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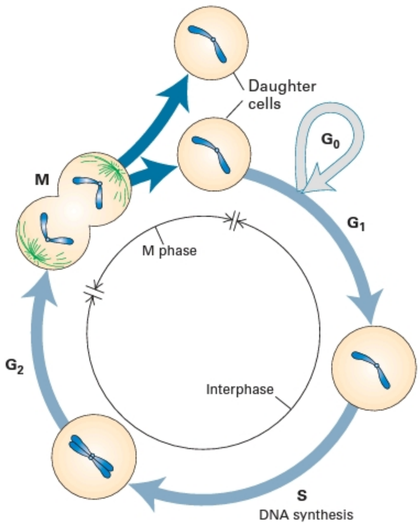

FIGURE 19-1 The fate of a single parent chromosome throughout the eukaryotic cell cycle. Following mitosis (M), daughter cells contain 2*n* chromosomes in diploid organisms and 1*n* chromosomes in haploid organisms. In proliferating cells, G_1 is the period between the "birth" of a cell following mitosis and the initiation of DNA synthesis, which marks the beginning of the S phase. At the end of the S phase, cells enter G_2 containing twice the number of chromosomes they had as G_1 cells (4*n* in diploid organisms, 2*n* in haploid organisms). The end of G_2 is marked by the onset of mitosis, during which numerous events leading to cell division occur. The G_1, S, and G_2 phases are collectively referred to as *Interphase*, the period between one mitosis and the next. Most nonproliferating cells in vertebrates leave the cell cycle in G_1, entering the G_0 state. Although chromosomes condense only during mitosis, here they are shown in condensed form throughout the cell cycle to emphasize the number of chromosomes at each stage. For simplicity, the nuclear envelope is not depicted.

occur in the proper order in every cell division. If a cell undergoes chromosome segregation before the replication of all chromosomes has been completed, at least one daughter cell will lose genetic information. Likewise, if a second round of replication occurs in one region of a chromosome before cell division occurs, the genes encoded in that region are increased in number out of proportion to other genes, a phenomenon that often leads to an imbalance of gene expression that is incompatible with viability.

High accuracy and fidelity are required to ensure that DNA replication is carried out correctly and that each daughter cell inherits the correct number of each chromosome. To achieve this, cell division is controlled by surveillance mechanisms known as *checkpoint pathways*, which prevent initiation of each step in cell division until the earlier steps on which it depends have been completed and any mistakes that occurred during the process have been corrected. Mutations that inactivate or alter the normal operation of these checkpoint pathways contribute to the generation of cancer cells because they result in chromosomal rearrangements and abnormal numbers of chromosomes, which lead to further mutations and changes in gene expression that cause uncontrolled cell growth (see Chapter 24).

In the late 1980s, it became clear that the molecular processes regulating the two key events in the cell cycle—chromosome replication and chromosome segregation—are fundamentally similar in all eukaryotic cells. Initially, it was surprising to many researchers that cells as diverse as budding yeast and developing human neurons use nearly identical proteins to regulate their division. However, like transcription and protein synthesis, control of cell division appears to be a fundamental cellular process that evolved and was largely optimized early in eukaryotic evolution. Because of this similarity, research with diverse organisms, each with its own particular experimental advantages, has contributed to a growing understanding of how cell cycle events are coordinated and controlled. Biochemical, genetic, imaging, and micromanipulation techniques have all been employed in studying various aspects of the eukaryotic cell cycle. These studies have revealed that cell division is controlled primarily by regulation of the timing of entry into the cell division cycle, DNA replication, and mitosis.

The master controllers of the cell cycle are a small number of *protein kinases*, each of which contains a regulatory subunit (cyclin) and a catalytic subunit (cyclin-dependent kinase, or CDK). These heterodimeric kinases regulate the activities of multiple proteins involved in entry into the cell cycle, DNA replication, and mitosis by phosphorylating those proteins at specific regulatory sites, activating some and inhibiting others to coordinate their activities. Regulated degradation of proteins also plays a prominent role in important cell cycle transitions. Since protein degradation is irreversible, it ensures that the processes move in only one direction through the cell cycle.

In this chapter, we first present an overview of the cell cycle and then describe the various experimental systems that have contributed to our current understanding of it. We then discuss cyclin-dependent kinases (CDKs) and the many different ways in which these key cell cycle controllers are regulated. Next we examine each cell cycle phase in greater detail, with an emphasis on how control of CDK activity governs the events that take place in each phase. We then discuss the checkpoint pathways that establish the order of the cell cycle and ensure that each cell cycle phase occurs with accuracy. The chapter concludes with a discussion of meiosis, a special type of cell division that generates haploid germ cells (eggs and sperm), and the molecular mechanisms that distinguish it from mitosis. In our discussion, we emphasize the general principles governing cell cycle progression

and use a species-spanning nomenclature when discussing the factors controlling each cell cycle phase.

19.1 Overview of the Cell Cycle and Its Control

are committed to cell division. The first step toward successful cell division is entry into the **S** (**synthesis**) **phase**, the period in which cells actively replicate their chromosomes. After progressing through a second gap phase, the **G_2 phase**, cells begin the complicated process of **mitosis**, also called the **M** (**mitotic**) **phase**, which is divided into several stages (Figure 19-2).

In discussing mitosis, we commonly use the term *chro*

and use a species-spanning nomenclature when discussing the factors controlling each cell cycle phase.

19.1 Overview of the Cell Cycle and Its Control

The cell cycle in eukaryotes is a highly conserved, well-ordered series of events. During each cycle, DNA replication leads to the creation of two identical DNA molecules, which are compacted and structured for their segregation into daughter cells. In this section, we begin our discussion by reviewing the stages of the eukaryotic cell cycle, then introduce the master regulators, the cyclin-dependent kinases, and conclude with an overview of the principles that govern the cell cycle.

The Cell Cycle Is an Ordered Series of Events Leading to Cell Replication

The cell cycle is divided into four major phases (see Figure 19-1). Cycling (replicating) mammalian somatic cells grow in size and synthesize the RNAs and proteins required for DNA synthesis during the G_1 (first gap) **phase**. When cells have reached the appropriate size and have synthesized the required proteins, they enter the cell cycle by traversing a point in G_1 known as *START* in yeast and the *restriction point* in mammals. Once this point has been crossed, cells are committed to cell division. The first step toward successful cell division is entry into the **S** (**synthesis**) **phase**, the period in which cells actively replicate their chromosomes. After progressing through a second gap phase, the G_2 **phase**, cells begin the complicated process of **mitosis**, also called the **M** (**mitotic**) **phase**, which is divided into several stages (Figure 19-2).

In discussing mitosis, we commonly use the term *chromosome* for the *replicated* structures that condense and become visible in the light microscope during the early stages of mitosis. Thus each chromosome is composed of two identical DNA molecules resulting from DNA replication, plus histones and other chromosome-associated proteins (see Figure 8-35). The two identical DNA molecules and associated chromosomal proteins that form one chromosome are called **sister chromatids**. Sister chromatids are attached to each other by protein cross-links.

During **interphase**, the part of the cell cycle between the end of one M phase and the beginning of the next, the outer nuclear membrane is continuous with the endoplasmic reticulum. With the onset of mitosis in **prophase**, the nuclear envelope retracts into the endoplasmic reticulum in most cells from higher eukaryotes, and the membranes of the Golgi complex break down into vesicles. This is necessary so that the microtubules, nucleated by the centrosomes, can interact with the chromosomes to form the **mitotic spindle**, consisting of a football-shaped bundle of microtubules with a star-shaped cluster of microtubules radiating from each end,

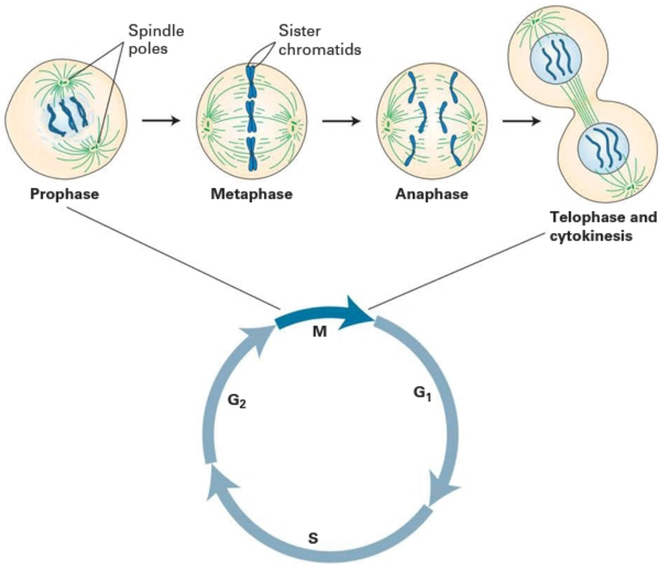

FIGURE 19-2 The stages of mitosis. During prophase, the nuclear envelope breaks down, microtubules form the mitotic spindle apparatus, and chromosomes condense. At metaphase, attachment of chromosomes to microtubules via their kinetochores is complete. During anaphase, motor proteins and the shortening of spindle microtubules pull the sister chromatids toward opposite spindle poles. After chromosome movement to the spindle poles, chromosomes decondense. Cells reassemble nuclear membranes around the daughter-cell nuclei and undergo cytokinesis.

or *spindle pole*. A multiprotein complex, the kinetochore, assembles at each centromere. After nuclear envelope breakdown, at **metaphase**, the kinetochores of sister chromatids associate with microtubules coming from opposite spindle poles (see Figure 18-37), and the chromosomes align in a plane in the center of the cell. During **anaphase**, sister chromatids separate. They are initially pulled by microtubules toward the spindle poles and are then further separated as the spindle poles move away from each other (see Figure 19-2).

Once chromosome separation is complete, the mitotic spindle disassembles and chromosomes decondense during **telophase**. The nuclear envelope re-forms around the segregated chromosomes as they decondense. The physical division of the cytoplasm, called *cytokinesis*, yields two daughter cells. Following mitosis, cycling cells enter the G_1 phase, embarking on another turn of the cycle.

The progression of cell cycle stages is the same for all eukaryotes, though the time it takes to complete one turn of the cycle varies considerably among organisms. Rapidly

Several Key Principles Govern the Cell Cycle

The goal of each cell division is to generate two daughter cells of identical genetic makeup. To achieve this, *cell cycle events must occur in the proper order*. DNA replication must always precede chromosome segregation. Today we know that the activity of the key proteins that promote cell cycle progression, the CDKs, *fluctuates during the cell cycle*. For example, CDKs that promote S phase are active during S phase but are inactive during mitosis. CDKs that promote mitosis are active only during mitosis. These *oscillations* in CDK activity are a fundamental aspect of eukaryotic cell cycle control, and we have gained some understanding as to how these oscillations are generated. Oscillations are generated by **positive feedback mechanisms**, whereby specific CDKs promote their own activation. These positive feedback loops are coupled to subsequent **negative feedback mechanisms** by which, indirectly or with a built-in delay, CDKs promote their own inactivation. Their oscillations not only propel the cell cycle forward

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The progression of cell cycle stages is the same for all eukaryotes, though the time it takes to complete one turn of the cycle varies considerably among organisms. Rapidly replicating human cells progress through the full cell cycle in about 24 hours: G_1 takes 9 hours; the S phase, 10 hours; G_2, 4.5 hours; and mitosis, 30 minutes. In contrast, the full cycle takes only 90 minutes in rapidly growing yeast cells. The cell divisions that take place during early embryonic development of the fruit fly *Drosophila melanogaster* are completed in as little as 8 minutes!

In multicellular organisms, most differentiated cells exit the cell cycle and survive for days, weeks, or in some cases (e.g., nerve cells and cells of the eye lens) even the lifetime of the organism without dividing again. Such *postmitotic* cells generally exit the cell cycle in G_1, entering a phase called $\mathbf{G_0}$ (see Figure 19-1). Some G_0 cells can return to the cell cycle and resume replicating; this re-entry is regulated, thereby providing control of cell proliferation.

Cyclin-Dependent Kinases Control the Eukaryotic Cell Cycle

As mentioned in the chapter introduction, passage through the cell cycle is controlled by heterodimeric protein kinases that comprise a catalytic subunit and a regulatory subunit. The catalytic subunits, the **cyclin-dependent kinases** (**CDKs**), have no kinase activity unless they are associated with a regulatory **cyclin** subunit. Each CDK can associate with a small number of different cyclins, which determine the substrate specificity of the complex—that is, which proteins it phosphorylates. Each cyclin is only present and active during the cell cycle stage it promotes and hence restricts the kinase activity of the CDKs to which it binds to that cell cycle stage. Cyclin-CDK complexes activate or inhibit hundreds of proteins involved in cell cycle progression by phosphorylating them at specific regulatory sites. Thus proper progression through the cell cycle is governed by activation of the appropriate cyclin-CDK complex at the appropriate time. As we will see, restricting cyclin expression to the appropriate cell cycle stage is one of the many mechanisms cells employ to regulate the activities of each cyclin-CDK heterodimer.

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Overlaid on the cell cycle oscillator machinery is a system of surveillance mechanisms that further ensures that the next cell cycle event is not activated before the preceding one has been completed or before errors that occurred during the preceding step have been corrected. These surveillance mechanisms are called *checkpoint pathways*, and their job is to ensure the accuracy of the chromosome replication and segregation processes. The system that ensures that chromosomes are segregated accurately is so efficient that a mis-segregation event occurs only once in 10^4–10^5 divisions! These multiple layers of control on the cell cycle control machinery ensure that the cell cycle is robust and error free.

KEY CONCEPTS OF SECTION 19.1

Overview of the Cell Cycle and Its Control

- The eukaryotic cell cycle is divided into four phases: G_1 (the period between mitosis and the initiation of nuclear DNA replication), S (the period of nuclear DNA replication), G_2 (the period between the completion of nuclear DNA replication and mitosis), and M (mitosis).
- Cells commit to a new cell division at a specific point in G_1 known as START or the restriction point.
- Cyclin-CDK complexes, composed of a regulatory cyclin subunit and a catalytic cyclin-dependent kinase (CDK) subunit, drive the progression of a cell through the cell cycle.
- Cyclins activate CDKs and are present only in the cell cycle stage that they promote.
- CDK activities oscillate during the cell cycle. Positive and negative feedback loops drive these oscillations.
- Surveillance mechanisms, called checkpoint pathways, guarantee that each cell cycle step is completed correctly before the next one is initiated.

19.2 Model Organisms and Methods of Studying the Cell Cycle

The unraveling of the molecular mechanisms governing cell cycle progression in eukaryotes was remarkably rapid and was fueled by a powerful combination of genetic and biochemical approaches. In this section, we discuss several model systems and their contributions to the discovery of the molecular mechanisms of cell division. The three most important systems employed to study the cell cycle are the single-celled yeasts *Saccharomyces cerevisiae* (budding yeast) and *Schizosaccharomyces pombe* (fission yeast) and the oocytes and early embryos of the frog *Xenopus laevis*. We also discuss the fruit fly *Drosophila melanogaster*, which proved extremely powerful in the study of the interplay between cell division and development. The study of mammalian tissue culture cells led to the characterization of cell cycle control in mammals.

Studies of the cell cycle in many different experimental systems also led to two remarkable discoveries about the

Budding and Fission Yeasts Are Powerful Systems for Genetic Analysis of the Cell Cycle

Budding and fission yeasts have proved to be valuable systems for the study of the cell cycle. Although they both belong to the kingdom Fungi, they are only distantly related. Both organisms can exist in the haploid state, carrying only one copy of each chromosome. The fact that these yeasts can exist as haploid cells makes them powerful genetic systems. It is easy to generate mutations that inactivate genes in haploids because there is only one copy of each gene (a diploid would require an inactivating mutation in each of the two copies of the gene to render its activity nonfunctional). Haploid yeast can be easily employed to screen or select for mutants with specific defects, such as defects in cell proliferation. Additional advantages of these two systems are the relative ease with which one can manipulate the expression of individual genes, and the ease with which yeasts can be cultivated and manipulated so that cultures of cells progress through the cell cycle in a synchronous manner.

Budding yeast cells are ovoid in shape and divide by bud-

propriate cyclin-CDK complex at the appropriate time. As we will see, restricting cyclin expression to the appropriate cell cycle stage is one of the many mechanisms cells employ to regulate the activities of each cyclin-CDK heterodimer.

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Studies of the cell cycle in many different experimental systems also led to two remarkable discoveries about the general control of the cell cycle. First, complex molecular processes such as initiation of DNA replication and entry into mitosis are all regulated and coordinated by a small number of master cell cycle regulatory proteins. Second, these master regulators and the proteins that control them are highly conserved, so that cell cycle studies in fungi, sea urchins, insects, frogs, and other species are directly applicable to all eukaryotic cells, including human cells.

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Budding yeast cells are ovoid in shape and divide by budding (Figure 19-3a). The bud, which is the future daughter cell, begins to form concomitant with the initiation of DNA replication and continues to grow throughout the cell cycle (Figure 19-3b). Cell cycle stage can therefore be inferred from the size of the bud, which makes *S. cerevisiae* a useful system for identifying mutants that are blocked at specific steps in the cell cycle. Indeed, it was in this organism that

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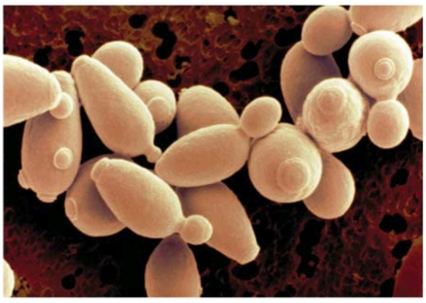

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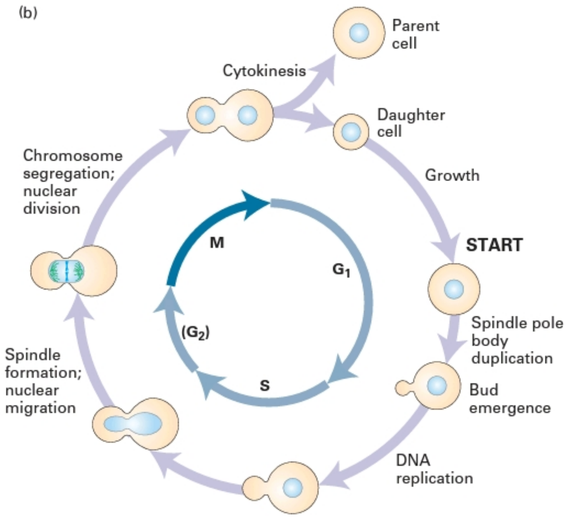

FIGURE 19-3 The budding yeast *S. cerevisiae*. (a) Scanning electron micrograph of *S. cerevisiae* cells at various stages of the cell cycle. The larger the bud, which emerges at the end of the G_1 phase, the farther along in the cycle the cell is. (b) Main events in the *S. cerevisiae* cell cycle. Daughter cells are born smaller than parent cells and must grow to a greater extent in G_1 before they are large enough to enter the S phase. START is the point in the cell cycle after which cells are irreversibly committed to undergoing a cell cycle. G_2 is not well defined in budding yeast and is therefore denoted in parentheses. Note that the nuclear envelope does not disassemble during mitosis in *S. cerevisiae* and other yeasts. The small *S. cerevisiae* chromosomes do not condense sufficiently to be visible by light microscopy. [Part (a) SCIMAT/Science Source.]

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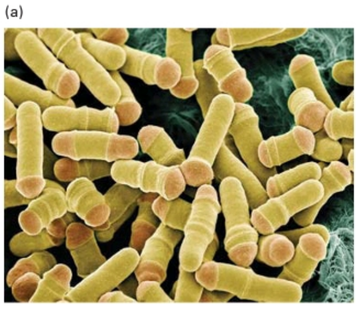

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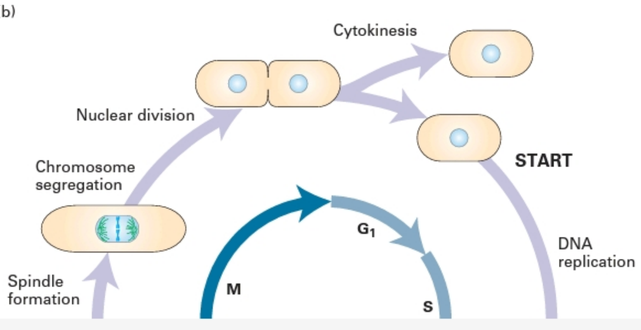

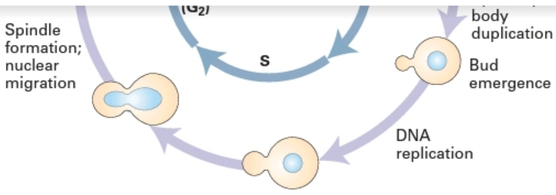

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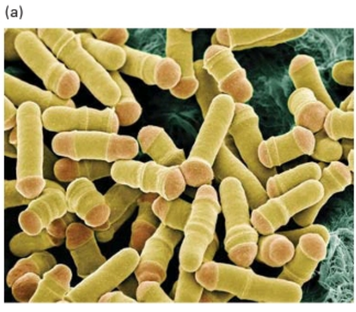

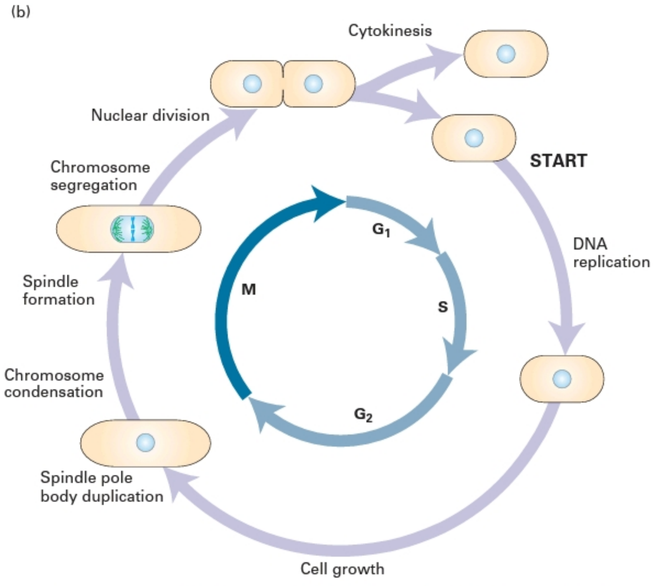

FIGURE 19-4 The fission yeast *S. pombe*. (a) Scanning electron micrograph of *S. pombe* cells at various stages of the cell cycle. Long cells are about to enter mitosis; short cells have just passed through cytokinesis. (b) Main events in the *S. pombe* cell cycle. START is the point in the cell cycle after which cells are irreversibly committed to cell division. As in *S. cerevisiae*, the nuclear envelope does not break down during mitosis. [Part (a) Steve Gschmeissner/Science Source.]

Lee Hartwell and colleagues first identified mutants that were defective in progressing through specific cell cycle stages. Like those of mammalian cells, the budding yeast cell cycle has a long G_1 phase, and the study of the budding yeast cell cycle shaped our understanding of how the G_1–S phase transition is controlled.

Fission yeast cells are rod-shaped and grow entirely by elongation at their ends (Figure 19-4a). After the completion of mitosis, cytokinesis occurs by the formation of a septum (Figure 19-4b). The molecular mechanisms governing G_2 and entry into mitosis in fission yeast and in metazoan cells are very similar, and studies with this organism revealed the molecular events surrounding the G_2–M phase transition.

Budding and fission yeasts are both useful for the isolation of mutants that are blocked at specific steps in the cell cycle or that exhibit altered regulation of the cycle. Because cell cycle progression is essential for viability, scientists isolated *conditional mutants* whose genes encode proteins that are functional at one temperature but become inactive at a different, often higher, temperature (e.g., due to protein misfolding at the nonpermissive temperature; see Figure 6-6). Mutants arrested at a particular cell cycle stage are easily distinguished from normally dividing cells by microscopic examination. Thus, in both of these yeasts, cells with **temperature-sensitive mutations** causing defects in specific proteins required to progress through the cell cycle were readily isolated. Such cells are called *cdc* (*c*ell *d*ivision *c*ycle) mutants. Identification of the genes mutated in these temperature-sensitive yeast strains provided a comprehensive list of genes critical for virtually all aspects of cell division.

Frog Oocytes and Early Embryos Facilitate Biochemical Characterization of the Cell Cycle Machinery

Biochemical studies require the preparation of cell extracts from many cells. For biochemical studies of the cell cycle, the eggs and early embryos of amphibians and marine invertebrates are particularly suitable. These organisms typically have large eggs, and fertilization is followed by multiple synchronous cell cycles. By isolating large numbers of eggs from females and fertilizing them simultaneously by addition of sperm (or by treating them in ways that mimic fertilization), researchers can obtain extracts from cells at specific points in the cell cycle for analysis of proteins and enzymatic activities.

To understand how *X. laevis* oocytes and eggs can be used for the analysis of cell cycle progression, we must first lay out the events of oocyte maturation, which can be recapitulated in vitro. So far, we have discussed mitotic division. Oocytes, however, undergo a meiotic division (see Figure 19-35 for an overview of meiosis). As oocytes develop in the frog ovary, they replicate their DNA and become arrested in G_2 for 8 months, during which time they grow in size to a diameter of 1 mm, stockpiling all the materials needed for the multiple

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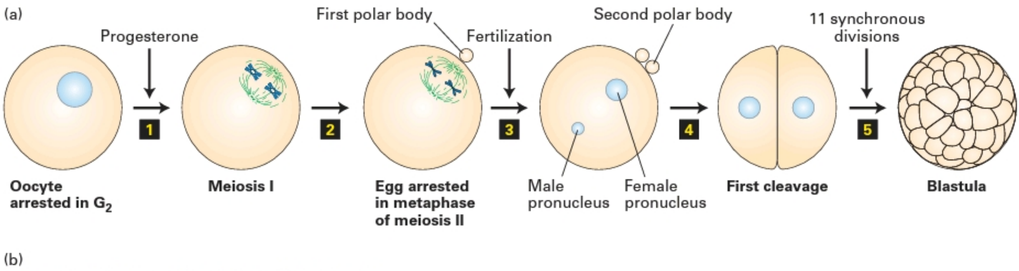

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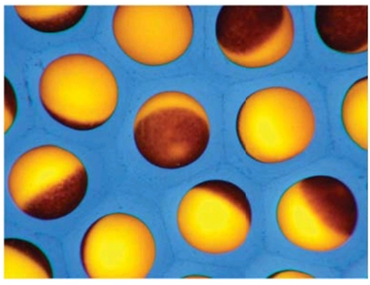

FIGURE 19-5 Progesterone stimulates maturation of *Xenopus* oocytes. (a) Step 1: Progesterone treatment of G_2-arrested *Xenopus* oocytes surgically removed from the ovary of an adult female causes the oocytes to enter meiosis I. Two pairs of synapsed homologous chromosomes (blue) connected to meiotic spindle microtubules (green) are shown schematically to represent cells in metaphase of meiosis I. Step 2: Segregation of homologous chromosomes and a highly asymmetric cell division expels half the chromosomes into a small cell called the *first polar body*. The oocyte immediately commences meiosis II and arrests in metaphase II to yield an egg. Two chromosomes connected to spindle microtubules are shown schematically to represent egg cells arrested in metaphase of meiosis II. Step 3: Fertilization by sperm releases eggs from their metaphase arrest, allowing them to proceed through anaphase of meiosis II and undergo a second highly asymmetric cell division that expels one chromatid of each chromosome into a second polar body. The resulting haploid female pronucleus fuses with the haploid sperm pronucleus to produce a diploid zygote. Step 4: The zygote undergoes DNA replication and the first mitosis. Step 5: The first mitosis is followed by 11 more synchronous divisions to form a blastula. (b) Micrograph of *Xenopus* eggs. [Part (b) © MICHEL DELARUE/ISM/Phototake.]

cell divisions of the early embryo. When stimulated by a male, an adult female's ovarian cells secrete the steroid hormone progesterone, which induces the G_2-arrested oocytes to mature and enter meiosis. As we will see in Section 19.8, meiosis consists of two consecutive chromosome segregation phases known as meiosis I and meiosis II. Progesterone triggers oocytes to undergo meiosis I and progress to the second meiotic metaphase, where they arrest and await fertilization (Figure 19-5). At this stage the cells are called eggs. When fertilized by sperm, the egg nucleus is released from its metaphase II arrest and completes meiosis. The resulting haploid egg nucleus then fuses with the haploid sperm nucleus, producing a diploid *zygote* nucleus. DNA replication follows, and the first mitotic division of embryogenesis begins. The resulting embryonic cells then proceed through 11 more rapid, synchronous cell cycles, generating a hollow sphere of cells called the *blastula*. Cell division then slows, and subsequent divisions are non-synchronous, with cells at different positions in the blastula dividing at different times.

The advantage of using *X. laevis* to study factors involved in mitosis is that large numbers of oocytes and eggs can be prepared that are all proceeding synchronously through the cell cycle events that follow progesterone treatment and fertilization. This makes it possible to prepare sufficient amounts of extract for biochemical experiments from cells that were all at the same point in the cell cycle. It was in this system that the cyclin-CDK complexes that trigger mitosis and the oscillatory nature of their activity were first discovered. This activity was called *maturation-promoting factor* (*MPF*) because of its ability to induce entry into meiosis and oocyte maturation when injected into G_2-arrested oocytes.

Fruit Flies Reveal the Interplay Between Development and the Cell Cycle

The development of complex tissues often requires specific modifications to the cell cycle. Understanding the interplay between development and cell division is thus crucial if we want to understand how complex organisms are built. *Drosophila melanogaster* has established itself as the premier model system for studying the interplay between development and the cell cycle. Not only does the development of this organism involve several highly unusual cell cycles, but the powerful genetic techniques that can be applied to fruit flies facilitated the discovery of genes involved in the developmental control of the cell cycle.