW™ at www.thomsonedu.com/login to access quizzing, animations, exercises, articles, and personalized homework help.

10.1 The Cycle of Cell Growth and Division: An Overview

- In mitotic cell division, DNA replication is followed by the equal separation—that is, segregation—of the replicated DNA molecules and their delivery to daughter cells. The process ensures that the two cell products of a division have the same genetic information as the parent cell entering division.
- Mitosis is the basis for growth and maintenance of body mass in multicelled eukaryotes, and for the reproduction of many single-celled eukaryotes.
- The DNA of eukaryotic cells is divided among individual, linear chromosomes located in the cell nucleus.
- DNA replication and duplication of chromosomal proteins converts each chromosome into two exact copies known as sister chromatids.

10.2 The Mitotic Cell Cycle

- Mitosis and interphase constitute the mitotic cell cycle. Mitosis occurs in five stages. In prophase (stage 1), the chromosomes condense into short rods and the spindle forms in the cytoplasm (Figures 10.3 and 10.4).
- In prometaphase (stage 2), the nuclear envelope breaks down, the spindle enters the former nuclear area, and the sister chromatids of each chromosome make connections to opposite spindle poles. Each chromatid has a kinetochore that attaches to spindle microtubules (Figures 10.3 and 10.6).
- In metaphase (stage 3), the spindle is fully formed and the chromosomes, moved by the spindle microtubules, become aligned at the metaphase plate (Figures 10.3 and 10.4).
- In anaphase (stage 4), the spindle separates the sister chromatids and moves them to opposite spindle poles. At this point, chromosome segregation is complete (Figures 10.3 and 10.4).
- In telophase (stage 5), the chromosomes decondense and return to the extended state typical of interphase and a new nuclear envelope forms around the chromosomes (Figures 10.3 and 10.4).
- Cytokinesis, the division of the cytoplasm, completes cell division by producing two daughter cells, each containing a daughter nucleus produced by mitosis (Figures 10.3 and 10.4).
- Cytokinesis in animal cells proceeds by furrowing, in which a band of microfilaments just under the plasma membrane contracts, gradually separating the cytoplasm into two parts (Figure 10.8).
- In plant cytokinesis, cell wall material is deposited along the plane of the former spindle midpoint; the deposition continues until a continuous new wall, the cell plate, separates the daughter cells (Figure 10.9).

Animation: The cell cycle

Animation: Mitosis step-by-step

Animation: Cytoplasmic division

10.3 Formation and Action of the Mitotic Spindle

- In animal cells, the centrosome divides and the two parts move apart. As they do so, the microtubules of the spindle form between them. In plant cells with no centrosome, the spindle microtubules assemble around the nucleus (Figure 10.10).
- In the spindle, kinetochore microtubules run from the poles to the kinetochores of the chromosomes, and nonkinetochore microtubules run from the poles to a zone of overlap at the spindle midpoint without connecting to the chromosomes (Figure 10.12).
- During anaphase, the kinetochores move along the kinetochore microtubules, pulling the chromosomes to the poles. The nonkinetochore microtubules slide over each other, pushing the poles farther apart (Figures 10.12 and 10.13).

Animation: Mechanisms for chromosome movement

10.4 Cell Cycle Regulation

- The cell cycle is controlled directly by complexes of cyclin and a cyclin-dependent protein kinase (CDK). CDK is activated when combined with a cyclin and then adds phosphate groups to target proteins, activating them. The activated proteins trigger the cell to progress to the next cell cycle stage. Each major stage of the cell cycle begins with activation of one or more cyclin/CDK complexes and ends with deactivation of the complexes by breakdown of the cyclins (Figure 10.15).
- Important internal controls create checkpoints to ensure that the reactions of one stage are complete before the cycle proceeds to the next stage.

- External controls are based primarily on surface receptors that recognize and bind signals such as peptide hormones and growth factors, surface groups on other cells, or molecules of the extracellular matrix. The binding triggers internal reactions that speed, slow, or stop cell division.
- In cancer, control of cell division is lost, and cells divide continuously and uncontrollably, forming a rapidly growing mass of cells that interferes with body functions. Cancer cells also break loose from their original tumor (metastasize) to form additional tumors in other parts of the body.

Animation: Cancer and metastasis

10.5 Cell Division in Prokaryotes

- Replication begins at the origin of replication of the bacterial chromosome in reactions catalyzed by enzymes located in the middle of the cell. Once the origin of replication is duplicated, the two origins migrate to the two ends of the cells. Division of the cytoplasm then occurs through a partition of cell wall material that grows inward until the cell is separated into two parts (Figure 10.17).

Questions

Self-Test Questions

1. During the cell cycle, the DNA mass of a cell:
   a. decreases during G_1.
   b. decreases during metaphase.
   c. increases during the S phase.
   d. increases during G_2.
   e. decreases during interphase.
2. A protein, p21, inhibits CDKs. The earliest effect of p21 on the cell cycle would be to stop the cell cycle at:
   a. early G_1.
   b. late G_1.
   c. the S phase.
   d. G_2.
   e. the mitotic prophase.
3. Which of the following is *not* characteristic of eukaryotic cell division?
   a. a system of internal molecular controls
   b. DNA replication
   c. external growth factors
   d. microtubular organizing center
   e. G_0 stage
4. The major microtubule organizing center of the animal cell is:
   a. chromosomes, composed of chromatids.
   b. the centrosome, composed of centrioles.
   c. the chromatin, composed of chromatids.
   d. chromosomes, composed of centromere.
   e. centrioles, composed of centrosome.
5. The chromatids separate into chromosomes:
   a. during prophase.
   b. going from prophase to metaphase.
   c. going from anaphase to telophase.
   d. going from metaphase to anaphase.
   e. going from telophase to interphase.
6. Which of the following statements about mitosis is *incorrect*?
   a. Microtubules from the spindle poles attach to the kinetochores on the chromosomes.
   b. In anaphase, the spindle separates sister chromatids and pulls them apart.
   c. In metaphase, spindle microtubules align the chromosomes at the spindle midpoint.
   d. Cytokinesis describes the movement of chromosomes.
   e. Both the animal cell furrow and the plant cell plate form at their former spindle midpoint.
7. Mitomycin C is an anticancer drug that stops cell division by inserting itself into the strands of DNA and binding them together. This action is thought to have its major effect at:
   a. late G_1, early S phases.
   b. late G_2.
   c. prophase.
   d. metaphase.
   e. anaphase.
8. Which of the following statements about cell cycle regulators is *incorrect*?
   a. Cyclin is synthesized during the S phase.
   b. Cyclin and CDKs are at the highest level during G_1.
   c. CDKs combine with cyclin to phosphorylate target proteins.
   d. CDKs combine with cyclin to move the cycle into mitosis.
   e. During anaphase of mitosis, cyclin is degraded, allowing mitosis to end.
9. Which of the following is *not* characteristic of cancer cells?
   a. metastasis
   b. contact inhibition
   c. avoidance of the G_0 stage
   d. oncogene overactivation of cyclin
   e. extra growth factor receptors
10. In bacteria:
    a. several chromosomes undergo mitosis.
    b. binary fission produces four daughter cells.
    c. replication begins at the origin, and the DNA strands separate.
    d. the plasma membrane plays an important role in separating the duplicated chromosomes into the two daughter cells.
    e. the daughter cells receive different genetic information from the parent cell.

Questions for Discussion

1. You have a means of measuring the amount of DNA in a single cell. You first measure the amount of DNA during G_1. At what points during the remainder of the cell cycle would you expect the amount of DNA per cell to change?
2. A cell has 38 chromosomes. After mitosis and cell division, one daughter cell has 39 chromosomes and the other has 37. What might have caused these abnormal chromosome numbers? What effects do you suppose this might have on cell function? Why?
3. Taxol (Bristol-Myers Squibb, New York), a substance derived from Pacific yew *(Taxus brevifolia)*, is effective in the treatment of breast and ovarian cancers. It works by stabilizing microtubules, thereby preventing them from disassembling. Why would this activity slow or stop the growth of cancer cells?
4. A cell has 24 chromosomes at G_1 of interphase. How many chromosomes would you expect it to have at G_2 of interphase? At metaphase of mitosis? At telophase of mitosis?

Experimental Analysis

Many chemicals in the food we eat potentially have effects on cancer cells. Chocolate, for example, contains a number of flavonoid compounds, which act as natural antioxidants. Design an experiment to determine whether any of the flavonoids in chocolate inhibit the cell cycle of breast cancer cells growing in culture.

Evolution Link

The genes and proteins involved in cell cycle regulation in prokaryotes and eukaryotes are very different. However, both types of organisms use similar molecular regulatory reactions to coordinate DNA synthesis with cell division. What does this observation mean from an evolutionary perspective?

How Would You Vote?

It is illegal to sell your organs, but you can sell your cells, including eggs, sperm, and blood cells. HeLa cells are still being sold all over the world by cell culture firms. Should the family of Henrietta Lacks share in the profits? Go to www.thomsonedu.com/login to investigate both sides of the issue and then vote.