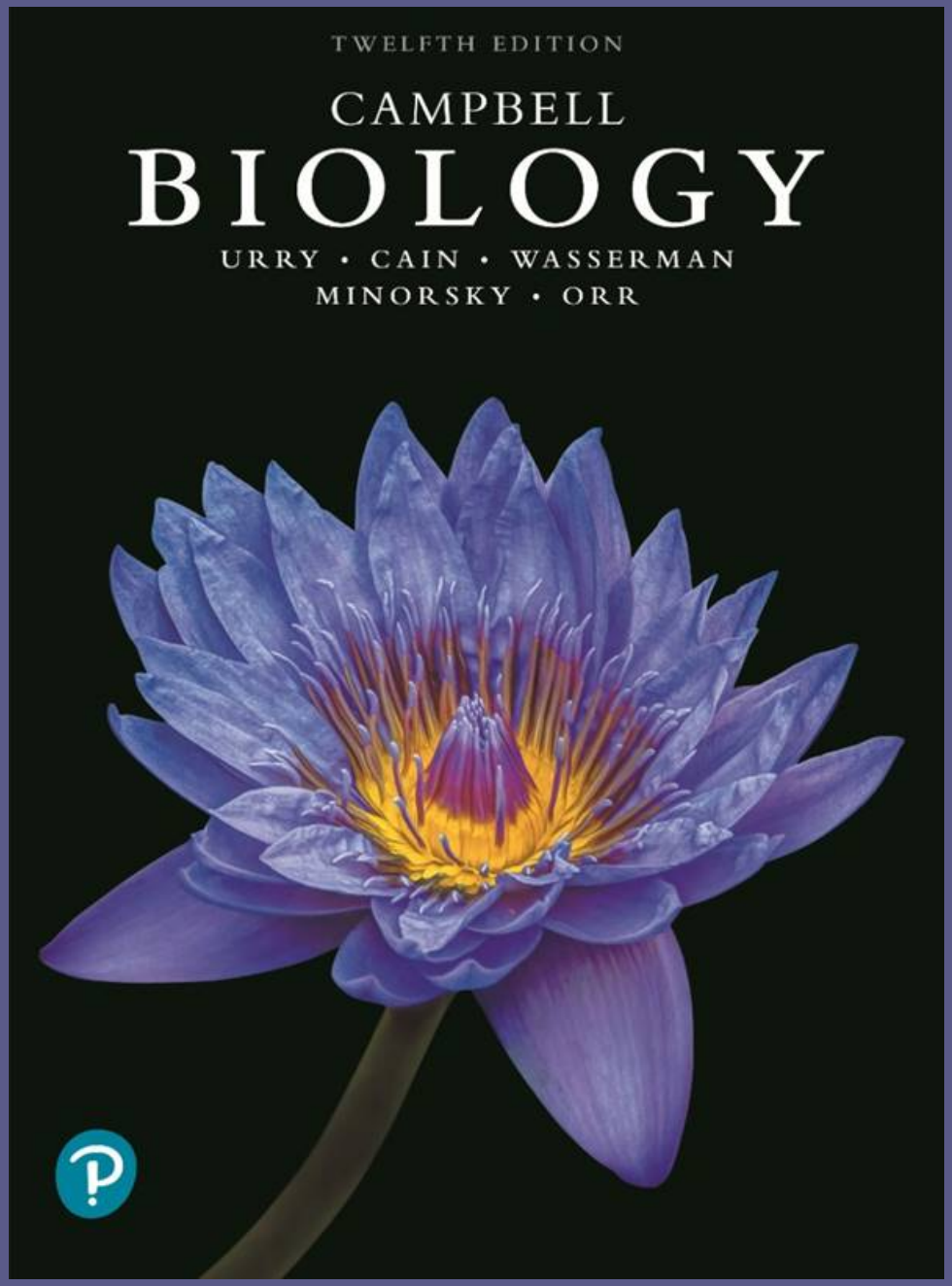


Chapter 12

The Cell Cycle

Lecture Presentations by
Nicole Tunbridge and
Kathleen Fitzpatrick

Figure 12.1a

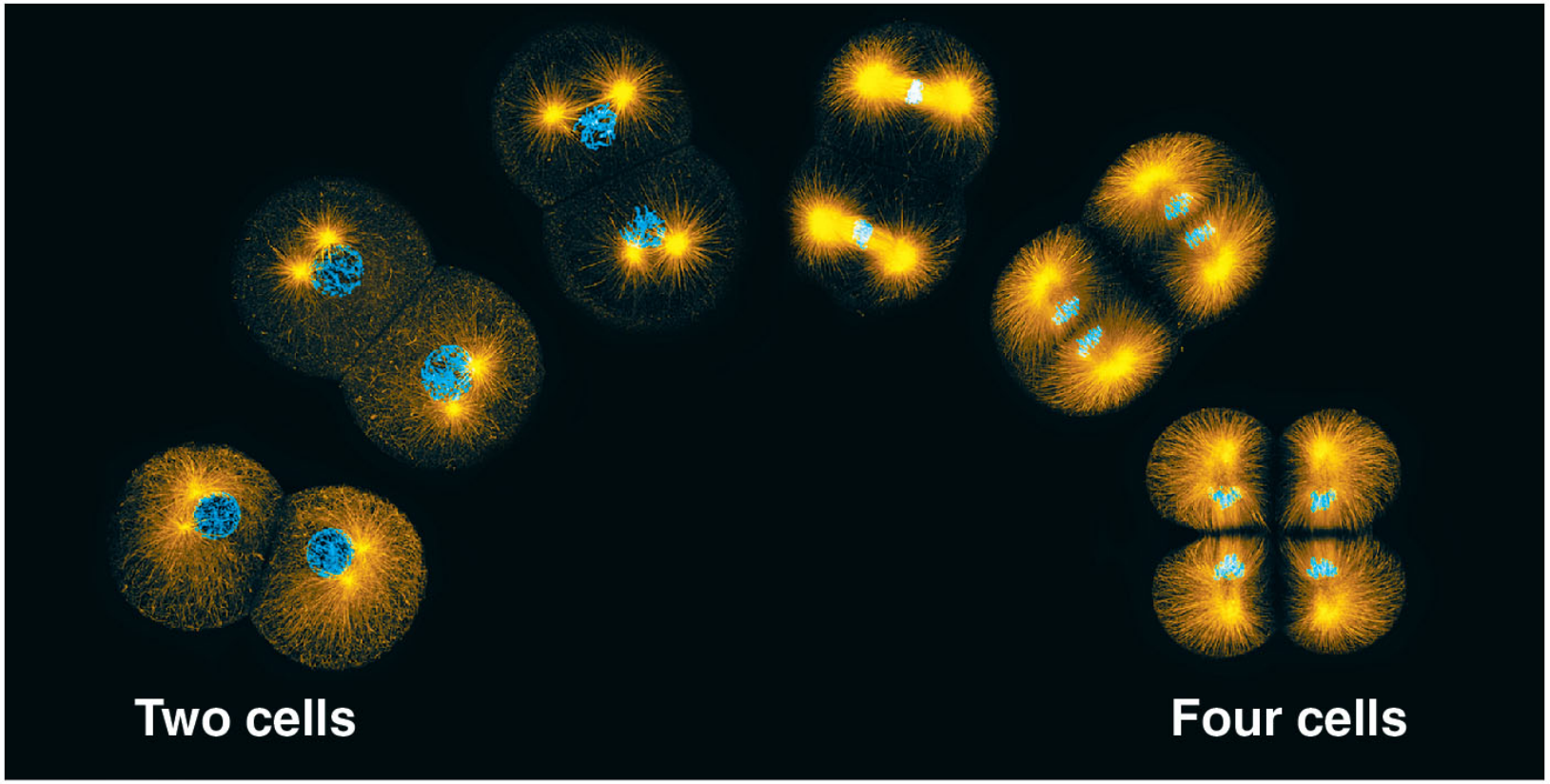
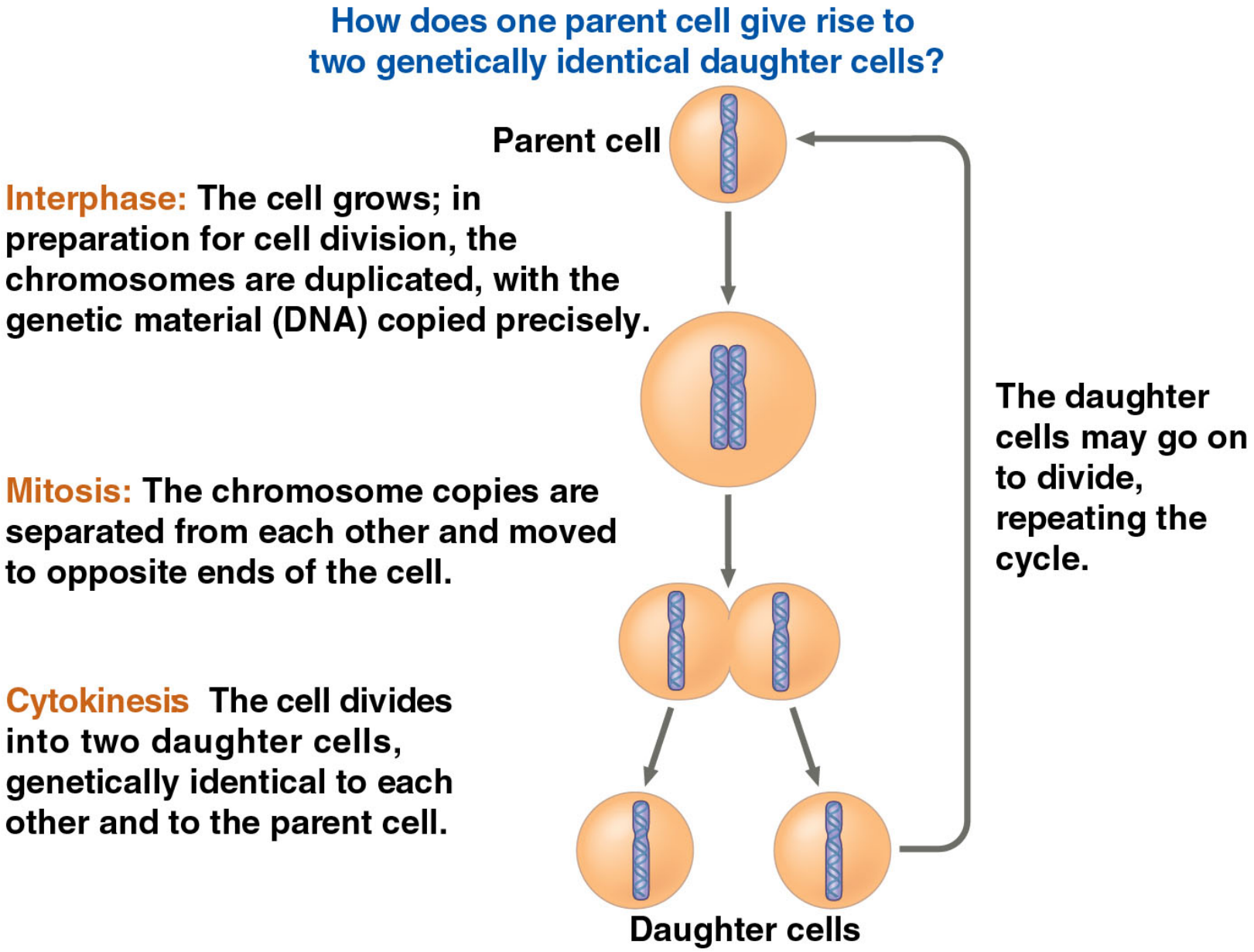


Figure 12.1b


How does one parent cell give rise to two genetically identical daughter cells?
Parent cell
Interphase: The cell grows; in preparation for cell division, the chromosomes are duplicated, with the genetic material (DNA) copied precisely.
Mitosis: The chromosome copies are separated from each other and moved to opposite ends of the cell.
Cytokinesis The cell divides into two daughter cells, genetically identical to each other and to the parent cell.
The daughter cells may go on to divide, repeating the cycle.
Daughter cells

Video: Cell Division in a Sea Urchin Embryo

CONCEPT 12.1: Most cell division results in genetically identical daughter cells

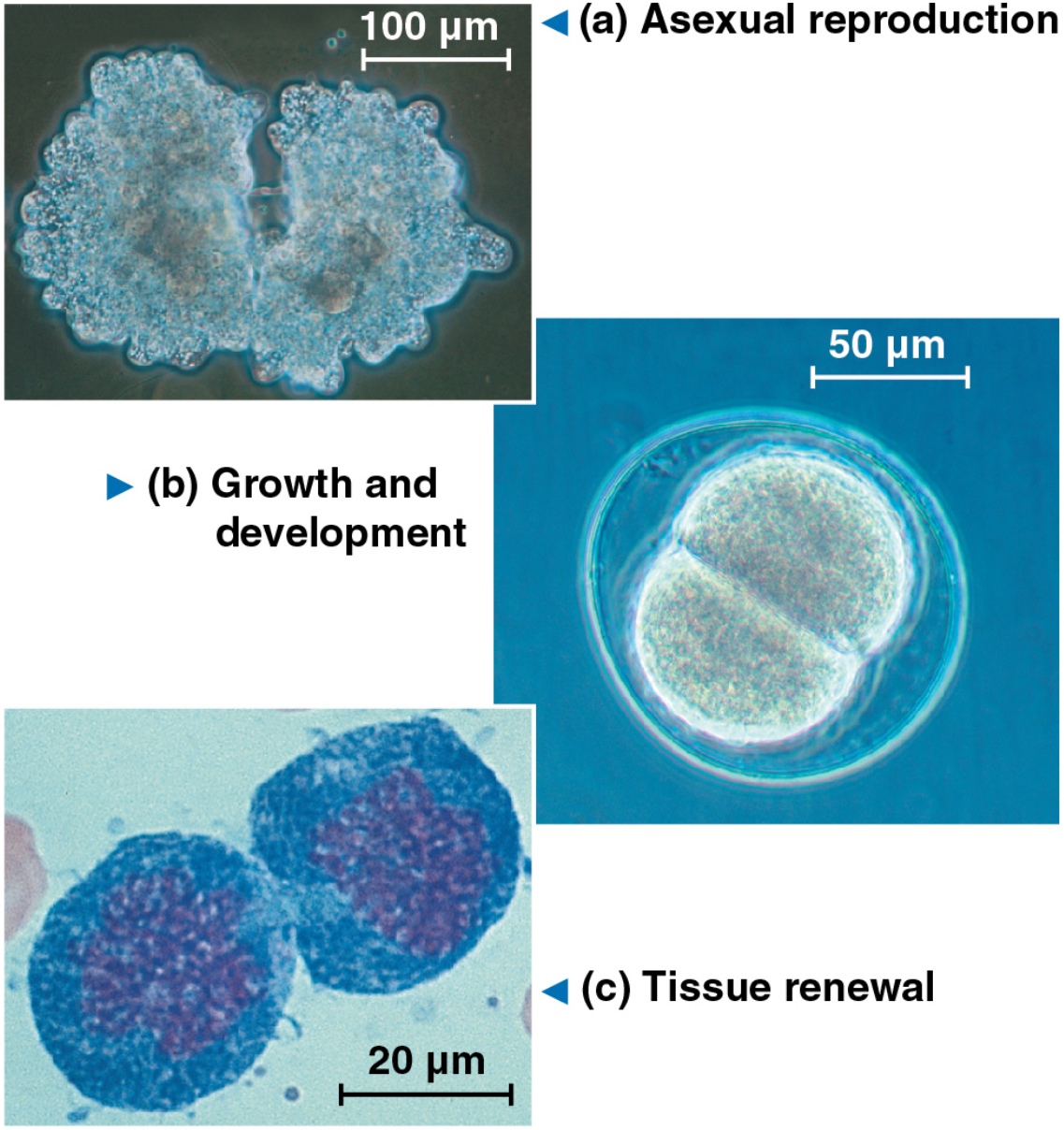
- The ability of organisms to produce more of their own kind is the one characteristic that distinguishes living things from nonliving matter
- The continuity of life is based on the reproduction of cells, or **cell division**

Key Roles of Cell Division

- Cell division plays several important roles in life
- Single-celled organisms give rise to new organisms through cell division
- Multicellular eukaryotes undergo embryonic development through cell division
- Cell division continues to function in renewal and repair in fully grown multicellular eukaryotes

- A crucial function of most cell division is the distribution of identical genetic material to the two daughter cells
- Cell division is remarkably accurate in passing DNA from one generation to the next

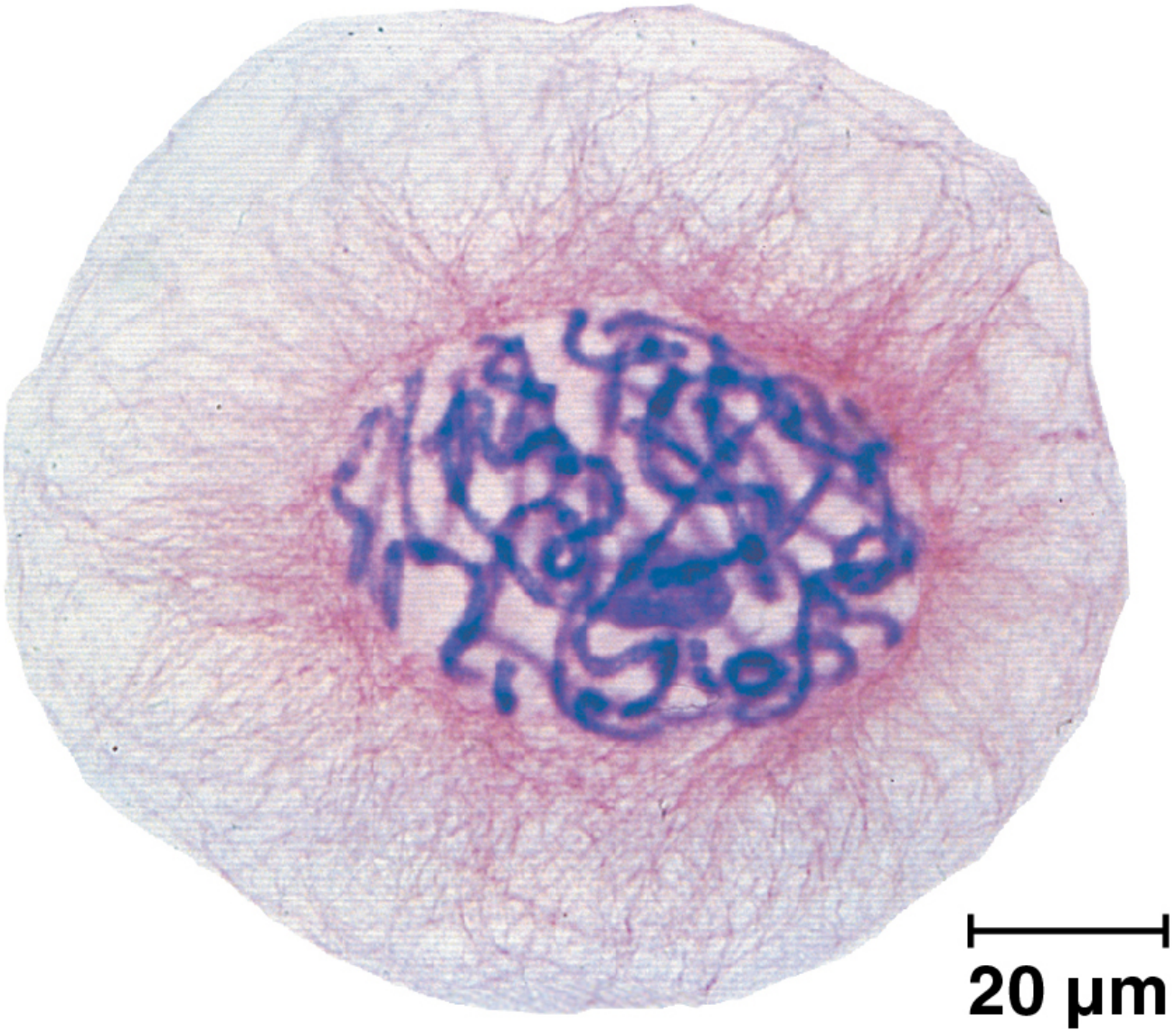
Figure 12.2


100 µm
(a) Asexual reproduction
50 µm
(b) Growth and development
20 µm
(c) Tissue renewal

Cellular Organization of the Genetic Material

- All the DNA in a cell constitutes the cell's **genome**
- A genome can consist of a single DNA molecule (common in prokaryotic cells) or a number of DNA molecules (common in eukaryotic cells)
- DNA molecules in a cell are packaged into **chromosomes**
- The DNA molecule of a chromosome carries several hundred to a few thousand genes

Figure 12.3

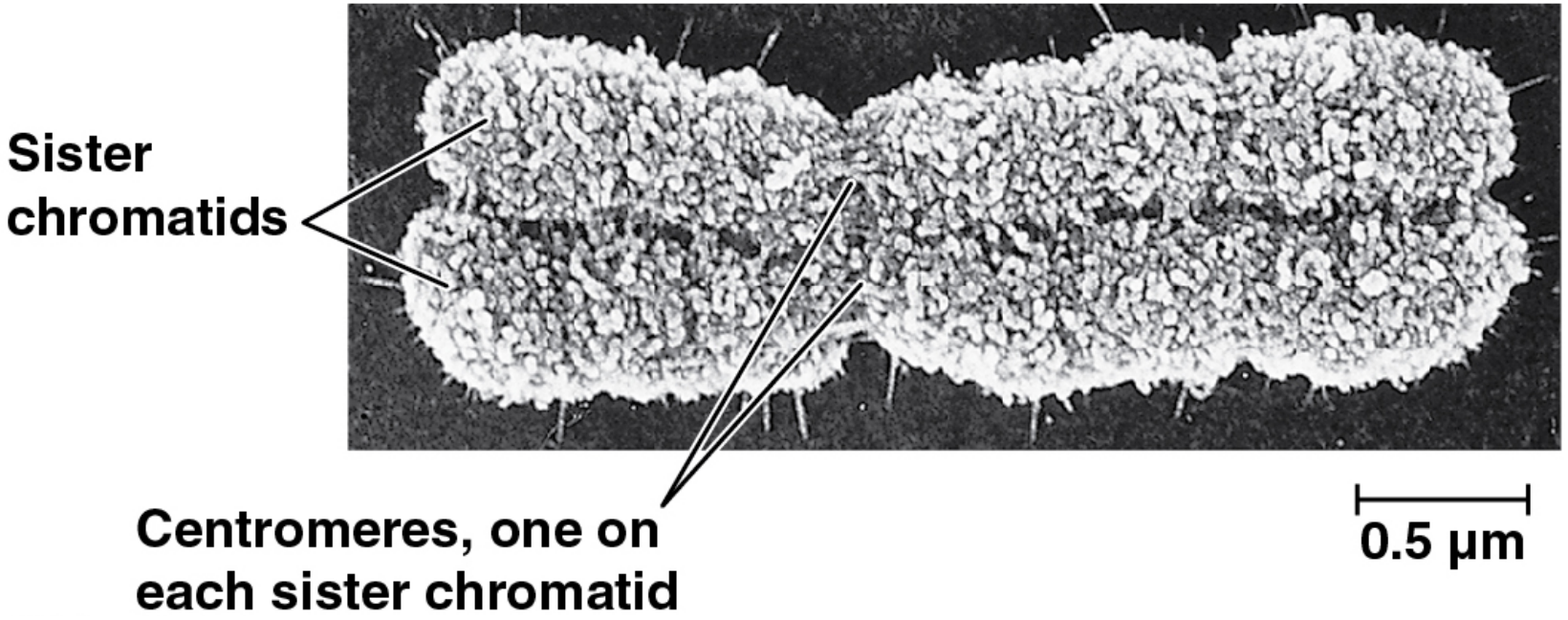


- Eukaryotic chromosomes consist of **chromatin**, a complex of DNA and protein that condenses during cell division
- Every eukaryotic species has a characteristic number of chromosomes in each cell nucleus
- **Somatic cells** (nonreproductive cells) have two sets of chromosomes
- **Gametes** (reproductive cells: sperm and eggs) have half as many chromosomes as somatic cells

Distribution of Chromosomes During Eukaryotic Cell Division

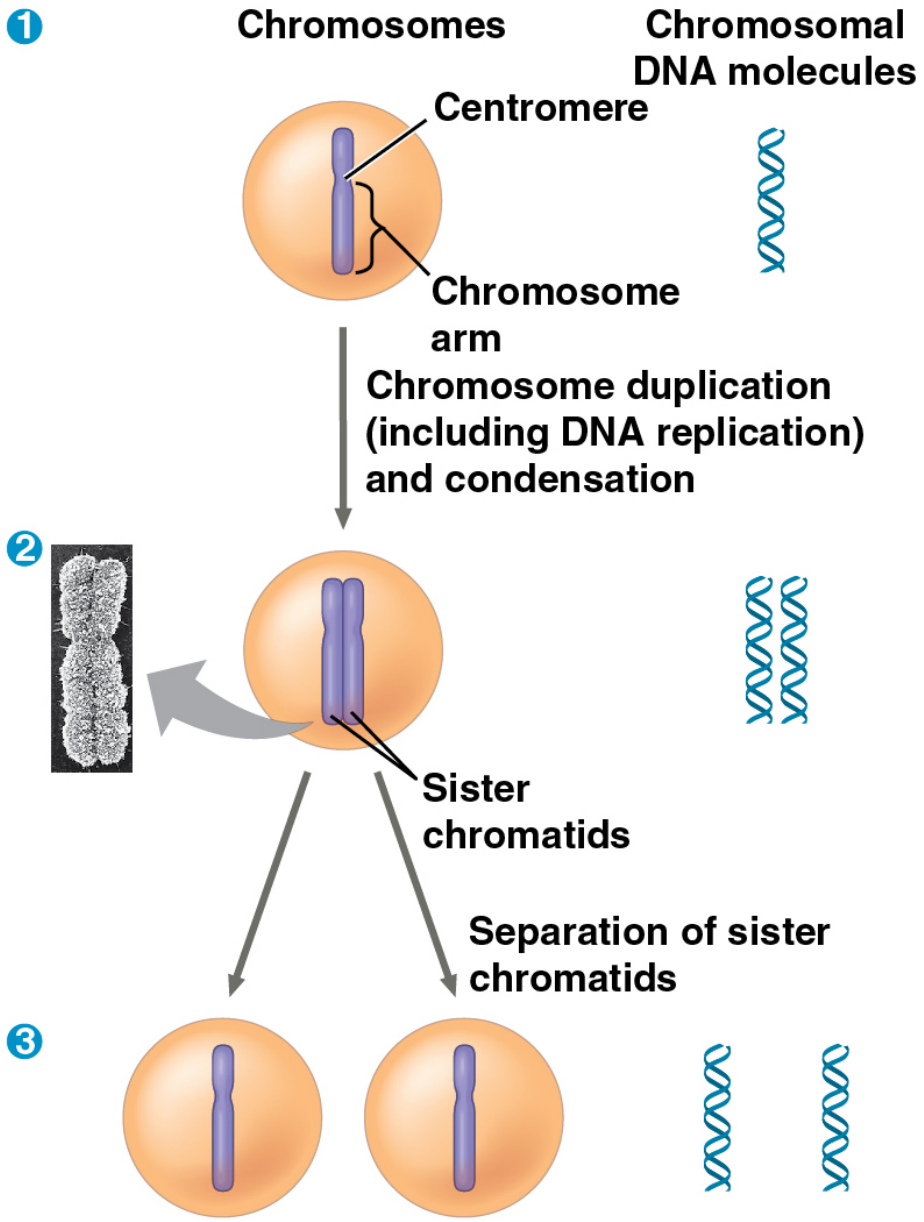
- In preparation for cell division, DNA is replicated and the chromosomes condense
- Each duplicated chromosome has two **sister chromatids** (joined copies of the original chromosome), attached along their lengths by *cohesins*
- The **centromere** is the narrow "waist" of the duplicated chromosome, where the two chromatids are most closely attached

Figure 12.4

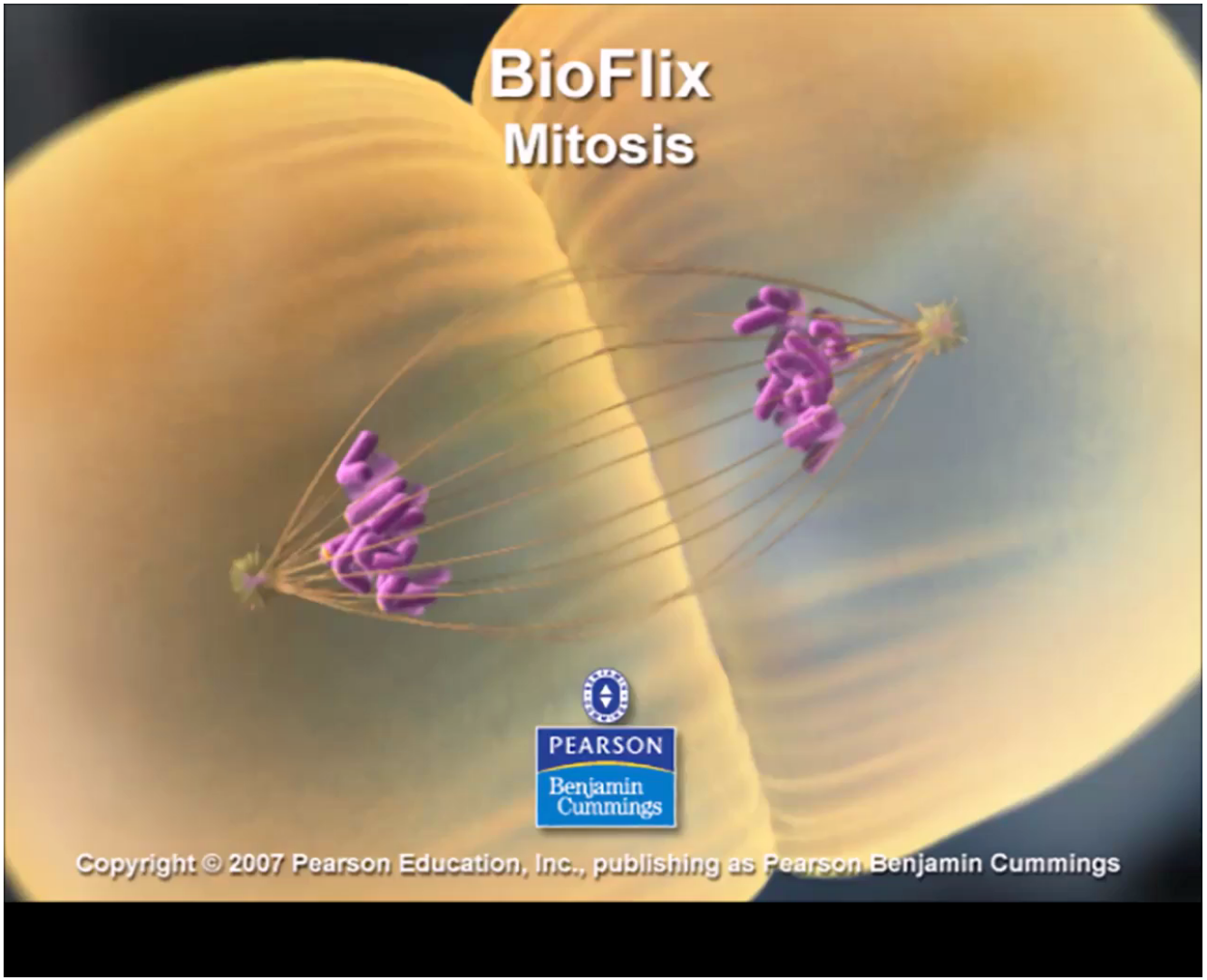

Sister chromatids
Centromeres, one on each sister chromatid
0.5 µm

- During cell division, the two sister chromatids of each duplicated chromosome separate and move into two nuclei
- Once separate, the chromatids are called chromosomes

Figure 12.5


1
Chromosomes
Chromosomal DNA molecules
Centromere
Chromosome arm
Chromosome duplication (including DNA replication) and condensation
2
Sister chromatids
Separation of sister chromatids
3

BioFlix® Animation: Chromosome Duplication



- Eukaryotic cell division consists of
  - **mitosis**, the division of the genetic material in the nucleus
  - **cytokinesis**, the division of the cytoplasm
- Gametes are produced by a variation of cell division called *meiosis*
- Meiosis yields nonidentical daughter cells that have half as many chromosomes as the parent cell

CONCEPT 12.2: The mitotic phase alternates with interphase in the cell cycle

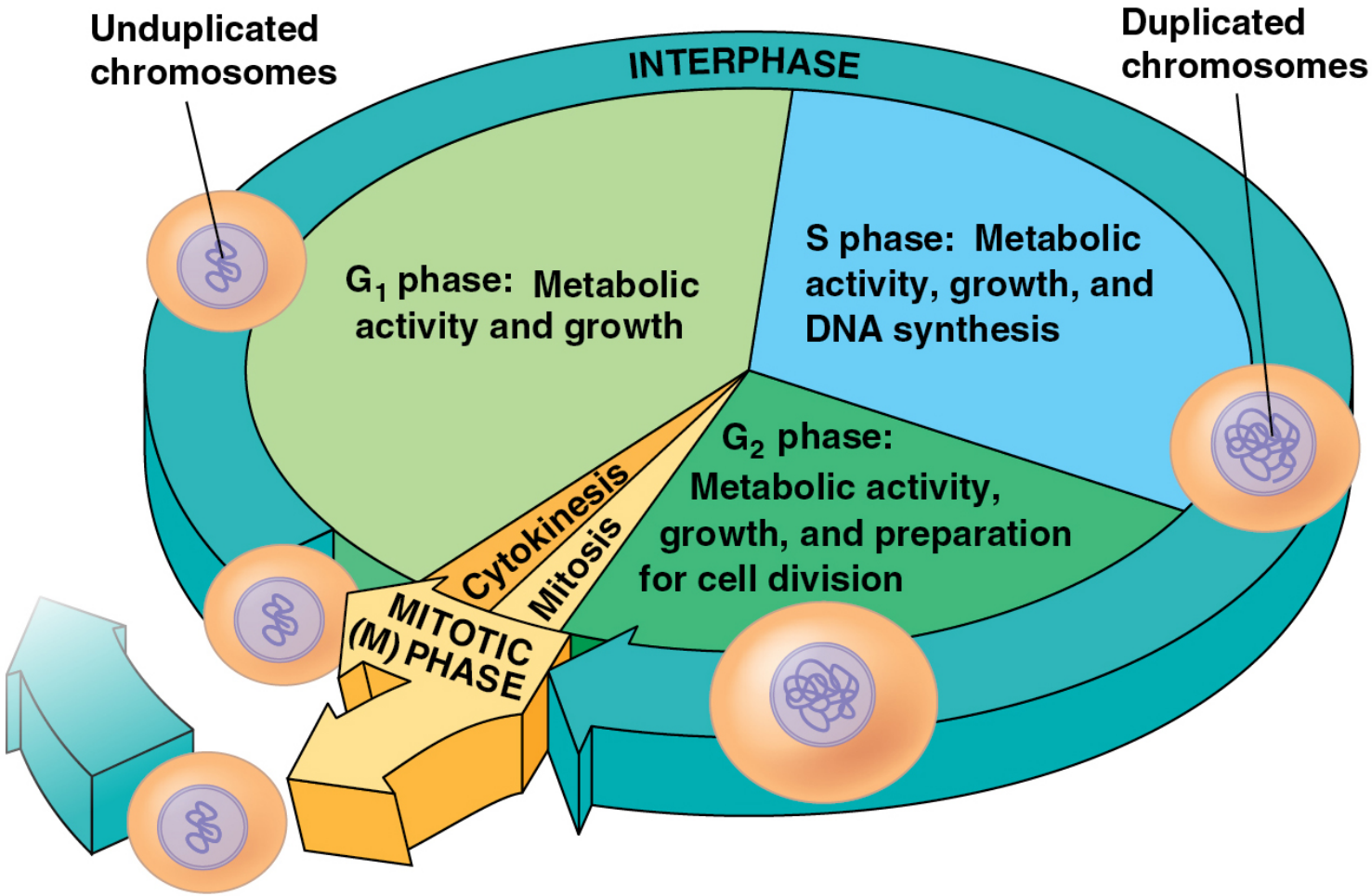
- In 1882, the German anatomist Walther Flemming developed dyes to observe chromosomes during mitosis and cytokinesis
- During the period between one cell division and the next, many critical events occur

Phases of the Cell Cycle

- The cell cycle consists of
  - **mitotic (M) phase** (mitosis and cytokinesis)
  - **interphase** (cell growth and copying of chromosomes in preparation for cell division)

- Interphase (about 90% of the cell cycle) can be divided into three phases:
  - **G_1 phase** (“first gap”)
  - **S phase** (“synthesis”)
  - **G_2 phase** (“second gap”)
- The cell grows during all three phases, but chromosomes are duplicated only during the S phase

Figure 12.6



MITOTIC (M) PHASE:
Mitosis: Distribution of chromosomes into two daughter nuclei
Cytokinesis: Division of cytoplasm, producing two daughter cells. Each daughter cell can start a new cell cycle.

- Mitosis is conventionally broken down into five stages:
  - **prophase**
  - **prometaphase**
  - **metaphase**
  - **anaphase**
  - **telophase**

Figure 12.7a

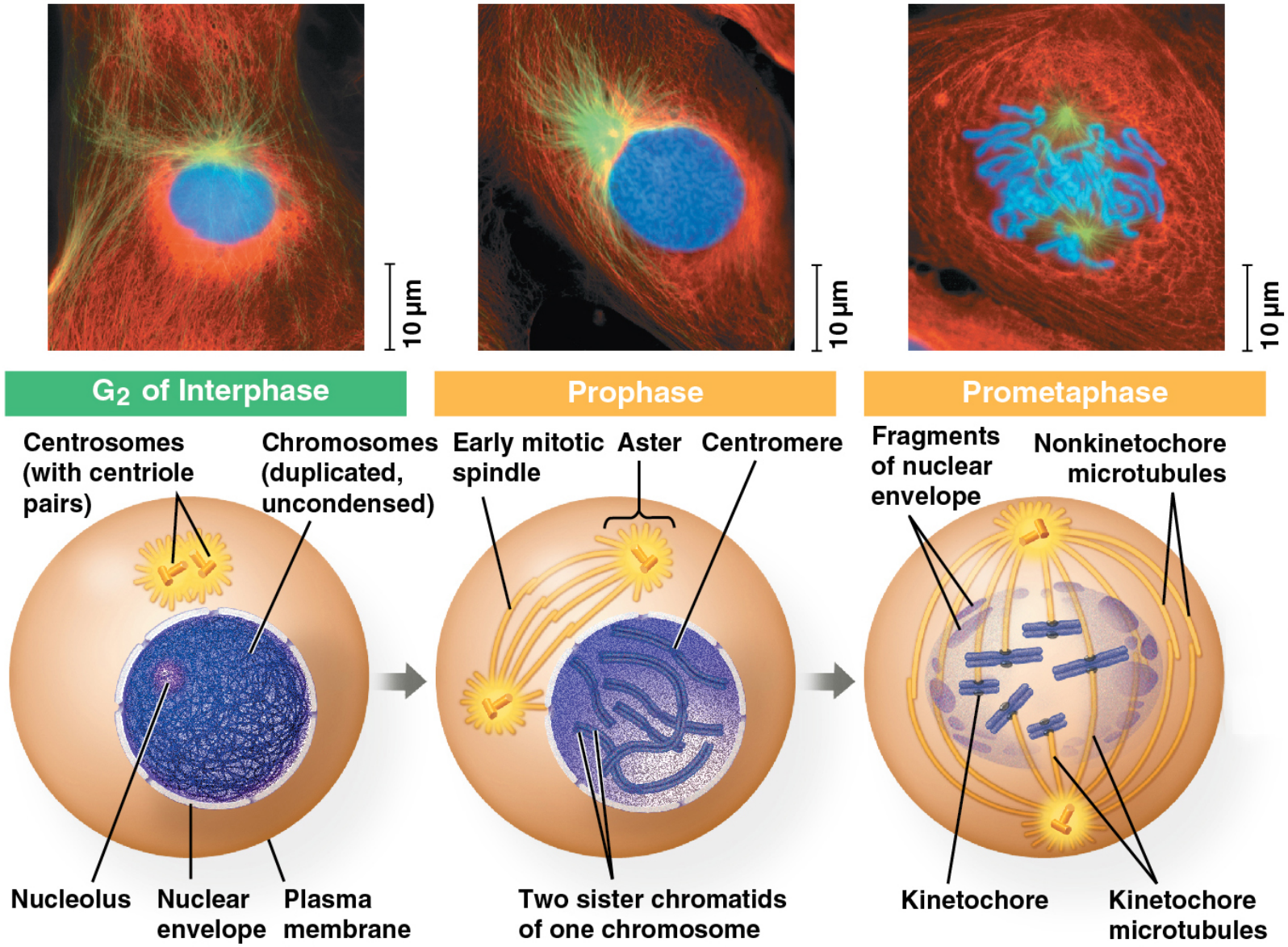
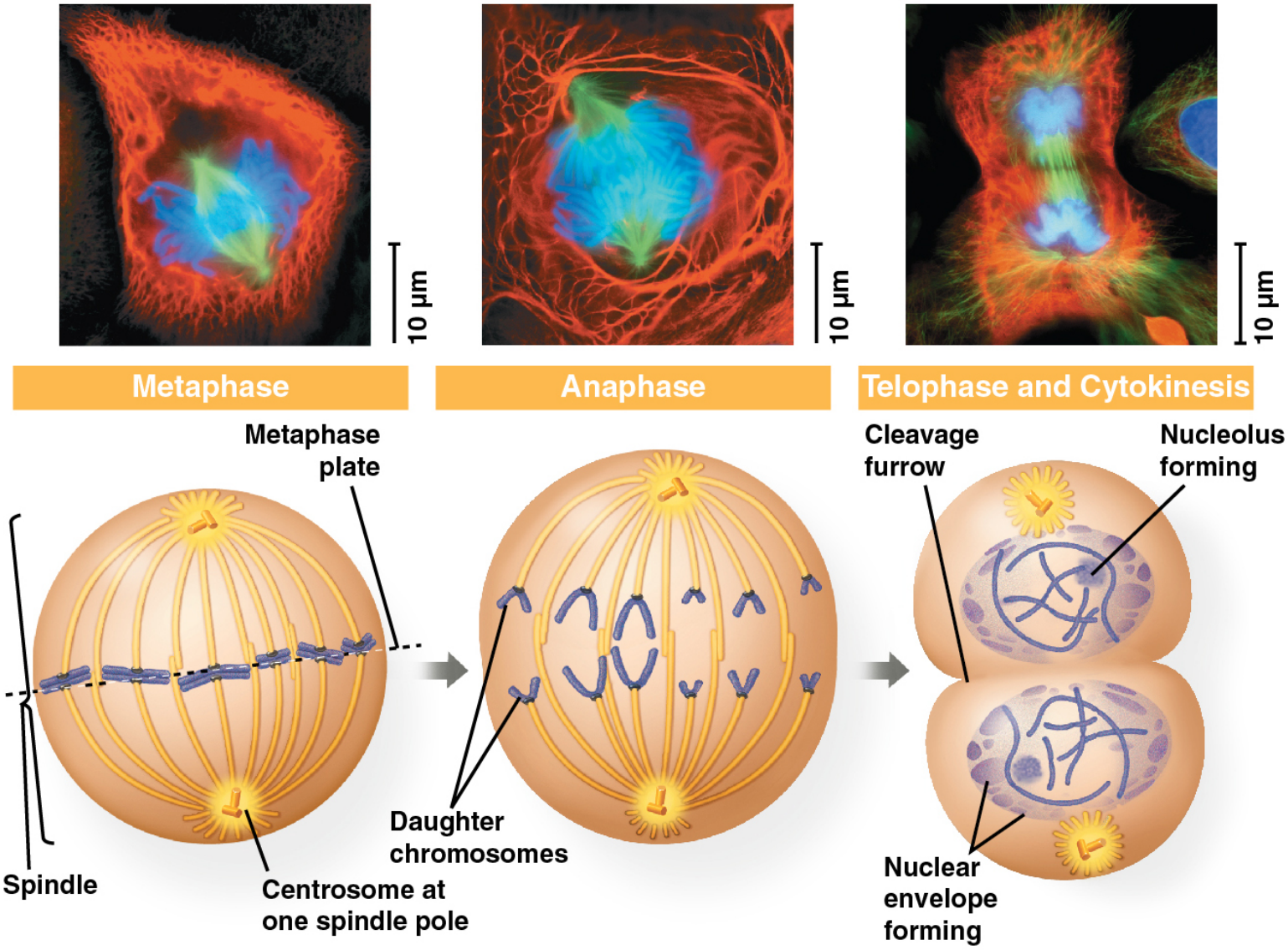
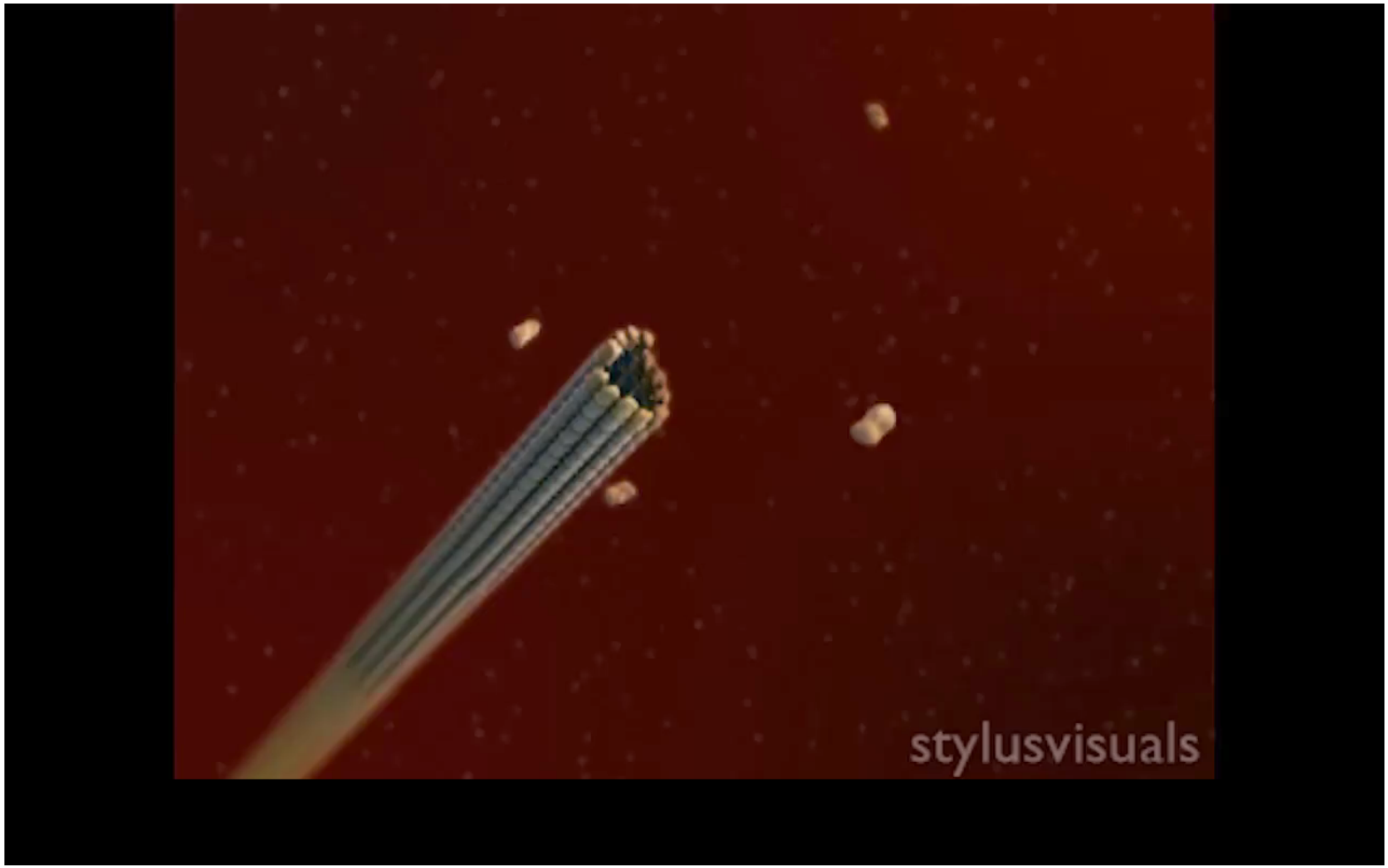

10 µm
10 µm
10 µm
G2 of Interphase
Prophase
Prometaphase
Centrosomes (with centriole pairs)
Chromosomes (duplicated, uncondensed)
Early mitotic spindle
Aster
Centromere
Fragments of nuclear envelope
Nonkinetochore microtubules
Nucleolus
Nuclear envelope
Plasma membrane
Two sister chromatids of one chromosome
Kinetochore
Kinetochore microtubules

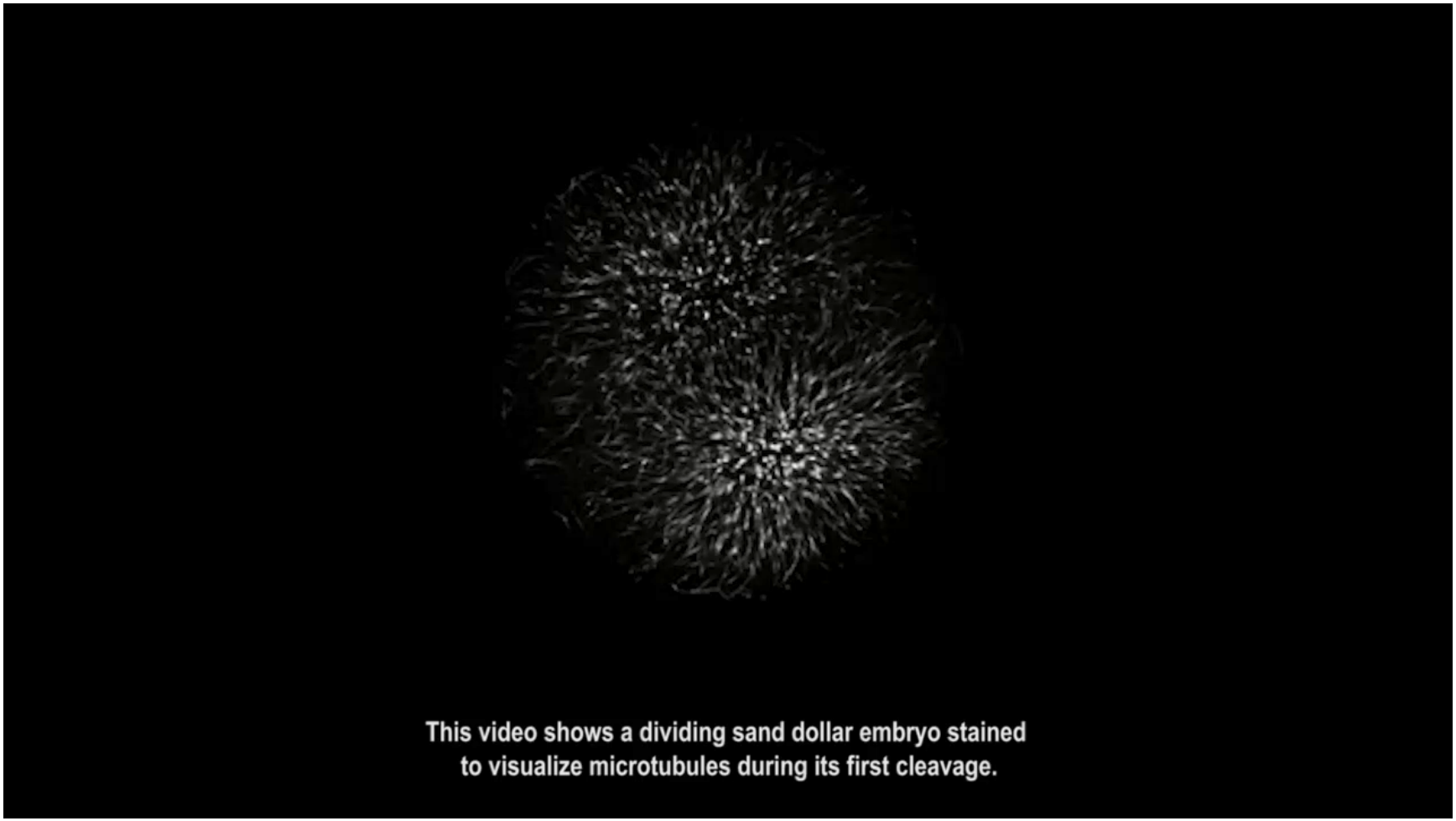
Figure 12.7b


10 µm
10 µm
10 µm
Metaphase
Anaphase
Telophase and Cytokinesis
Metaphase plate
Spindle
Centrosome at one spindle pole
Daughter chromosomes
Cleavage furrow
Nucleolus forming
Nuclear envelope forming

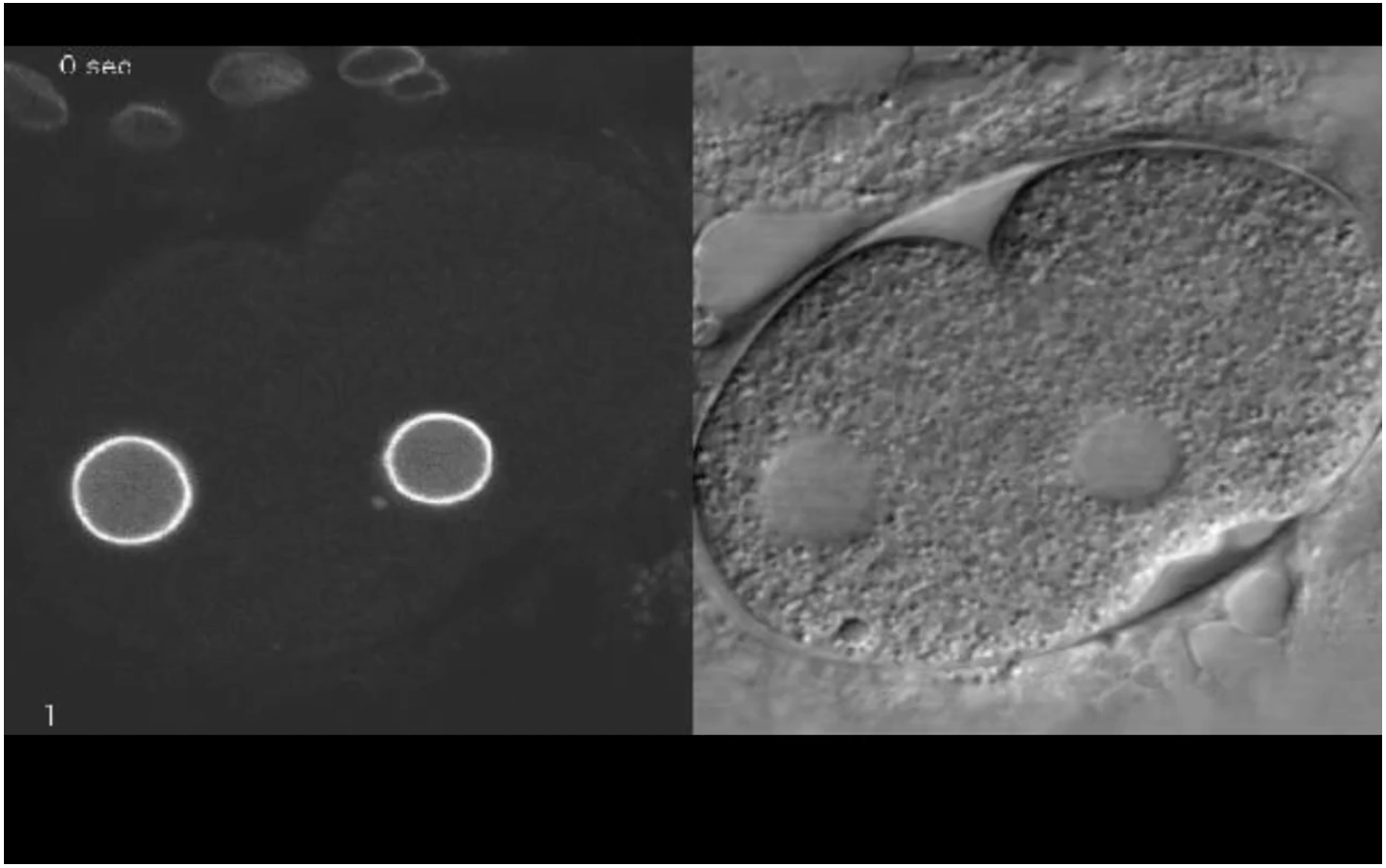
Animation: Microtubule Depolymerization



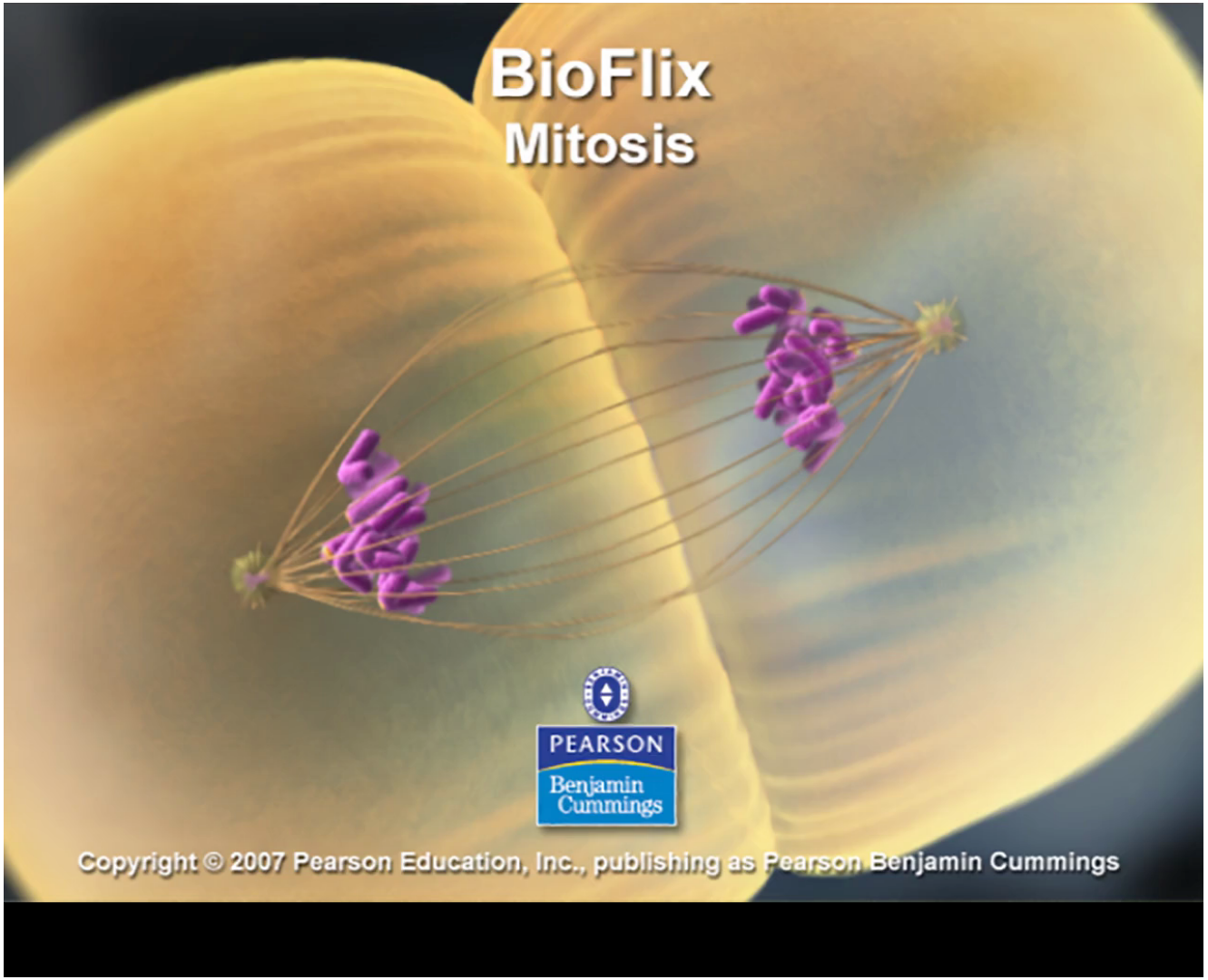
Video: Microtubules in Anaphase



Video: Nuclear Envelope Breakdown and Formation During Mitosis in *C. elegans*, a Eukaryote



BioFlix® Animation: Mitosis



Video: Animal Mitosis (Time-Lapse)

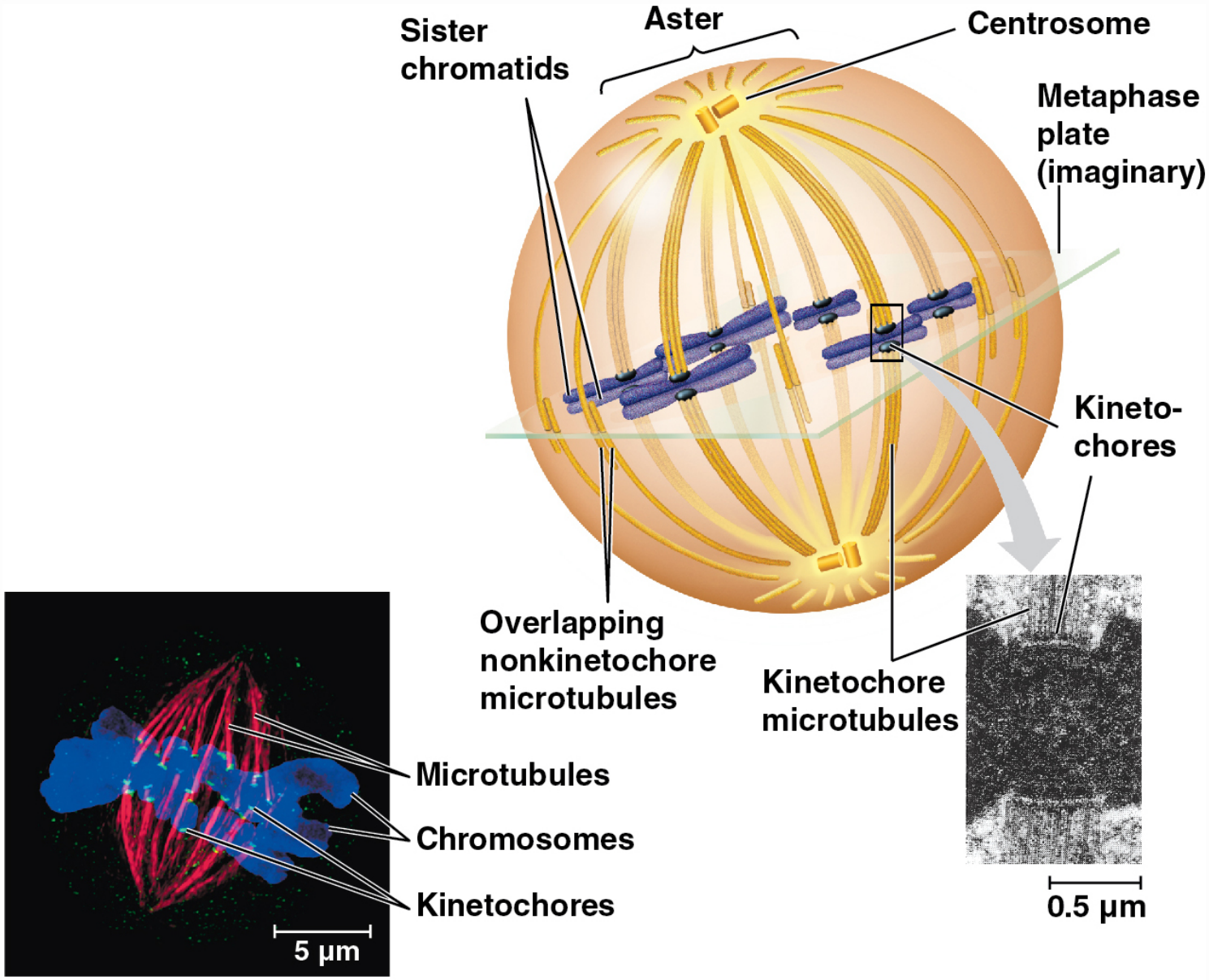
The Mitotic Spindle: *A Closer Look*

- The **mitotic spindle** is a structure made of microtubules that controls chromosome movement during mitosis
- In animal cells, assembly of spindle microtubules begins in the **centrosome**, a type of microtubule-organizing center
- The centrosome replicates during interphase, forming two centrosomes that migrate to opposite ends of the cell during prophase and prometaphase

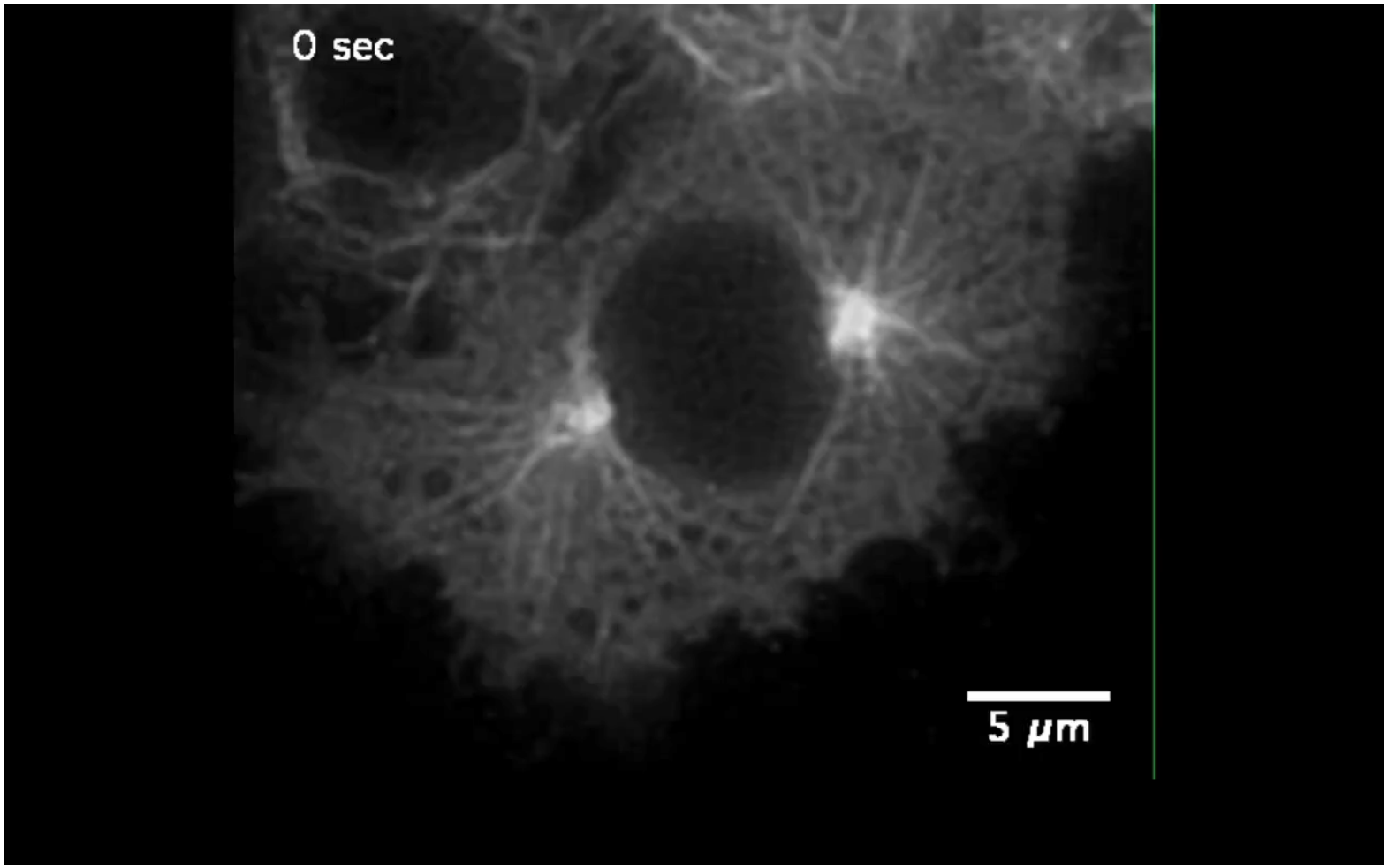
- By the end of prometaphase, the two centrosomes are at opposite end of the cell
- An aster (a radial array of short microtubules) extends from each centrosome
- The spindle includes the centrosomes, the spindle microtubules, and the asters

- Each sister chromatid has a kinetochore
- A **kinetochore** is a protein complex associated with centromeres
- During prometaphase, some spindle microtubules (*kinetochore microtubules*) attach to the kinetochores
- At metaphase, the chromosomes are all lined up at the **metaphase plate**, an imaginary plane midway between the spindle's two poles

Figure 12.8


Sister chromatids
Aster
Centrosome
Metaphase plate (imaginary)
Kineto-chores
Overlapping nonkinetochore microtubules
Kinetochore microtubules
0.5 µm
Microtubules
Chromosomes
Kinetochores
5 µm

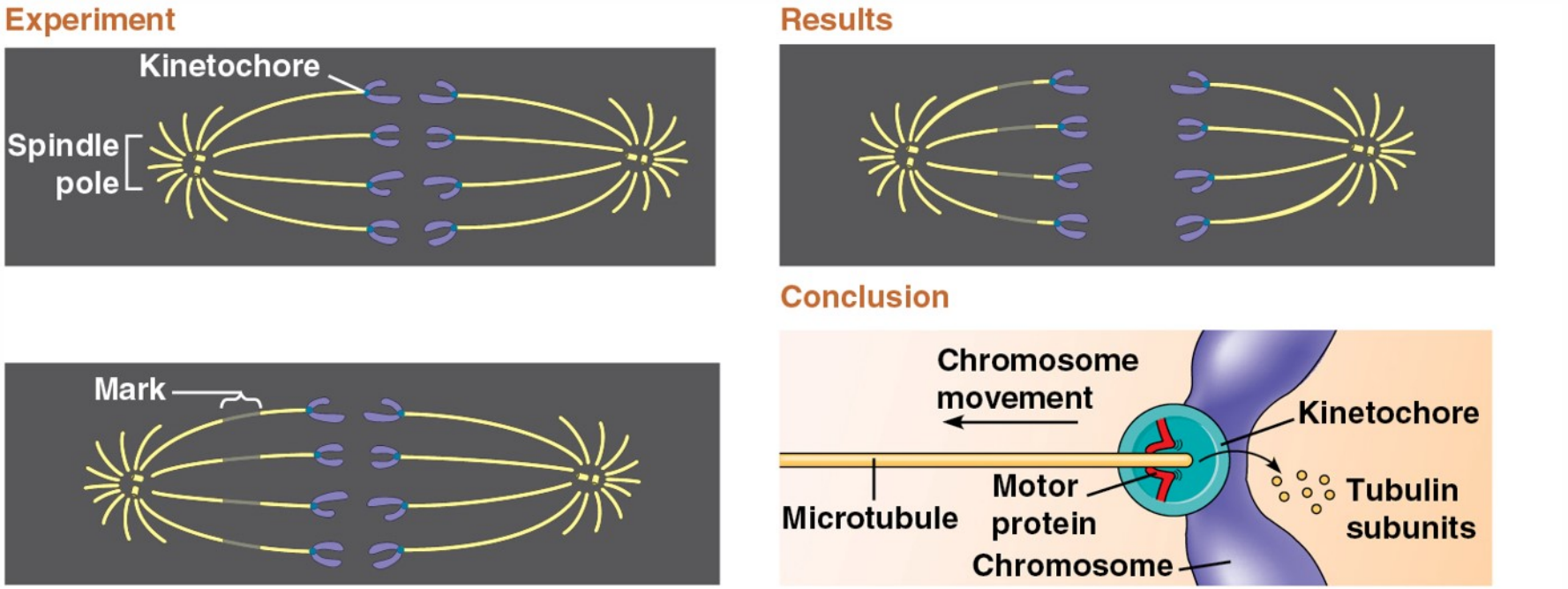
Video: Spindle Formation During Mitosis



- In anaphase, the cohesins are cleaved by an enzyme called separase
- Sister chromatids separate and move along the kinetochore microtubules toward opposite ends of the cell
- The microtubules shorten by depolymerizing at their kinetochore ends

- Results of a clever experiment suggest that motor proteins on kinetochores “walk” the chromosomes along the microtubules during anaphase
- The depolymerization of the microtubules at the kinetochore ends occurs after the motor proteins have passed
- This is called the “Pac-man” mechanism

Figure 12.9



Data from G. J. Gorbsky, P. J. Sammak, and G. G. Borisy, Chromosomes move poleward in anaphase along stationary microtubules that coordinately disassemble from their kinetochore ends, *Journal of Cell Biology* 104:9–18 (1987)

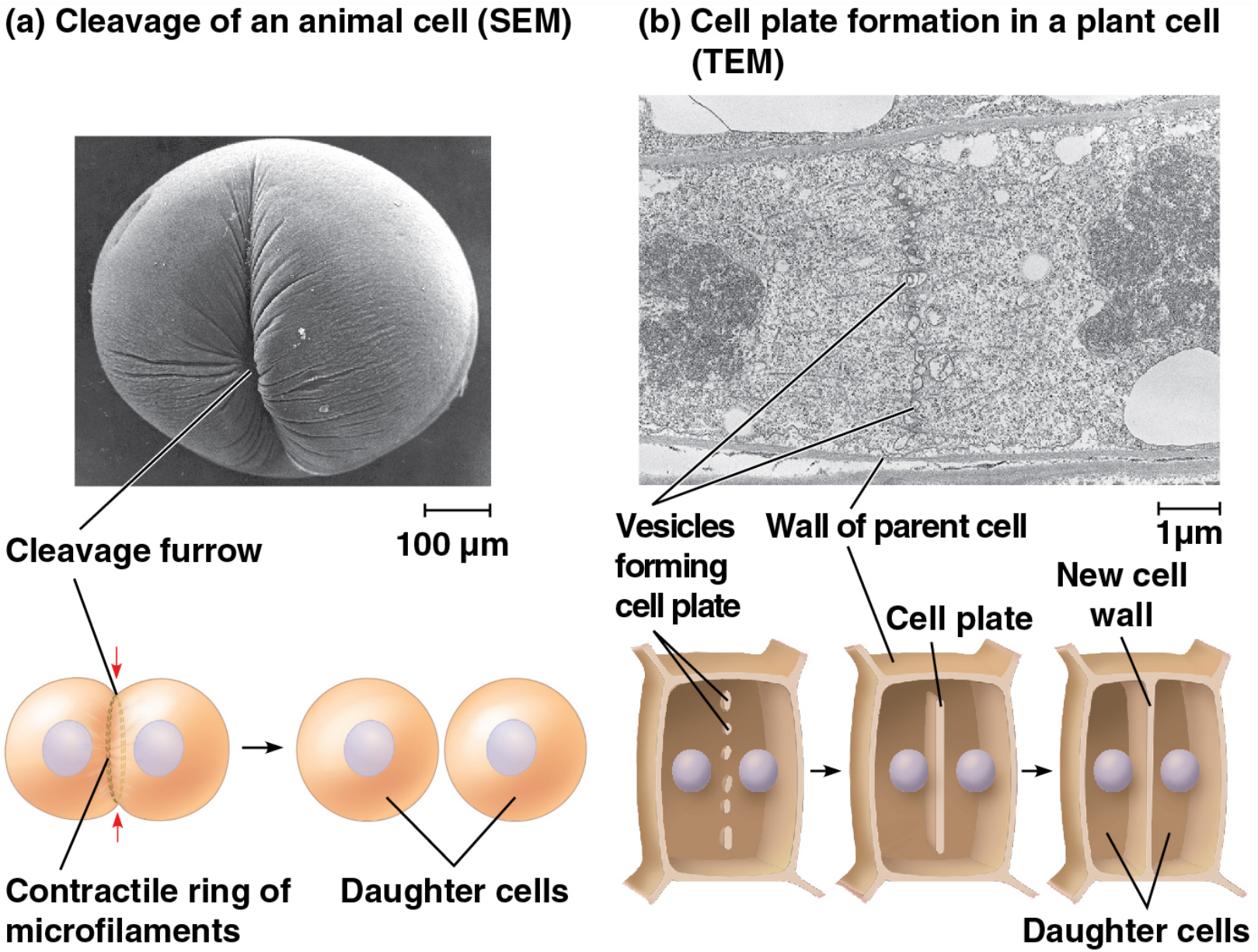
- Other research shows that chromosomes are “reeled in” by motor proteins at the spindle poles
- Microtubules depolymerize after they pass by the motor proteins at the poles
- The general consensus is that both mechanisms are used

- Nonkinetochore microtubules from opposite poles overlap and push against each other, elongating the cell
- At the end of anaphase, duplicate groups of chromosomes have arrived at opposite ends of the elongated cell
- Cytokinesis begins during anaphase or telophase, and the spindle eventually disassembles

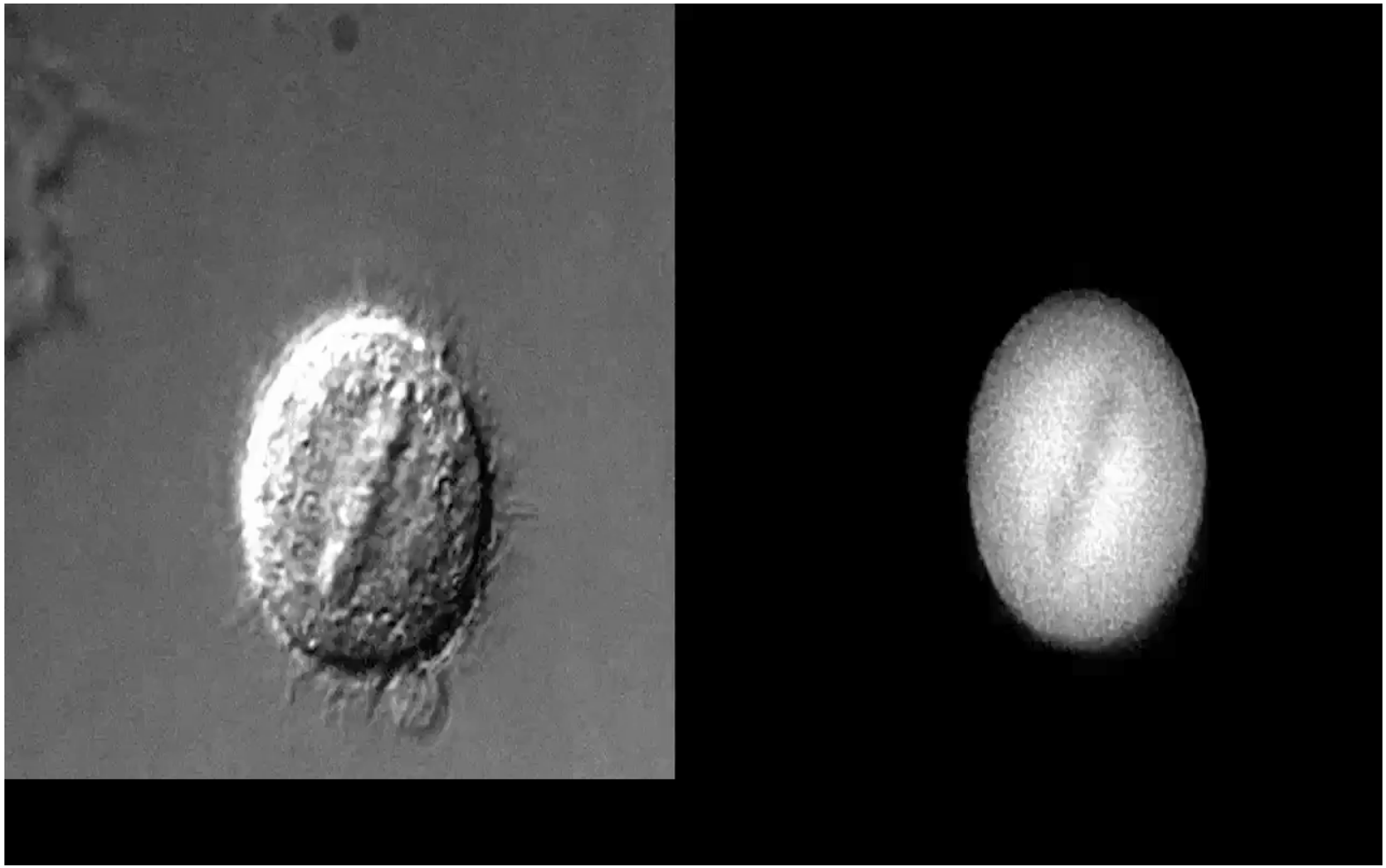
Cytokinesis: *A Closer Look*

- In animal cells, cytokinesis occurs by a process known as **cleavage**
- The first sign of cleavage is the appearance of a **cleavage furrow**, a shallow groove in the cell surface near the old metaphase plate
- In plant cells, a **cell plate** forms during cytokinesis

Figure 12.10


(a) Cleavage of an animal cell (SEM)
Cleavage furrow
100 µm
Contractile ring of microfilaments
Daughter cells
(b) Cell plate formation in a plant cell (TEM)
Vesicles forming cell plate
Wall of parent cell
1µm
Cell plate
New cell wall
Daughter cells

Video: Cytokinesis in an Animal Cell



Video: Myosin and Cytokinesis

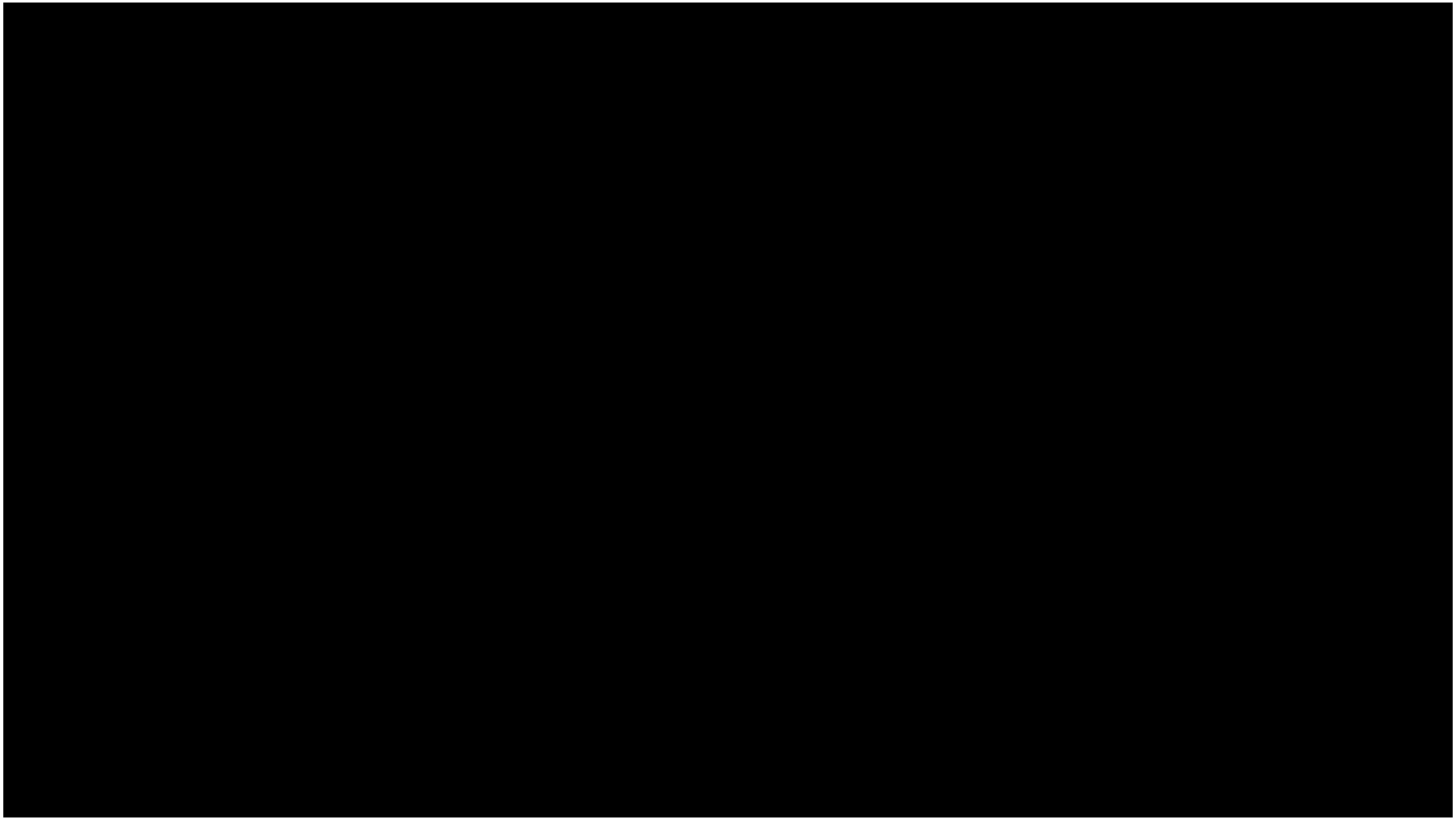
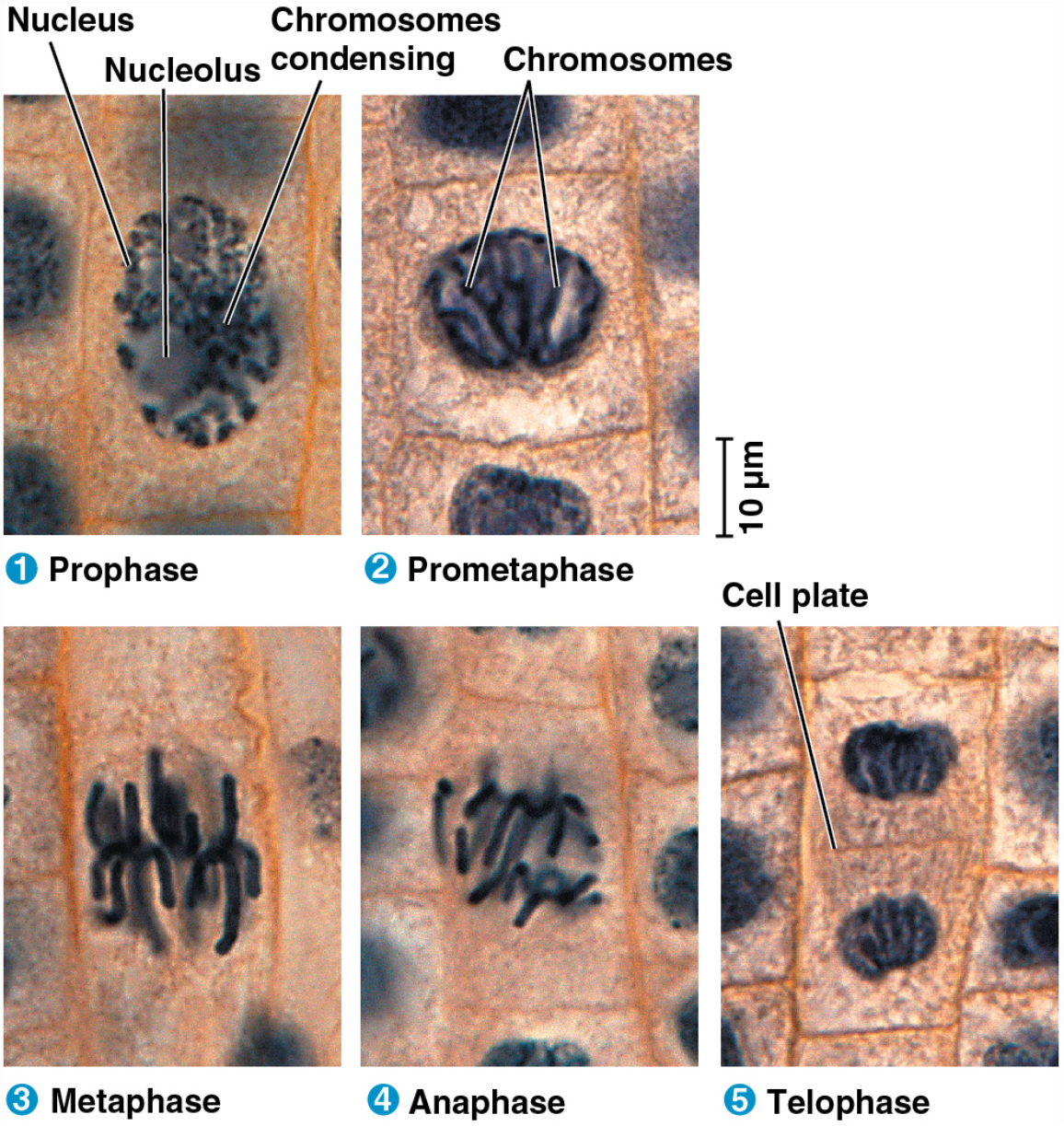


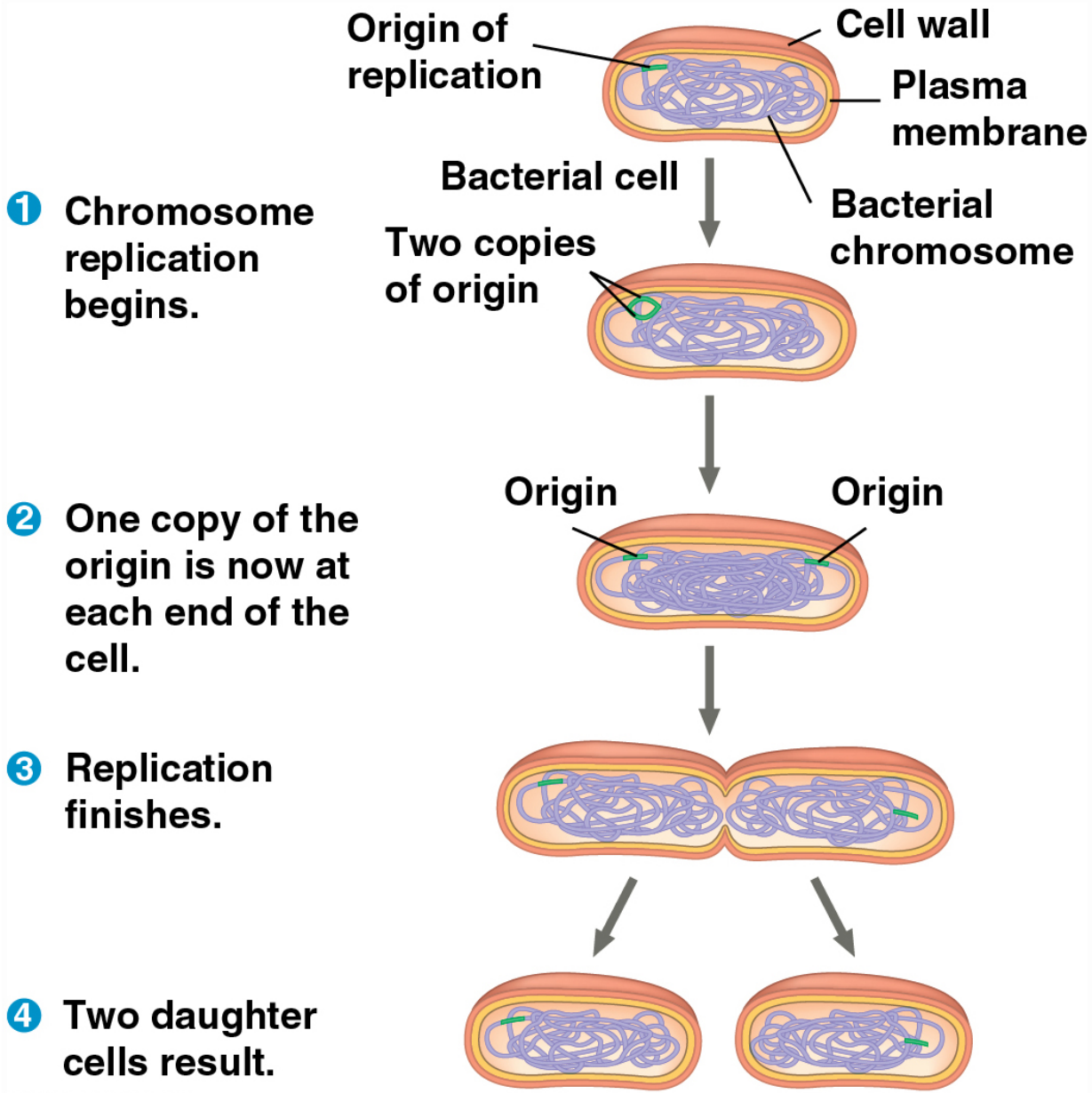
Figure 12.11


Nucleus
Nucleolus
Chromosomes condensing
Chromosomes
10 µm
1 Prophase
2 Prometaphase
Cell plate
3 Metaphase
4 Anaphase
5 Telophase

Binary Fission in Bacteria

- Prokaryotes (bacteria and archaea) reproduce by a type of cell division called **binary fission**
- In binary fission, the chromosome replicates (beginning at the **origin of replication**), and the two daughter chromosomes actively move apart
- The plasma membrane pinches inward, dividing the cell into two
- How bacterial chromosomes move and their location established are active areas of research

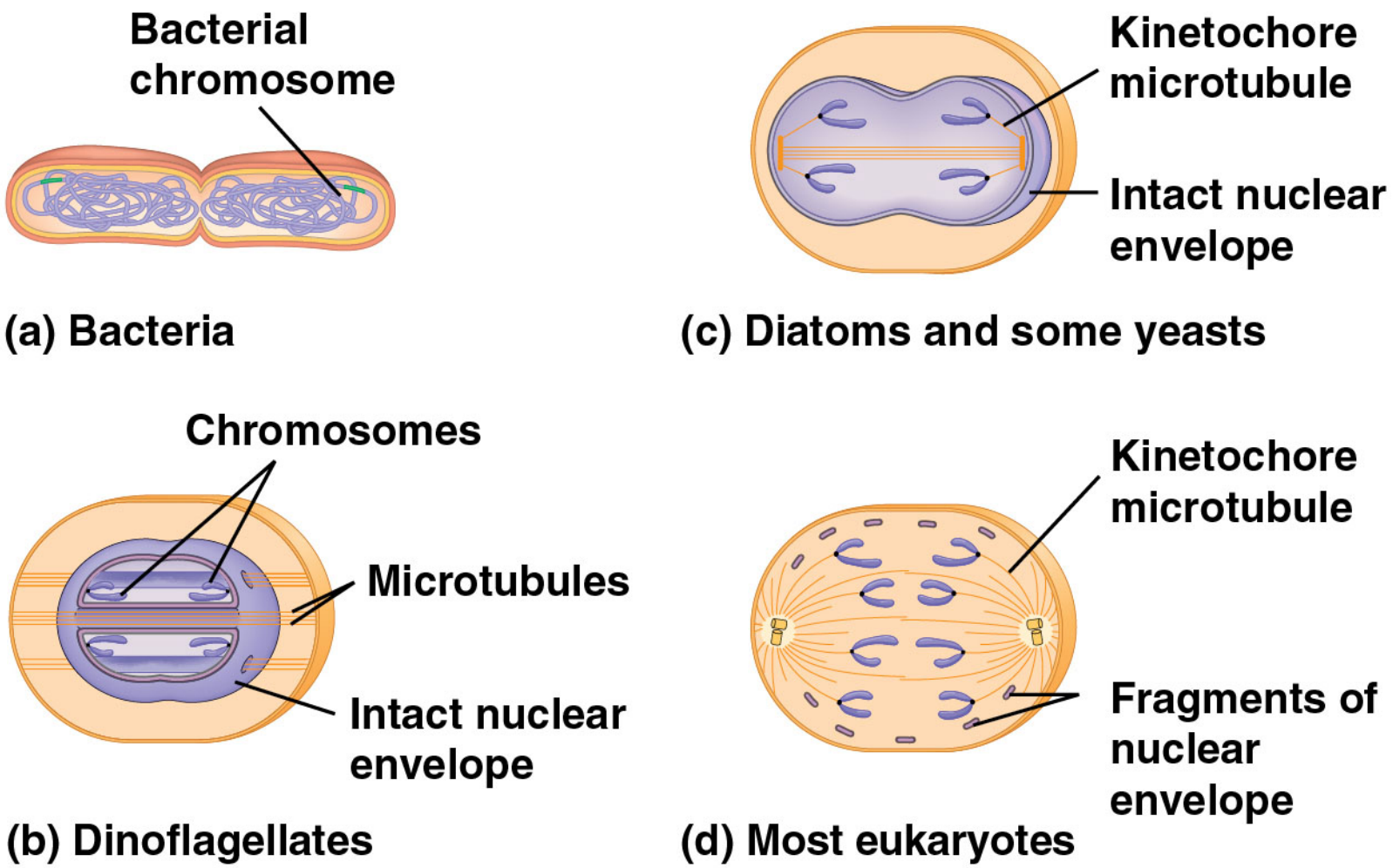
Figure 12.12


Origin of replication
Cell wall
Plasma membrane
Bacterial cell
Bacterial chromosome
Two copies of origin
1 Chromosome replication begins.
Origin
Origin
2 One copy of the origin is now at each end of the cell.
3 Replication finishes.
4 Two daughter cells result.

The Evolution of Mitosis

- Because prokaryotes evolved before eukaryotes, mitosis probably evolved from binary fission
- Certain unicellular eukaryotes exhibit types of cell division that seem intermediate between binary fission and mitosis

Figure 12.13


Bacterial chromosome
(a) Bacteria
Chromosomes
Microtubules
Intact nuclear envelope
(b) Dinoflagellates
Kinetochore microtubule
Intact nuclear envelope
(c) Diatoms and some yeasts
Kinetochore microtubule
Fragments of nuclear envelope
(d) Most eukaryotes

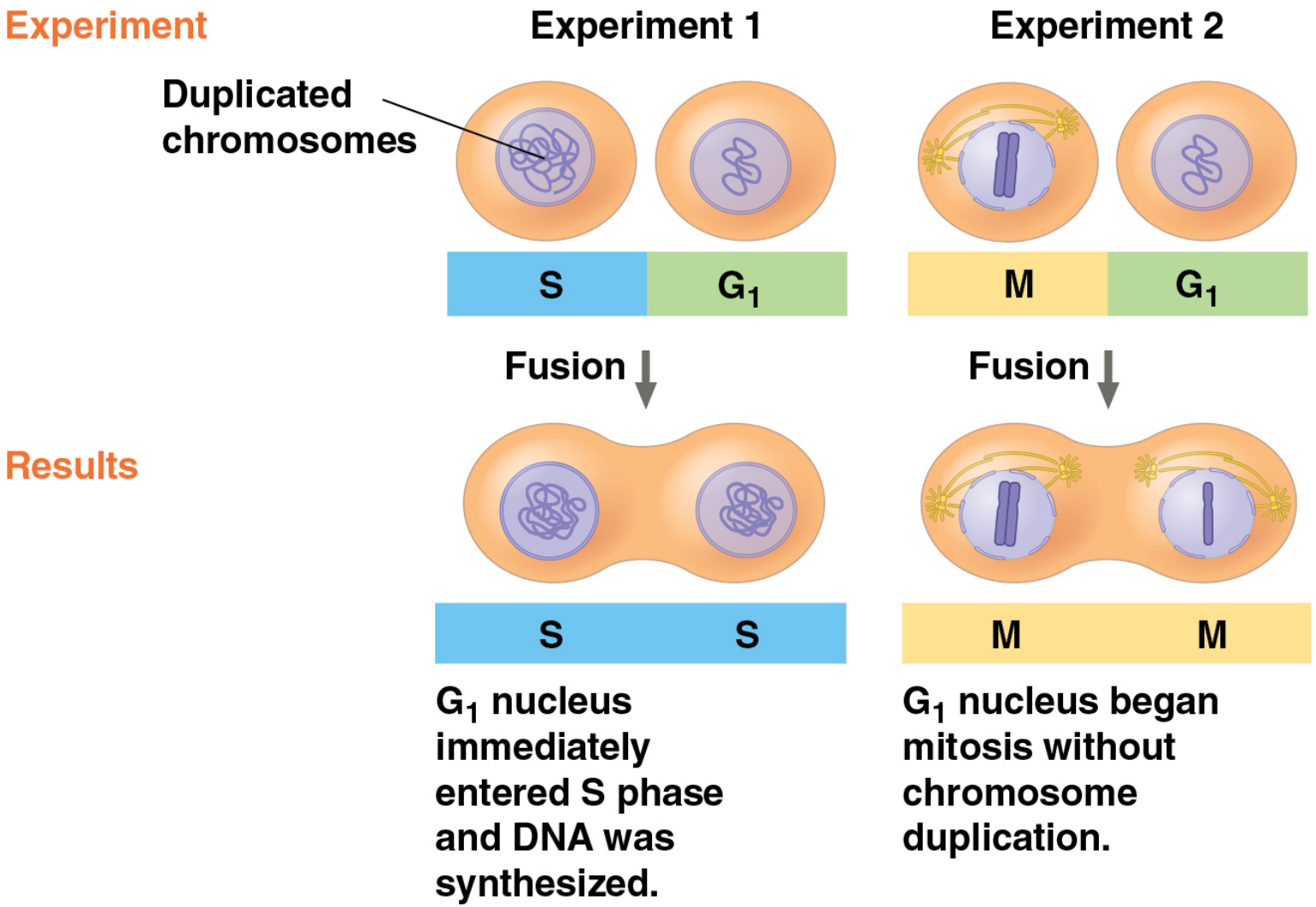
CONCEPT 12.3: The eukaryotic cell cycle is regulated by a molecular control system

- The frequency of cell division varies with the type of cell
- These differences result from regulation at the molecular level
- Cancer cells manage to escape the usual controls on the cell cycle

The Cell Cycle Control System

- The cell cycle appears to be driven by specific signaling molecules present in the cytoplasm
- Some evidence for this hypothesis comes from experiments in which cultured mammalian cells at different phases of the cell cycle were fused to form a single cell with two nuclei
- Signals in the cytoplasm of the fused cell caused both nuclei to enter the same phase of the cell cycle

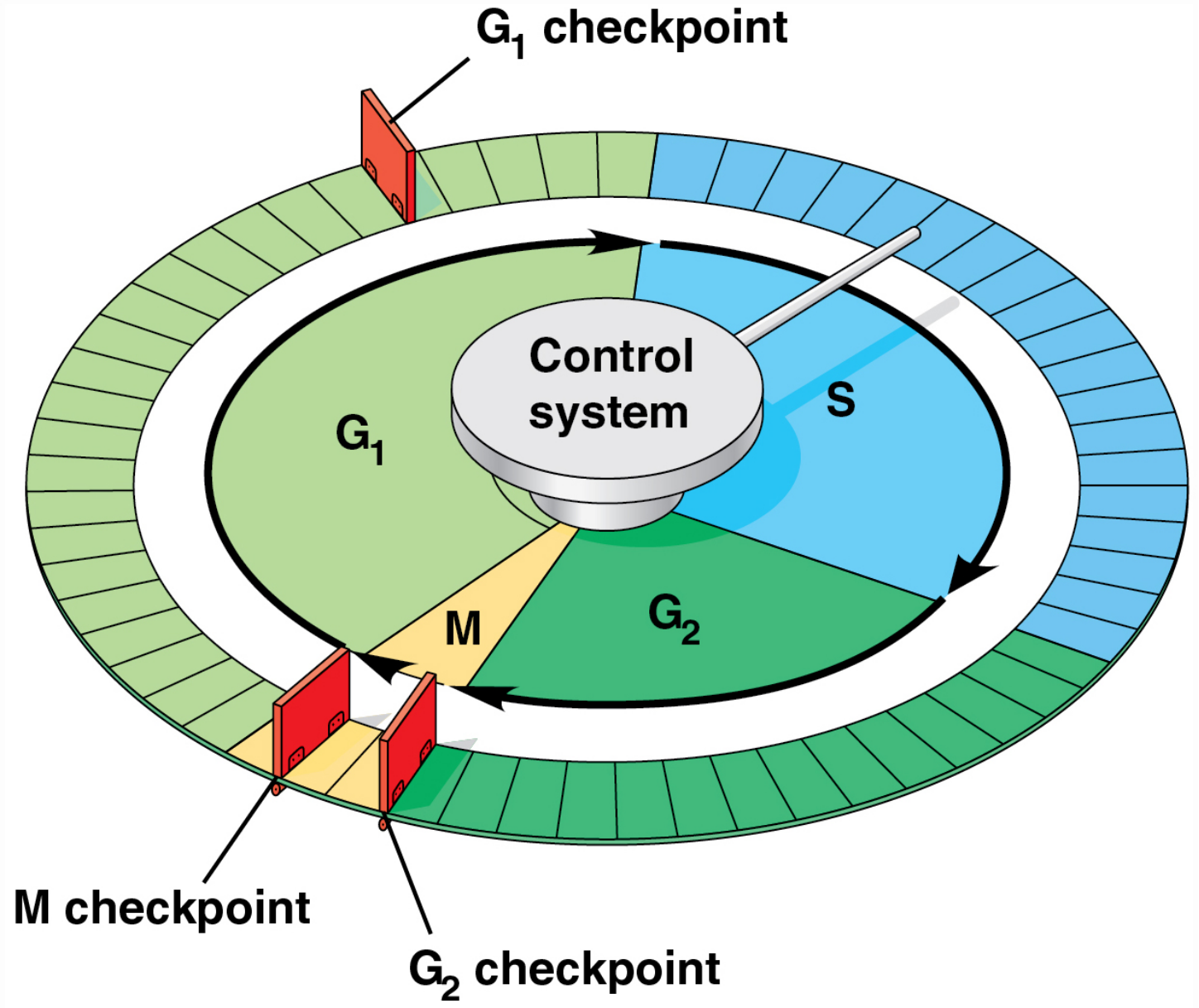
Figure 12.14



Data from R. T. Johnson and P. N. Rao, Mammalian cell fusion: Induction of premature chromosome condensation in interphase nuclei, *Nature* 226:717–722 (1970).

- The sequential events of the cell cycle are directed by a distinct **cell cycle control system**
- The cell cycle control system is regulated by both internal and external controls
- The clock has specific **checkpoints** where the cell cycle stops until a go-ahead signal is received

Figure 12.15

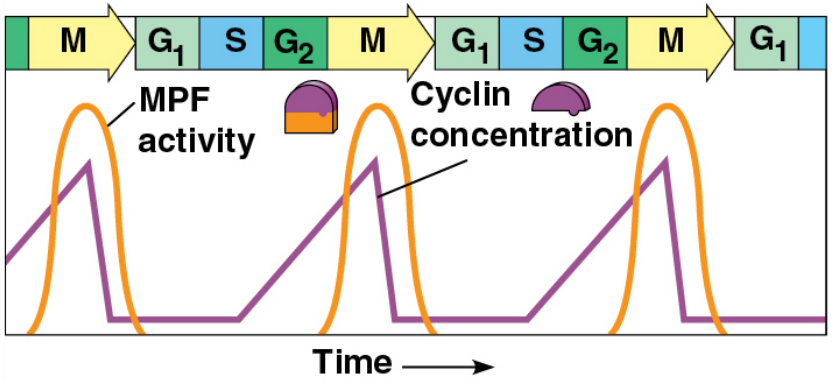

G1 checkpoint
Control system
G1
S
M
G2
M checkpoint
G2 checkpoint

The Cell Cycle Clock: Cyclins and Cyclin-Dependent Kinases

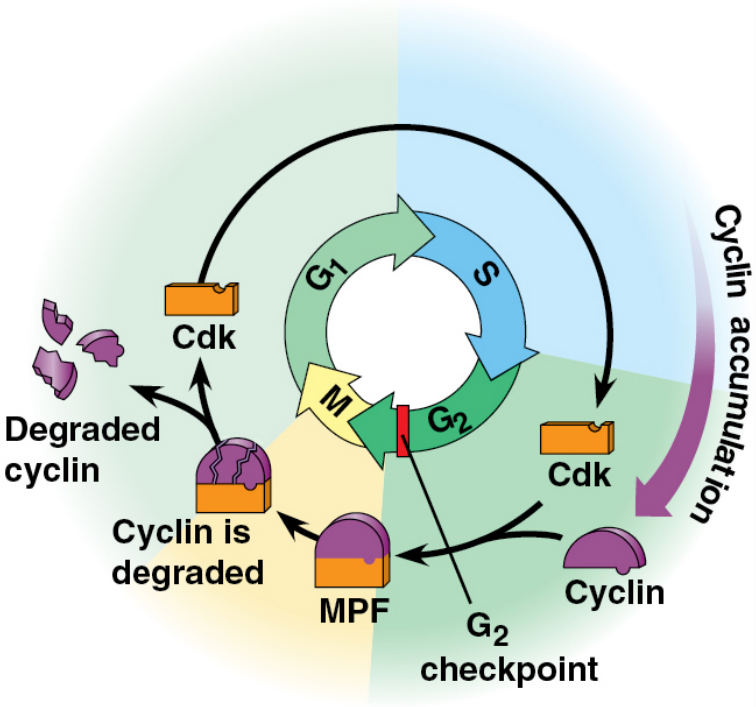
- Two types of regulatory proteins are involved in cell cycle control: **cyclins** and **cyclin-dependent kinases** (**Cdks**)
- Cyclins are named for their cyclically fluctuating concentrations in the cell
- The activity of a Cdk rises and falls with changes in concentration of its cyclin partner
- Cdks must be attached to a cyclin to be active

- **MPF** (maturation-promoting factor) is a cyclin-Cdk complex that triggers a cell's passage past the G_2 checkpoint into the M phase
- Peaks of MPF activity correspond to the peaks of cyclin concentration
- MPF acts both as a kinase and indirectly through activating other kinases

Figure 12.16



(a) Fluctuation of MPF activity and cyclin concentration during the cell cycle



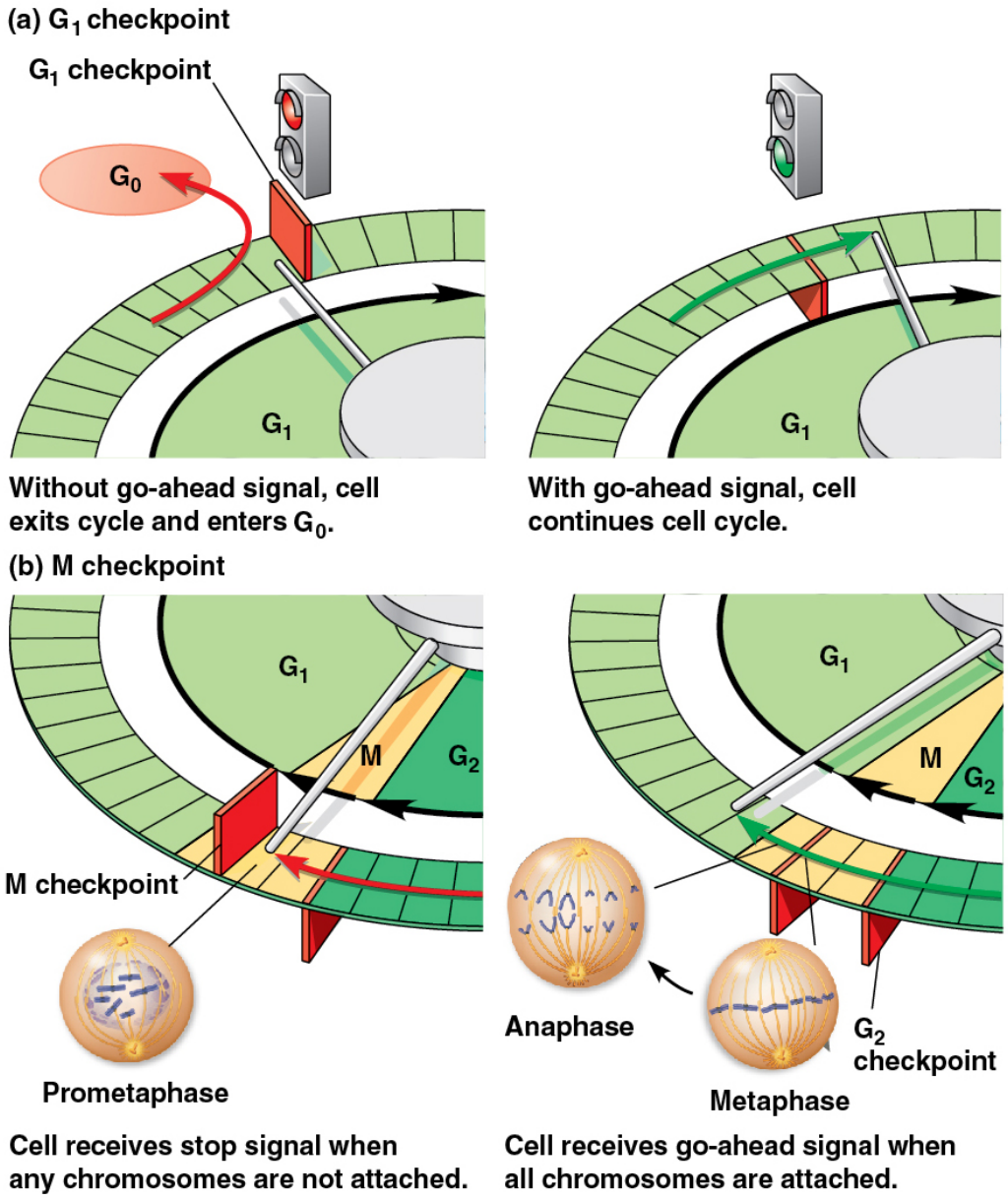
(b) Molecular mechanisms that help regulate the cell cycle

Stop and Go Signs: Internal and External Signals at the Checkpoints

- Many signals registered at checkpoints come from cellular surveillance mechanisms within the cell
- Checkpoints also register signals from outside the cell
- Three important checkpoints are those in the G_1, G_2, and M phases

- For many cells, the G_1 checkpoint seems to be the most important
- If a cell receives a go-ahead signal at the G_1 checkpoint, it will usually complete the S, G_2, and M phases and divide
- If the cell does not receive the go-ahead signal, it will exit the cycle, switching into a nondividing state called the **G_0 phase**

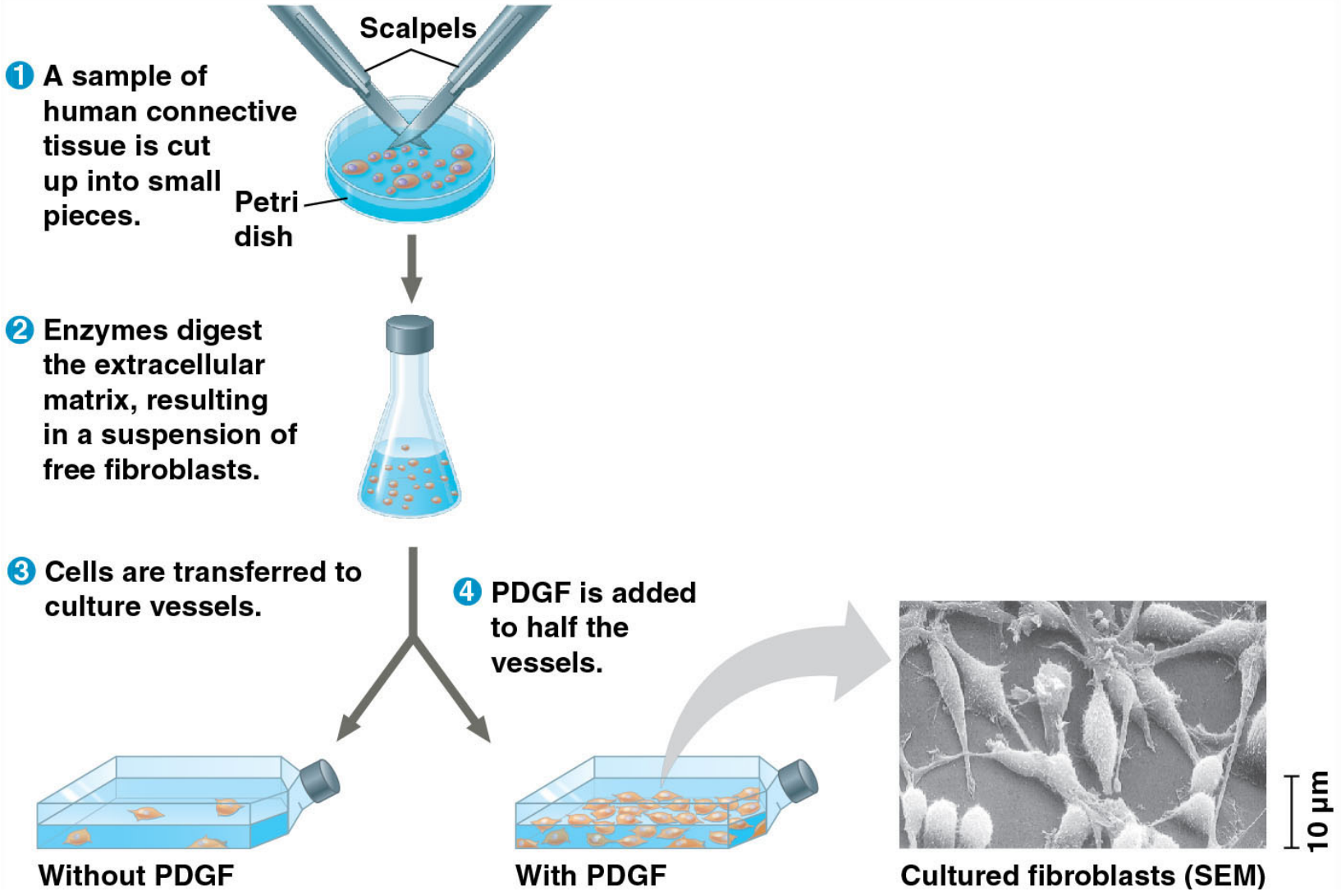
Figure 12.17


(a) G_1 checkpoint
G_1 checkpoint
G_0
G_1
Without go-ahead signal, cell exits cycle and enters G_0.
G_1
With go-ahead signal, cell continues cell cycle.
(b) M checkpoint
G_1
M
G_2
M checkpoint
Prometaphase
Cell receives stop signal when any chromosomes are not attached.
G_1
M
G_2
Anaphase
G_2 checkpoint
Metaphase
Cell receives go-ahead signal when all chromosomes are attached.

- An example of an internal signal is that cells will not begin anaphase until all chromosomes are properly attached to the spindle at the metaphase plate
- This mechanism ensures that daughter cells have the correct number of chromosomes

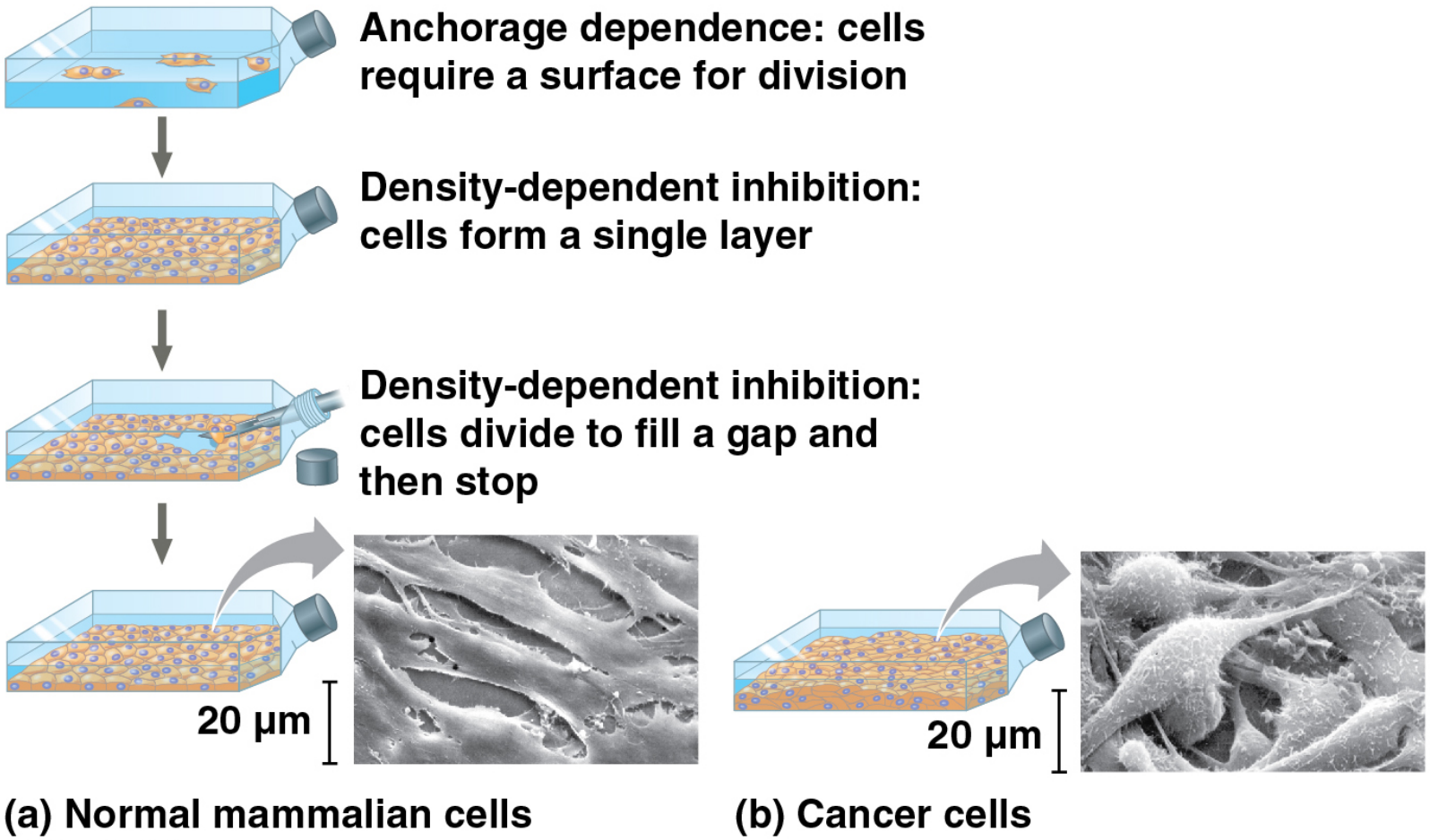
- External factors, both chemical and physical influence cell division
- **Growth factors** are released by certain cells and stimulate other cells to divide
- *Platelet-derived growth factor (PDGF)* is made by blood cell fragments called platelets
- PDGF is required for the division of cultured fibroblasts

Figure 12.18


Scalpels
1 A sample of human connective tissue is cut up into small pieces.
Petri dish
2 Enzymes digest the extracellular matrix, resulting in a suspension of free fibroblasts.
3 Cells are transferred to culture vessels.
4 PDGF is added to half the vessels.
Without PDGF
With PDGF
Cultured fibroblasts (SEM)
10 µm

- In **density-dependent inhibition**, crowded cells will stop dividing
- Most animal cells also exhibit **anchorage dependence**—to divide, they must be attached to a substratum
- Density-dependent inhibition and anchorage dependence check the growth of cells at an optimal density
- Cancer cells exhibit neither type of regulation of their division

Figure 12.19


Anchorage dependence: cells require a surface for division
Density-dependent inhibition: cells form a single layer
Density-dependent inhibition: cells divide to fill a gap and then stop
20 µm
20 µm
(a) Normal mammalian cells
(b) Cancer cells

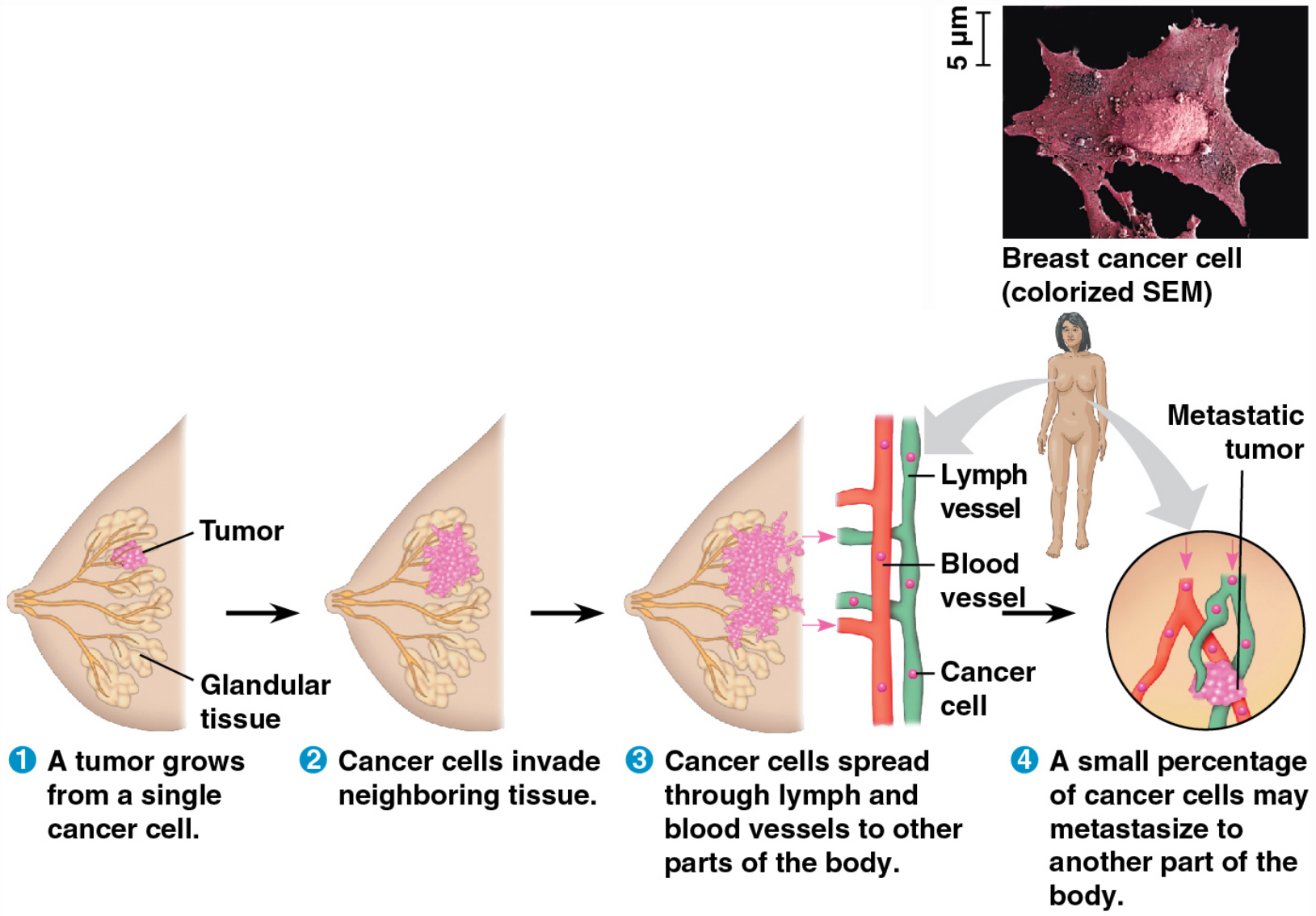
Loss of Cell Cycle Controls in Cancer Cells

- Cancer cells do not heed the normal signals that regulate the cell cycle
- They do not stop dividing when growth factors are depleted
- Cancer cells do not need growth factors to grow and divide:
  - They may make their own growth factor
  - They may convey a growth factor's signal without the presence of the growth factor
  - They may have an abnormal cell cycle control system

- Cells that acquire the ability to divide indefinitely have undergone **transformation**
- Cancer cells that are not eliminated by the immune system form tumors, masses of abnormal cells within otherwise normal tissue
- If abnormal cells remain only at the original site, the lump is called a **benign tumor**
- Most benign tumors do not cause serious problems (depending on their location)

- **Malignant tumors** invade surrounding tissues and can undergo **metastasis**, the spread of cancer cells to other parts of the body, where they may form additional tumors
- Localized tumors may be treated with high-energy radiation, which damages the DNA in the cancer cells
- The majority of cancer cells have lost the ability to repair DNA damage

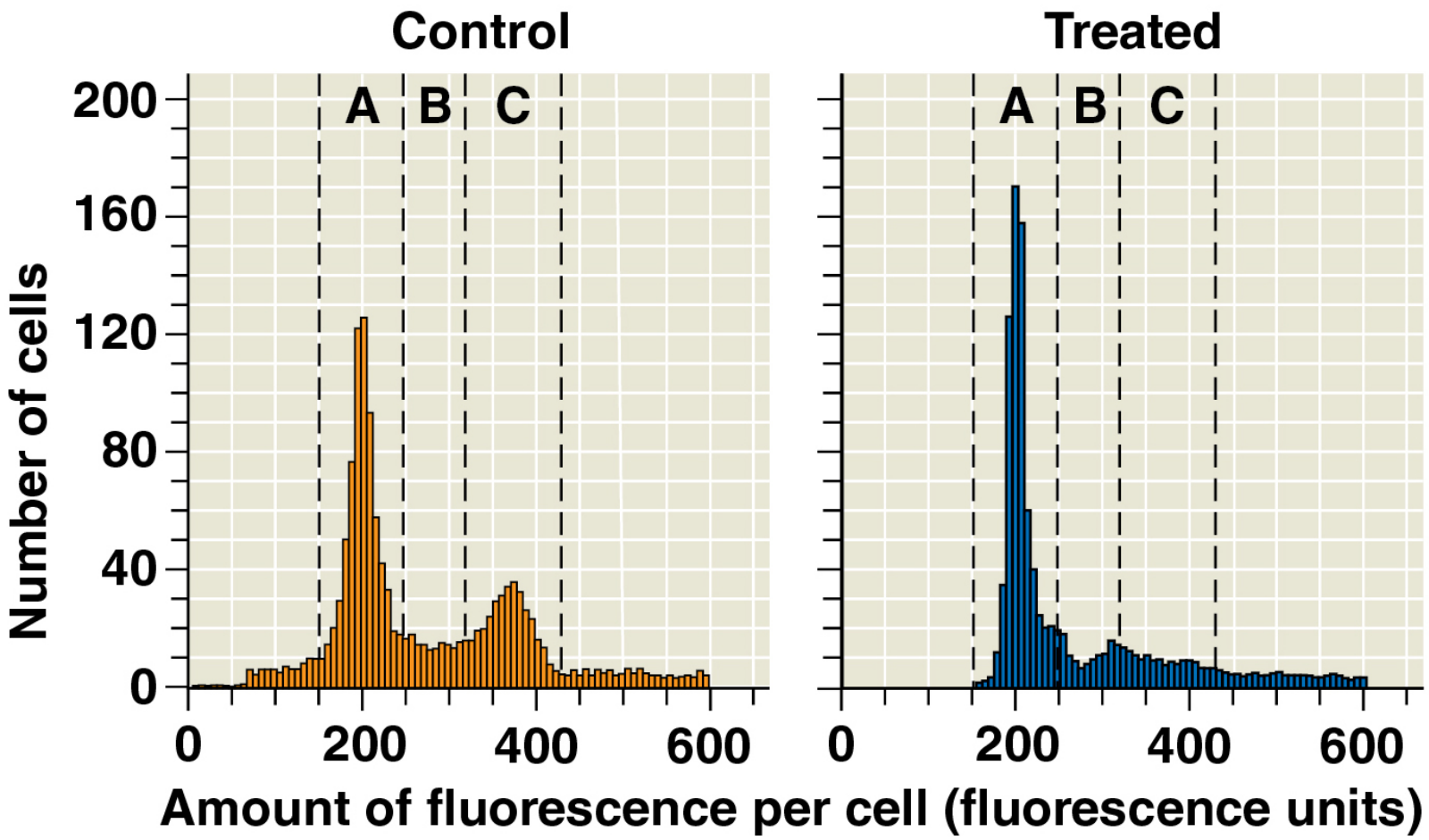
Figure 12.20


5 µm
Breast cancer cell
(colorized SEM)
Tumor
Glandular tissue
Lymph vessel
Blood vessel
Cancer cell
Metastatic tumor
1 A tumor grows from a single cancer cell.
2 Cancer cells invade neighboring tissue.
3 Cancer cells spread through lymph and blood vessels to other parts of the body.
4 A small percentage of cancer cells may metastasize to another part of the body.

- Metastatic tumors are treated with chemotherapeutic drugs that target the cell cycle
- Side effects of chemotherapy are due to the effects of the drugs on normal cells that divide frequently
- Researchers are producing a flood of information about cell-signaling pathways and their relationship to cancer
- Coupled with new molecular techniques, treatments for cancer are becoming more “personalized” to a particular patient’s tumor

Figure 12.UN01a

Data from the Experiment



Data from K. K. Velpula et al., Regulation of glioblastoma progression by cord blood stem cells is mediated by downregulation of cyclin D1, *PLoS ONE* 6(3):e18017 (2011).

Figure 12.UN01b

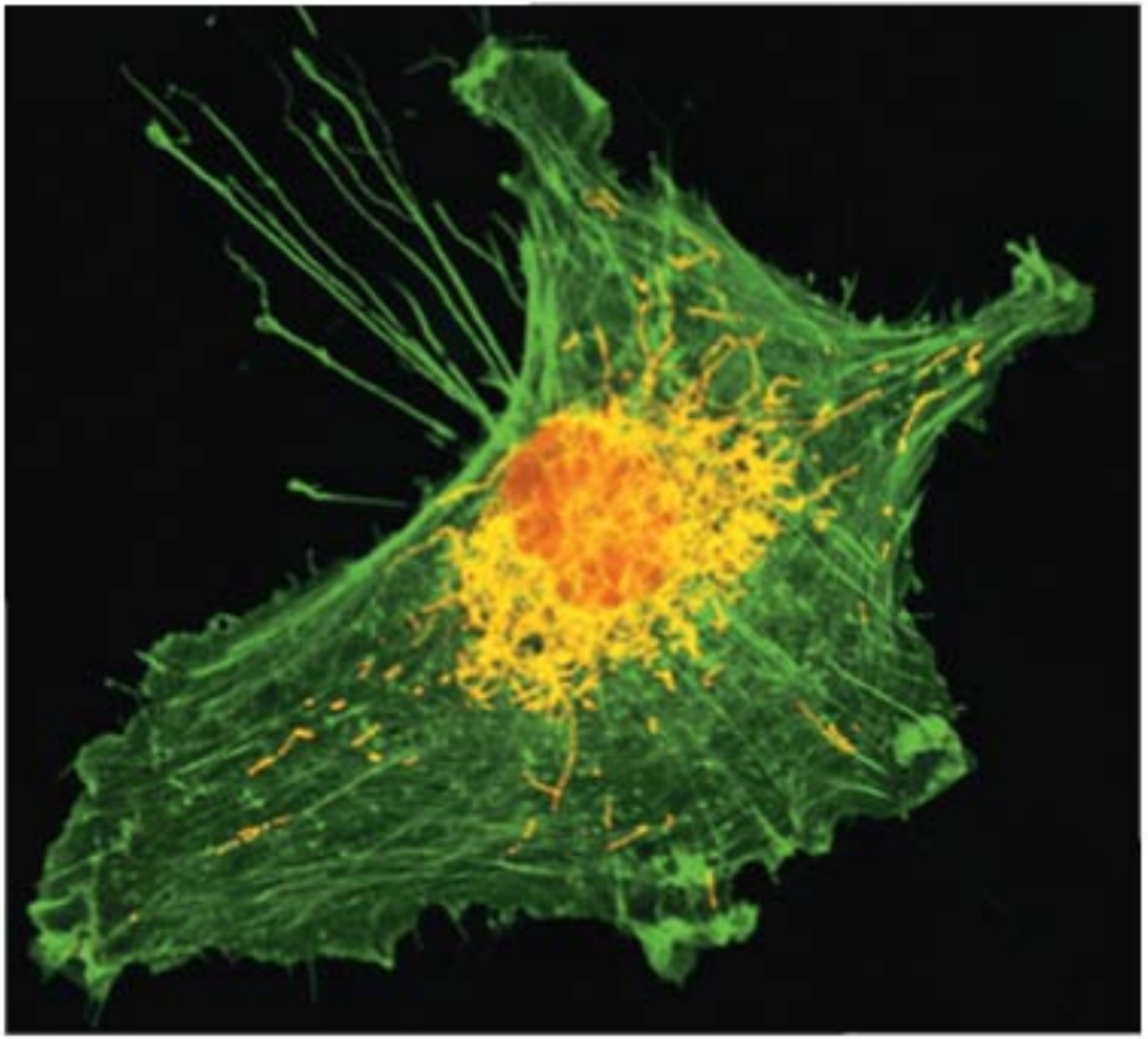


Figure 12.UN03

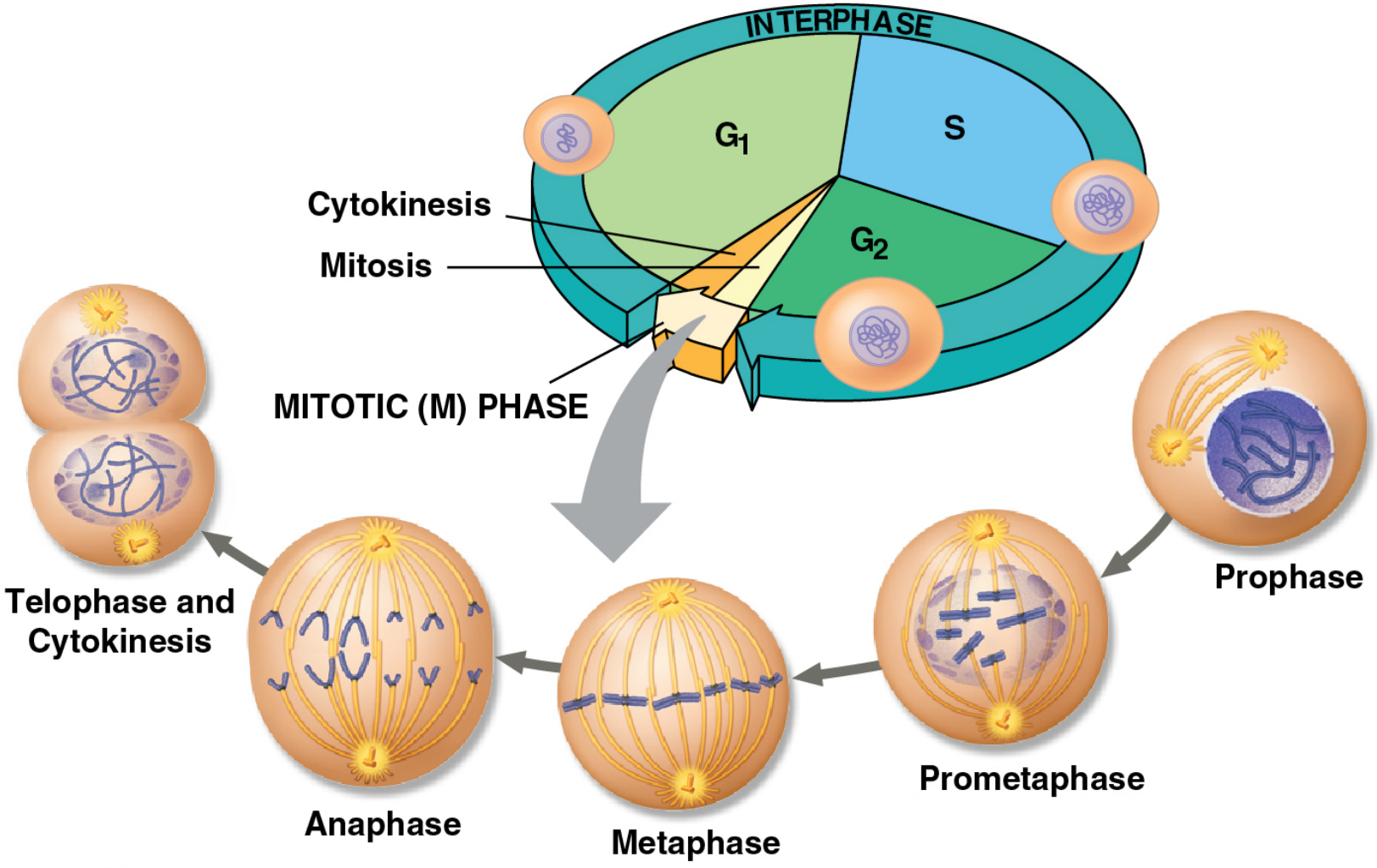


Figure 12.UN04

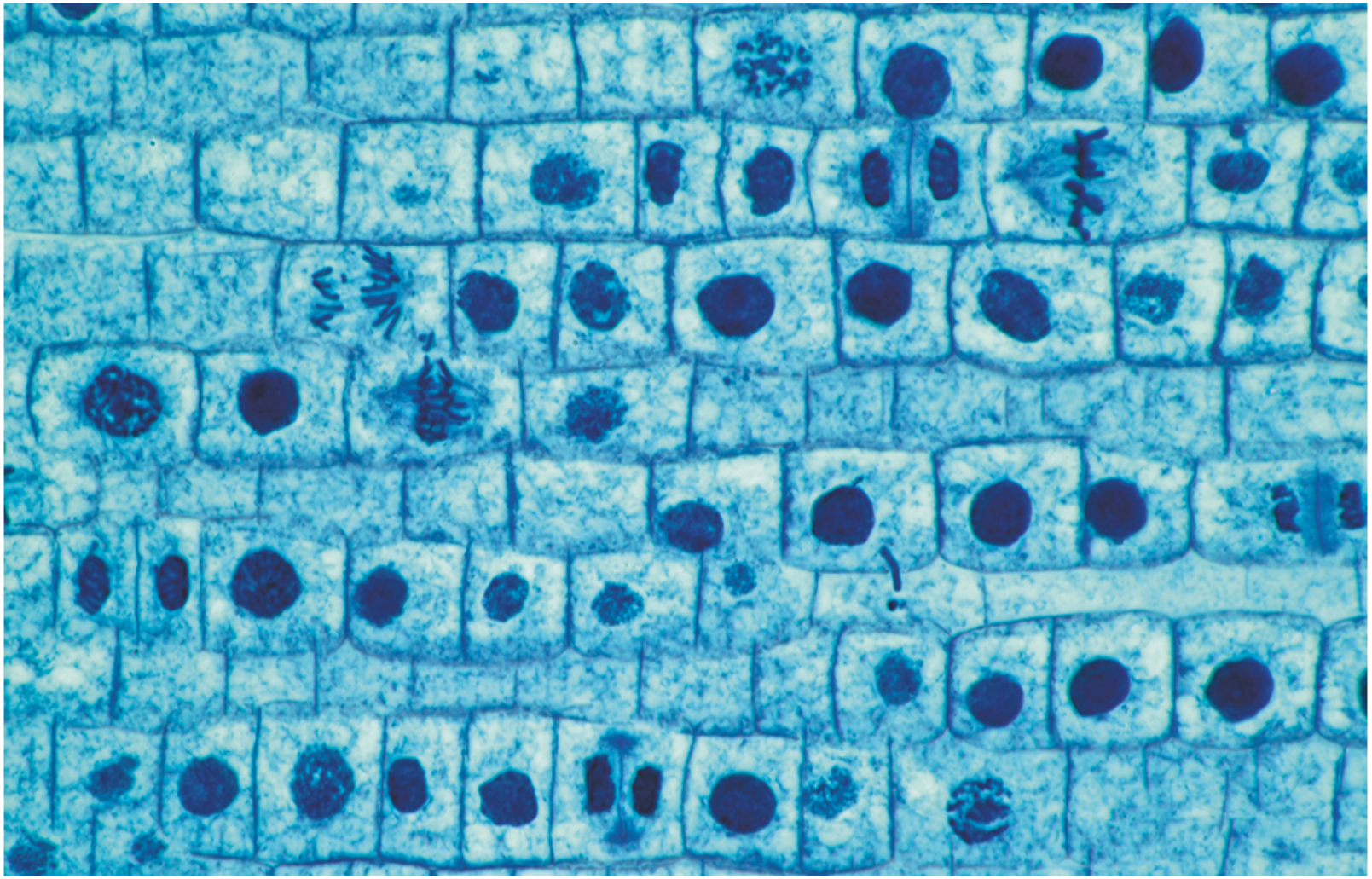


Figure 12.UN05