A cell reproduces by carrying out an orderly sequence of events in which it duplicates its contents and then divides in two. This cycle of duplication and division, known as the cell cycle, is the essential mechanism by which all living things reproduce. The details of the cell cycle vary from organism to organism and at different times in an individual organism’s life. In unicellular organisms, such as bacteria and yeasts, each cell division produces a complete new organism, whereas many rounds of cell division are required to make a new multicellular organism from a fertilized egg. Certain features of the cell cycle, however, are universal, as they allow every cell to perform the fundamental task of copying and passing on its genetic information to the next generation of cells.
One of the properties that distinguishes various types of cells within a multicellular plant or animal is their capacity to grow and divide. We can recognize three broad categories of cells:

1. Cells, such as nerve cells, muscle cells, or red blood cells, that are highly specialized and lack the ability to divide. Once these cells have differentiated, they remain in that state until they die.

2. Cells that normally do not divide but can be induced to begin DNA synthesis and divide when given an appropriate stimulus. Included in this group are liver cells, which can be induced to proliferate by the surgical removal of part of the liver, and lymphocytes, which can be induced to proliferate by interaction with an appropriate antigen.

3. Cells that normally possess a relatively high level of mitotic activity. Included in this category are stem cells of various adult tissues, such as hematopoietic stem cells that give rise to red and white blood cells.
Interphase Most of the time in the cell cycle is spent in a preliminary phase: interphase. Interphase can be further subdivided into phases: G1, S and G2.

DNA replication occurs in the ‘S’ phase (the ‘Synthesis’ phase). The ‘G’ phases (also called gap phases) represent periods of growth in preparation for the division of the cell. **Checkpoints** also exist at these phases to ensure the cell is ready to divide.
**G1 phase** The first phase of interphase and the cell cycle is called G1. During G1, the cell is preparing to replicate DNA by synthesizing the mRNAs and proteins required to execute the future steps. The cell usually grows larger, and some organelles are copied.

**S phase** During the S phase, all the genetic information in the cell is copied by the process of DNA replication. This process of replication generates sister chromatids which are identical pairs of chromosomes. These sister chromatids are attached to each other by a centromere. Centromere is a specialized sequence of DNA that links sister chromatids and is important throughout mitosis.

**G2 phase** The final phase of interphase is G2 Phase. During this time, the cell undergoes additional growth, replenishes energy stores and preparation for division, including duplicating some organelles and dismantling the cytoskeleton. G2 ends when mitosis begins.

**Mitosis (M)**

The mitotic phase describes a series of processes during which the replicated DNA condenses into visible chromosomes, which are aligned, separated, and passed on to two new daughter cells. The movement of chromosomes is orchestrated by specialized structures called microtubules.
Mitosis can be further subdivided into four main phases: prophase, prometaphase, metaphase, anaphase and telophase (PPMAT). Sometimes, prometaphase is not considered a separate phase. These phases result in the division of the cell nucleus (also called karyokinesis), and then the separation of the cytoplasm to form two new daughter cells (also called cytokinesis).

**Prophase**
The first phase of mitosis is called prophase. During prophase, the chromosomes start to condense the nuclear envelope breaks down, and the associated organelles break up and move towards the edge of the cell. A structure called the mitotic spindle also starts to form here. This structure is made of microtubules and is important in moving chromosomes around during mitosis. The mitotic spindles extend from either side of the cell (at opposite poles).

**Prometaphase**
Prometaphase is sometimes not classified as an independent step and can be referred to as late prophase. During prometaphase, the processes begun in prophase continue: the nuclear envelope is broken down, and the chromosomes are fully condensed. The mitotic spindle grows and begins to organise the chromosomes. A special structure called the kinetochore appears at this stage. The kinetochore is a protein structure is important for linking the chromosomes to the mitotic spindle and is assembled on the centromere.
Metaphase

During metaphases, the mitotic spindle facilitates the movement of chromosomes such that they align along the centre of the cell, at the metaphase plate. At this point, sister chromatids are still attached to one another. Following metaphase, there is an important checkpoint called the spindle checkpoint. This ensures anaphase will not proceed unless all the chromosomes are at the metaphase plate and attached to microtubules (by the kinetochore). This is a hugely important checkpoint ensuring that each daughter cell receives the correct number of chromosomes.

Anaphase

When the chromosomes are properly aligned, anaphase can proceed. Anaphase is the process during which the sister chromatids separate at the centromere and are pulled to the edge of the cell. These chromatids are now referred to as chromosomes.

Telophase

During telophase, the spindle disappears and a new the nuclear envelope forms around the chromosomes. The chromosomes also start to decondense as cytokinesis is taking place.
Cytokinesis

Cytokinesis completes the cell cycle, and usually overlaps with the final stages of mitosis. Cytokinesis involves the physical separation of the cytoplasm and its components into daughter cells. This occurs when a ring of cytoskeletal fibres (called the contractile ring) form at the centre of the cell, making an indentation called the cleavage furrow. This ring tightens, eventually pinching the cell enough that it separates two to give two new daughter cells.

Cytokinesis is more complex in plant cells, which have a cell wall. Dividing plant cells overcome this by creating a structure called the cell plate, which is made from vesicles containing plasma membrane and cell wall components. The cell plate enlarges until it merges with the cell walls. This divides the cell in two and allows the cell wall to be regenerated.

G0 phase and cell cycle exit

Not all cells are actively dividing. A cell in the G0 phase is said to be in a resting phase, and these cells are also called quiescent. This means it is not dividing or preparing to divide. Cells can enter G0 temporarily until there is a signal to divide, or can remain in G0 indefinitely. Examples of cells in G0 include neurons, which are metabolically active but not dividing.
To ensure that they replicate all their DNA and organelles, and divide in an orderly manner, eukaryotic cells possess a complex network of regulatory proteins known as the **cell-cycle control system**. It ensures the events of the cell cycle—DNA replication, mitosis, and so on—occur in a set sequence and that each process has been completed before the next one begins.

Checkpoints are surveillance mechanisms that halt the progress of the cell cycle if

1. any of the chromosomal DNA is damaged, or

2. certain critical processes, such as DNA replication during S phase or chromosome alignment during M phase, have not been properly completed.
The cell-cycle control system regulates progression through the cell cycle at three main transition points. At the transition from **G1 to S phase**, the control system confirms that the environment is favorable for proliferation before committing to DNA replication. Cell proliferation in animals requires both sufficient nutrients and specific signal molecules in the extracellular environment; if these extracellular conditions are unfavorable, cells can delay progress through G1 and may even enter a specialized resting state known as **G0** (G zero). At the transition from **G2 to M phase**, the control system confirms that the DNA is undamaged and fully replicated, ensuring that the cell does not enter mitosis unless its DNA is intact. Finally, during mitosis, the cell-cycle control machinery ensures that the duplicated chromosomes are properly attached to a cytoskeletal machine, called the **mitotic spindle**, before the spindle pulls the chromosomes apart and segregates them into the two daughter cells.
The Cell-Cycle Control System Depends on Cyclically Activated Protein Kinases called Cdks

The cell-cycle control system governs the cell-cycle machinery by cyclically activating and then inactivating the key proteins and protein complexes that initiate or regulate DNA replication, mitosis, and cytokinesis.

Entry of a cell into M phase is initiated by a protein called maturation promoting factor (MPF). MPF consists of two subunits: (1) a subunit with kinase activity that transfers phosphate groups from ATP to specific serine and threonine residues of specific protein substrates and (2) a regulatory subunit called cyclin. The term cyclin was coined because the concentration of this regulatory protein rises and falls in a predictable pattern with each cell cycle (This regulation is carried out largely through the phosphorylation and dephosphorylation of proteins involved in these essential processes).

Switching these kinases on and off at the appropriate times is partly the responsibility of another set of proteins in the control system—the cyclins. Cyclins have no enzymatic activity themselves, but they need to bind to the cell-cycle kinases before the kinases can become enzymatically active. The kinases of the cell-cycle control system are therefore known as cyclin-dependent protein kinases, or Cdks. Cyclins are so-named because, unlike the Cdks, their concentrations vary in a cyclical fashion during the cell cycle.
The activity of Cdk’s during cell cycle progression is regulated by four molecular mechanisms. As already discussed for Cdk1, the first level of regulation involves the association of Cdk’s with their cyclin partners. Thus the formation of specific Cdk/cyclin complexes is controlled by cyclin synthesis and degradation. Second, activation of Cdk/cyclin complexes requires phosphorylation of a conserved Cdk threonine residue around position 160. This activating phosphorylation of the Cdk’s is catalyzed by an enzyme called CAK (for Cdk-activating kinase), which is itself composed of a Cdk (Cdk7) complexed with cyclin H. Complexes of Cdk7 and cyclin H are also associated with the transcription factor TFIH, which is required for initiation of transcription by RNA polymerase II (see Chapter 6), so this member of the Cdk family participates in transcription as well as cell cycle regulation.

In contrast to the activating phosphorylation by CAK, the third mechanism of Cdk regulation involves inhibitory phosphorylation of tyrosine residues near the Cdk amino terminus, catalyzed by the Wee1 protein kinase. In particular, both Cdk1 and Cdk2 are inhibited by phosphorylation of tyrosine-15, and the adjacent threonine-14 in vertebrates. These Cdk’s are then activated by dephosphorylation of these residues by members of the Cdc25 family of protein phosphatases.

In addition to regulation of the Cdk’s by phosphorylation, their activities are also controlled by the binding of inhibitory proteins (called Cdk inhibitors or CKIs). In mammalian cells, two families of Cdk inhibitors are
Combinations between various cyclins and cyclin-dependent kinases at different stages in the mammalian cell cycle.

Cdk activity during early G₁ is very low, which promotes the formation of prereplication complexes at the origins of replication.

By mid-G₁, Cdk activity is evident due to the association of Cdk4 and Cdk6 with the D-type cyclins.

The G₁–S transition, which includes the initiation of replication, is driven by the activity of the cyclin E–Cdk2 and cyclin A–Cdk2 complexes.

The transition from G₂ to M and passage through early M is driven by the sequential activity of cyclin A–Cdk1 and cyclin B₁–Cdk1 complexes, which phosphorylate such diverse substrates as cytoskeletal proteins, histones, and proteins of the nuclear envelope.
FIGURE 16.25 Targets of Cdk1/cyclin B The Cdk1/cyclin B complex induces multiple nuclear and cytoplasmic changes at the onset of M phase both by activating other protein kinases and by phosphorylating proteins such as condensins, components of the nuclear envelope, Golgi matrix proteins, and proteins associated with centrosomes and microtubules.
The production of offspring by sexual reproduction includes the union of two cells, each with a haploid set of chromosomes. The doubling of the chromosome number at fertilization is compensated by an equivalent reduction in chromosome number at a stage prior to formation of the gametes. This is accomplished by meiosis, a term coined in 1905 from the Greek word meaning “reduction.” Meiosis ensures production of a haploid phase in the life cycle, and fertilization ensures a diploid phase. Without meiosis, the chromosome number would double with each generation, and sexual reproduction would not be possible.
The first stage of prophase I is **leptotene**, during which the chromosomes become compacted and visible in the light microscope. Although the chromosomes have replicated at an earlier stage, there is no indication that each chromosome is actually composed of a pair of identical chromatids. In the electron microscope, however, the chromosomes are revealed to be composed of paired chromatids.

The second stage of prophase I, which is called **zygotene**, is marked by the visible association of homologues with one another. This process of chromosome pairing is called **synapsis**. Chromosome synapsis is accompanied by the formation of a complex structure called the synaptonemal complex. The **synaptonemal complex (SC)** is a ladder-like structure with transverse protein filaments connecting the two lateral elements.
The complex formed by a pair of synapsed homologous chromosomes is called a **bivalent** or a **tetrad**. The former term reflects the fact that the complex contains two homologues, whereas the latter term calls attention to the presence of four chromatids. The end of synapsis marks the end of zygotene and the beginning of the next stage of prophase I, called **pachytene**, which is characterized by a fully formed synaptonemal complex. During pachytene, the homologues are held closely together along their length by the SC. The DNA of sister chromatids is extended into parallel loops.

The beginning of **diplotene**, the next stage of meiotic prophase I, is recognized by the dissolution of the SC, which leaves the chromosomes attached to one another at specific points by X-shaped structures, termed **chiasma** (singular **chiasma**). Chiasma are located at sites on the chromosomes where crossing-over between DNA molecules from the two chromosomes had previously occurred. Chiasmata are formed by covalent junctions between a chromatid from one homologue and a nonsister chromatid from the other homologue.
During the final stage of meiotic prophase I, called **diakinesis**, the meiotic spindle is assembled and the chromosomes are prepared for separation. In those species in which the chromosomes become highly dispersed during diplotene, the chromosomes become recompacted during diakinesis. Diakinesis ends with the disappearance of the nucleolus, the breakdown of the nuclear envelope, and the movement of the tetrads to the metaphase plate.
At metaphase I, the two homologous chromosomes of each bivalent are connected to the spindle fibers from opposite poles. In contrast, sister chromatids are connected to microtubules from the same spindle pole, which is made possible by the side-by-side arrangement of their kinetochores. The orientation of the maternal and paternal chromosomes of each bivalent on the metaphase I plate is random. Consequently, when homologous chromosomes separate during anaphase I, each pole receives a random assortment of maternal and paternal chromosomes.

Telophase I of meiosis I produces less dramatic changes than telophase of mitosis. Although chromosomes often undergo some dispersion, they do not reach the extremely extended state of the interphase nucleus. The nuclear envelope may or may not reform during telophase I.
The stage between the two meiotic divisions is called *interkinesis* and is generally short-lived. Interkinesis is followed by prophase II, a much simpler prophase than its predecessor. If the nuclear envelope had reformed in telophase I, it is broken down again. The chromosomes become recompacted and line up at the metaphase plate. Unlike metaphase I, the kinetochores of sister chromatids of metaphase II face opposite poles and become attached to opposing sets of chromosomal spindle fibers. Anaphase II begins with the synchronous splitting of the centromeres, which had held the sister chromatids together, allowing them to move toward opposite poles of the cell. Meiosis II ends with telophase II, in which the chromosomes are once again enclosed by a nuclear envelope.