GENETICS

Cell Division

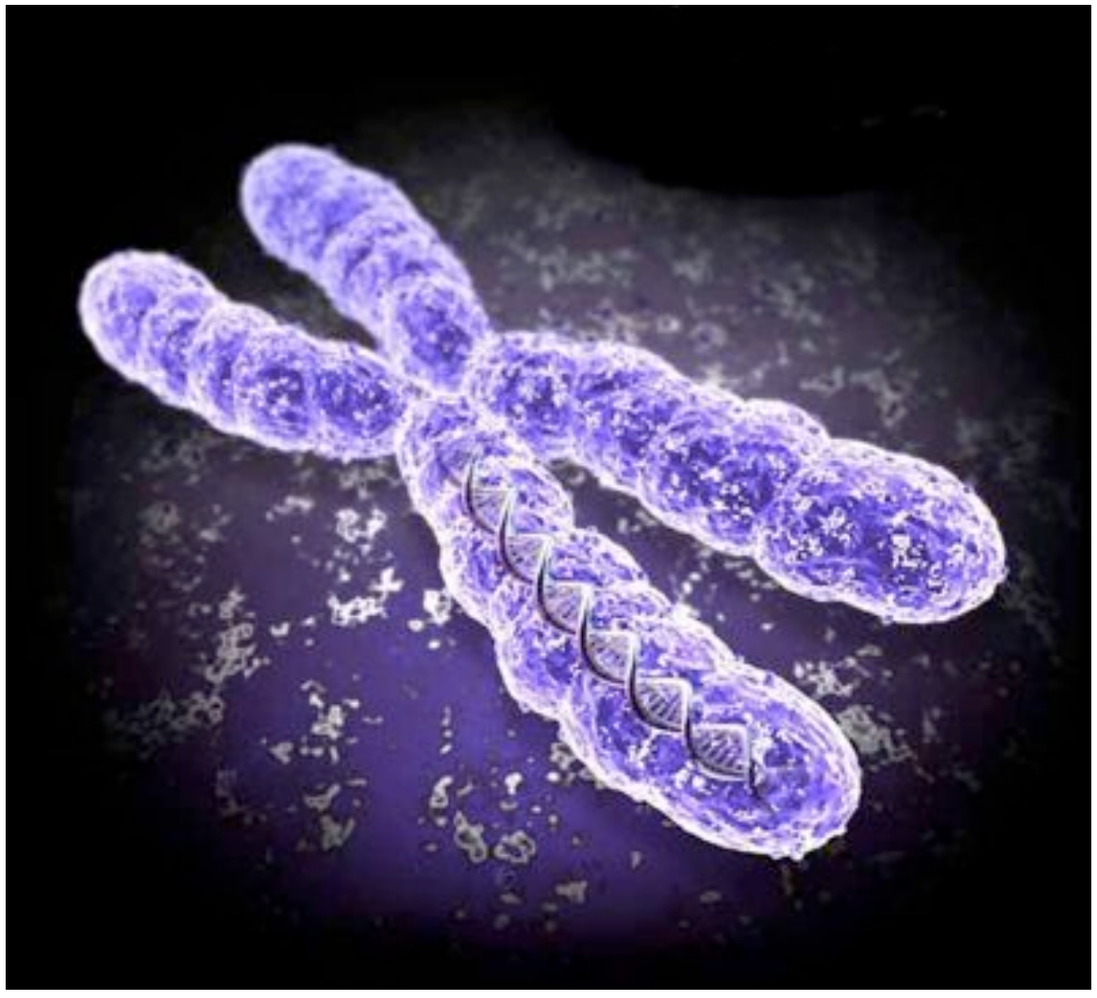
PREFACE

- **The Roles of Cell Division**
  - **Reproduction-** Unicellular organisms reproduce using cell division
  - **Development-**Multicellular organisms use cell division to grow and develop from a zygote.
  - **Repair-** Multicellular organisms use cell division to fix damaged cells or replace old worn out cells

The Cell Cycle

I.

Main Idea: A dividing cell duplicates its DNA, allocates each copy to opposite ends of the cell and then splits into two two daughter cells.



Organization of Genetic Material

- **Genome-** a cell's endowment of genetic information (DNA)
  - Eukaryotes have far more DNA than prokaryotes.
- **Chromosomes-** are structures that package the DNA molecules.
  - each consists of a very long DNA molecule associated with proteins
    - the DNA contains the genes that code inherited traits
    - the proteins maintain structure and help to control the activity genes
  - together the DNA and the protein make up that make up the chromosome is called **chromatin.**

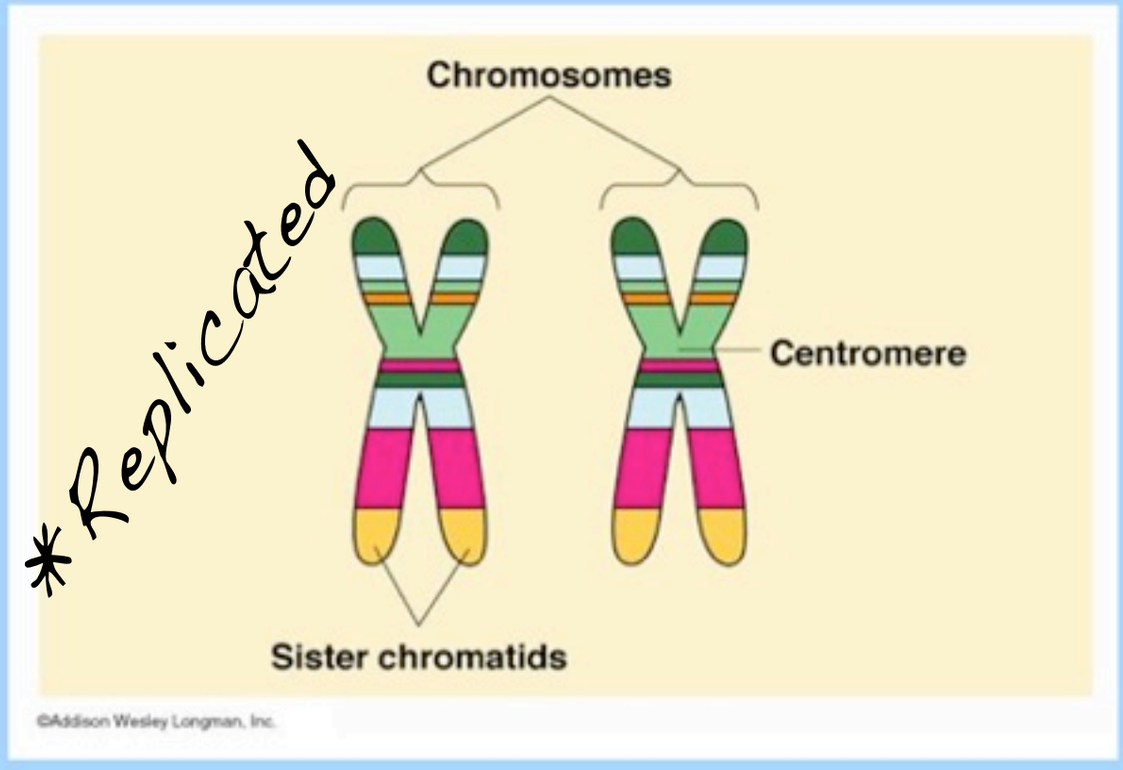
Chromosomes vs. Chromatin

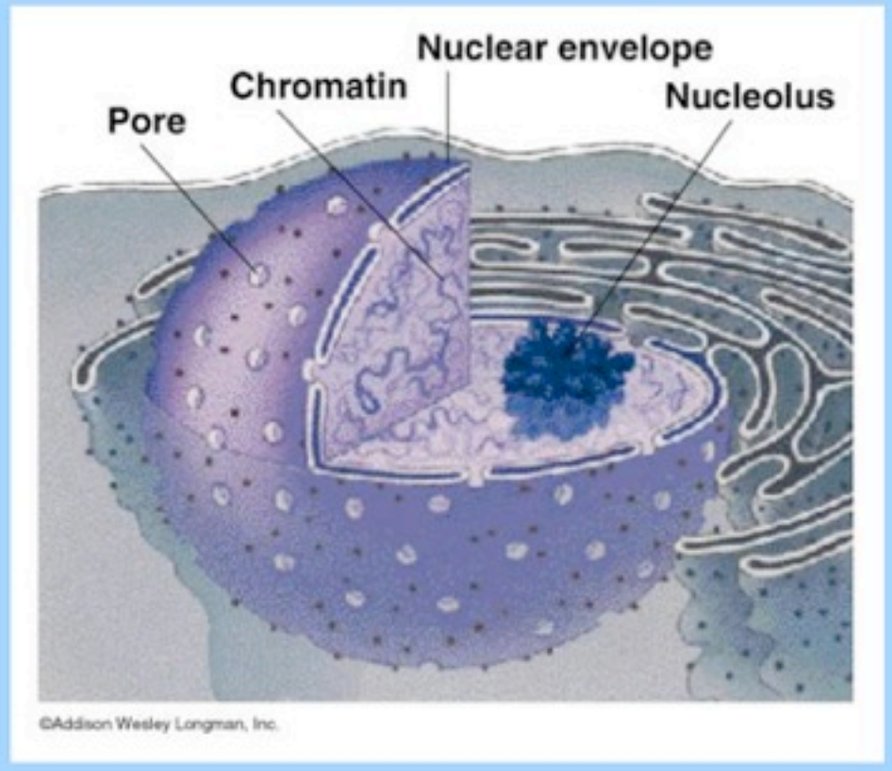
Chromosomes

- Tightly packaged DNA
- Found only during cell division
- DNA is not being used for macromolecule synthesis

Chromatin

- Unwound DNA
- Found throughout Interphase
- DNA *is* being used for macromolecule synthesis





Organization of Genetic Material

- Every eukaryotic species has a characteristic number of chromosomes in each cell's nucleus.
    - *varies greatly in eukaryotes: Jack Jumper female ant has 2 and the Adders-tongue fern has 1440*

Somatic Cells- body cells, all cells excluding sperm and egg have TWO sets of chromosomes.

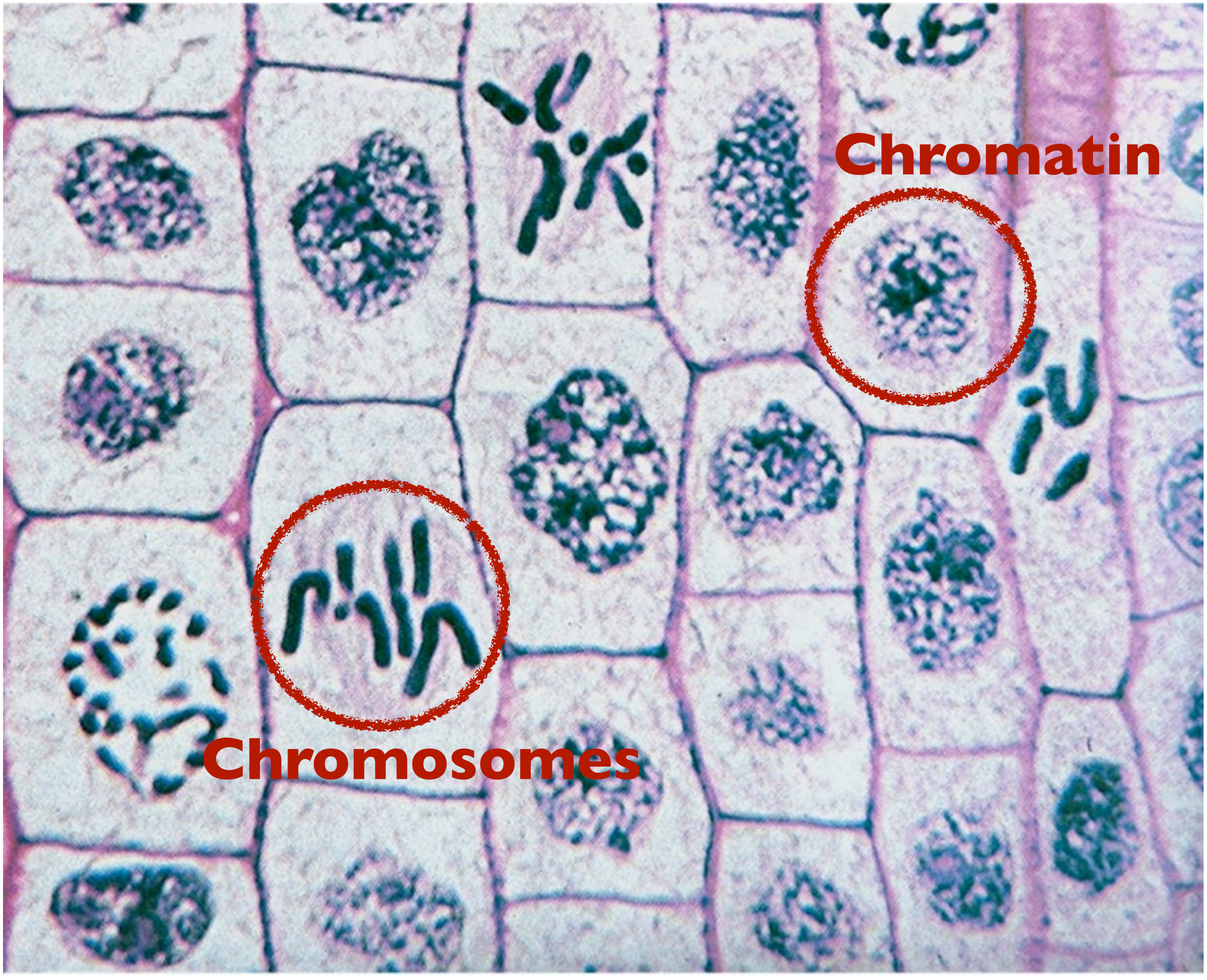
- One from mom, One from dad
- 46 in humans

Reproductive Cells- only sperm and egg have ONE set of chromosomes.

- 23 in humans

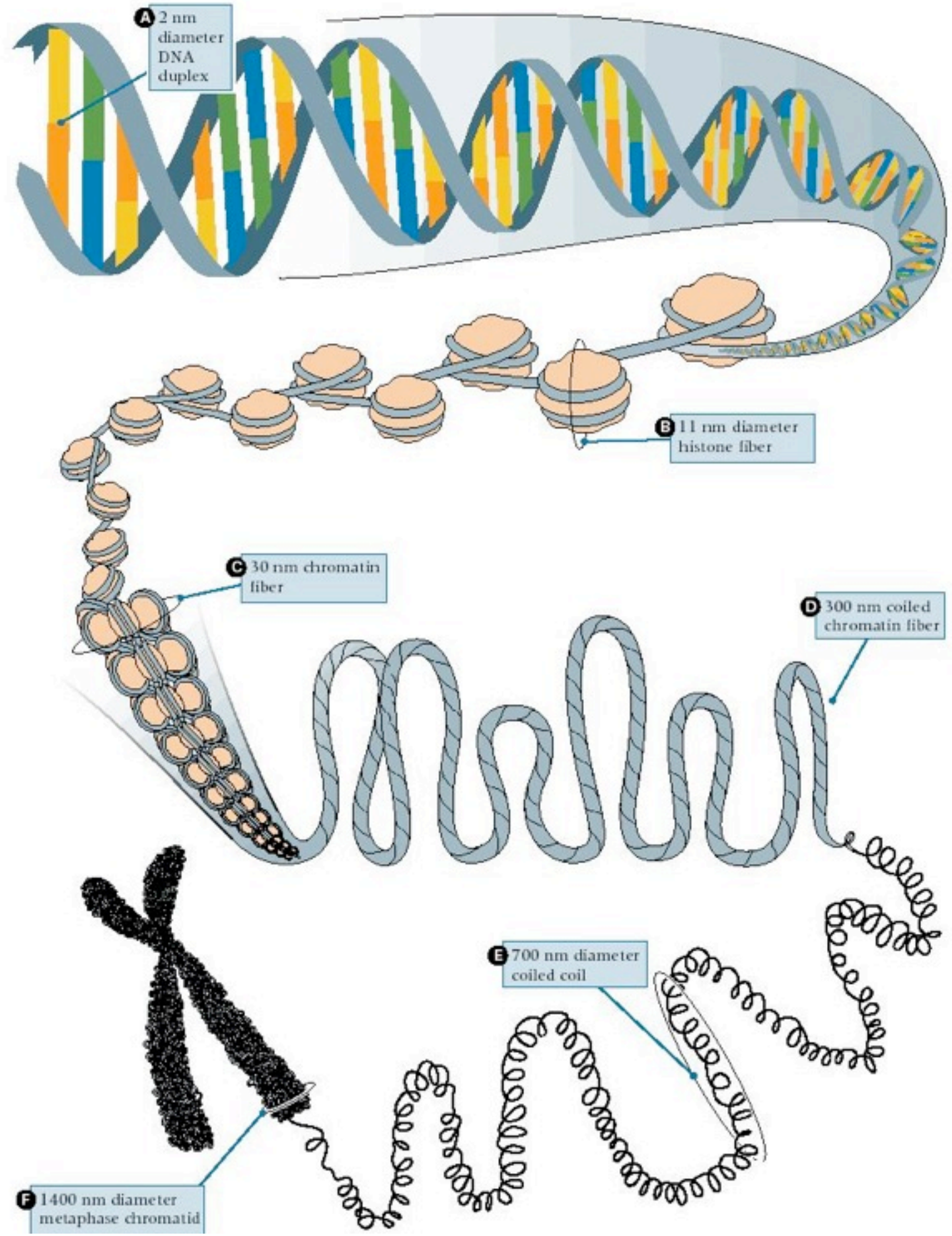
Distribution of Chromosomes During Cell Division

- Most of the time the cells chromosomes are "unravelled" and referred to as chromatin.
  - This "accessible" form makes gene transcription and DNA replication possible
- After DNA replication (in preparation for cell division) the chromatin folds over and over again on itself.
  - This condensed form is more easily "moveable".
  - It is this form that cells manipulate during cell division.
  - *This condensed form is more easily seen under the microscope and consequently it is the form most commonly referred to by the name chromosome.*


Chromatin
Chromosomes

SIDE BAR: Structural Levels of Chromosomes

4-5 Levels of folding , the more folding the less accessible the DNA

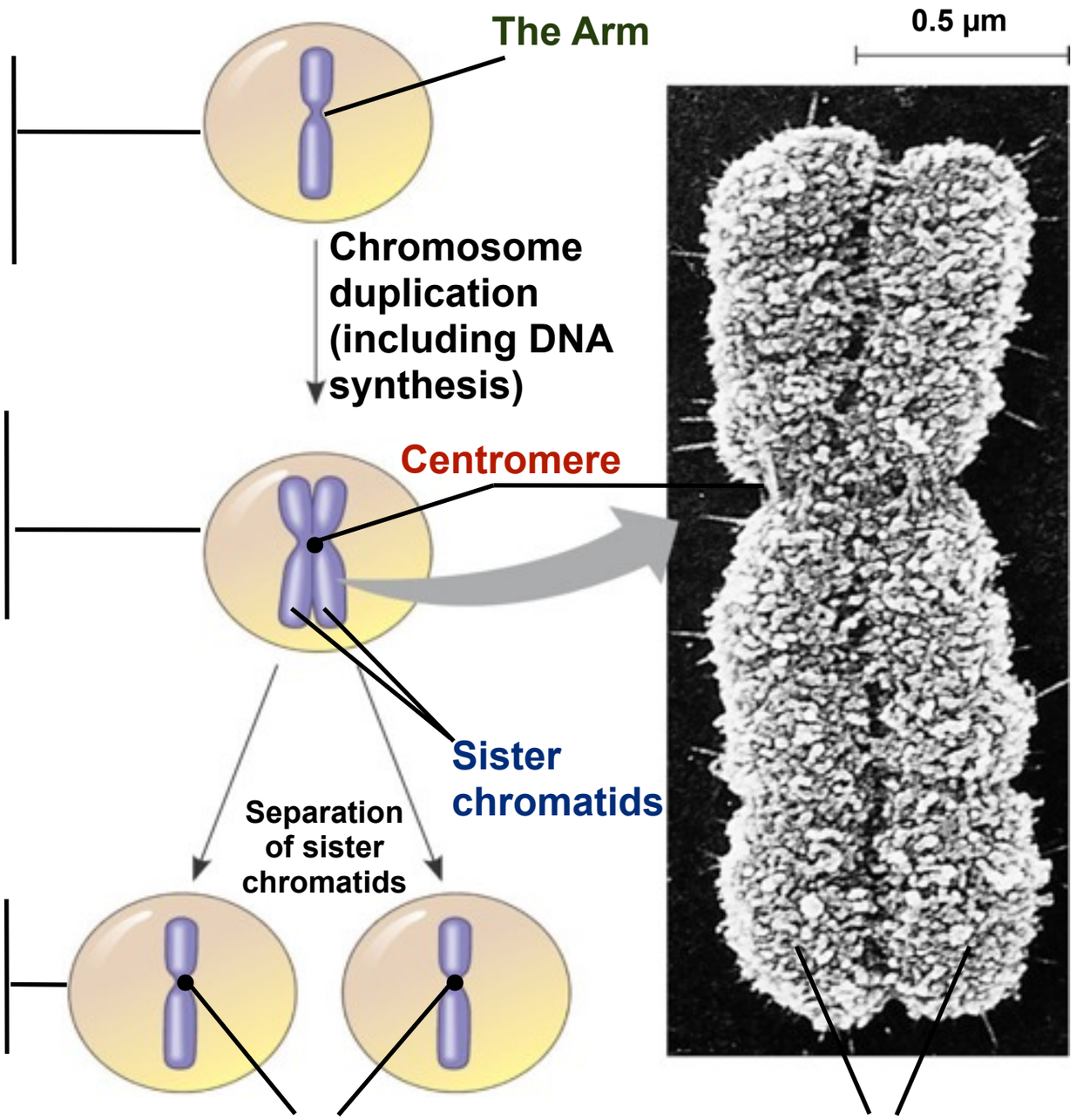


Chromatids and Chromosomes

A eukaryotic cell has multiple chromosomes, one of which is represented here. Before duplication, each chromosome has a single DNA molecule.

Once duplicated, a chromosome consists of two sister chromatids connected at the centromere. Each chromatid contains a copy of the DNA molecule.

Mechanical processes separate the sister chromatids into two chromosomes and distribute them to two daughter cells.

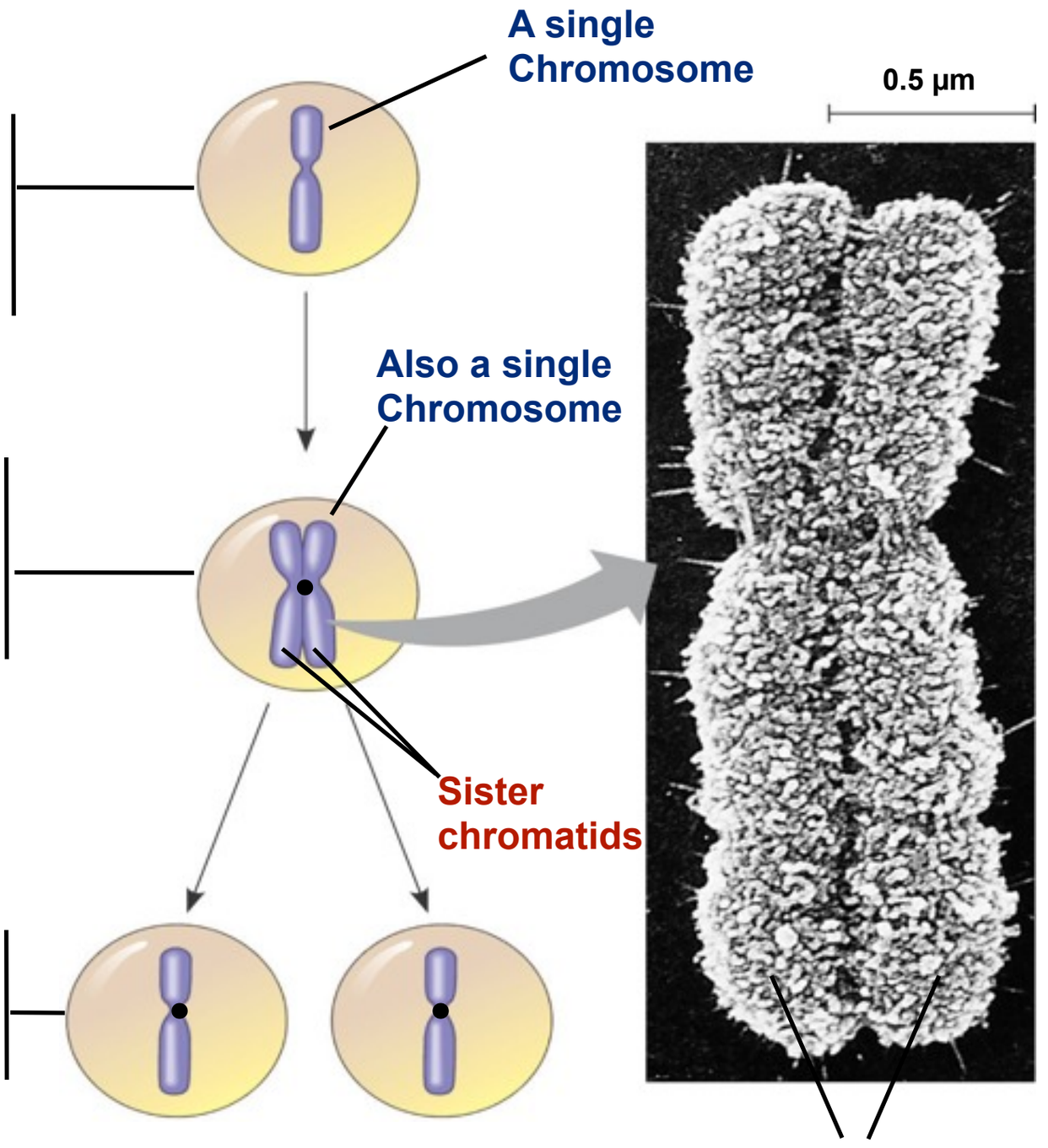


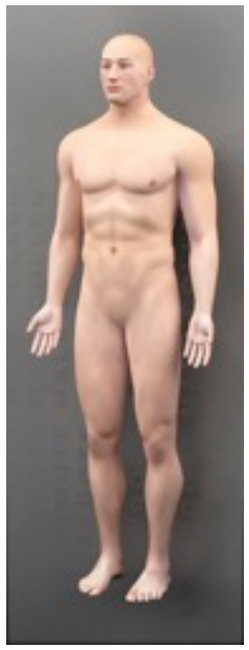
"Semantics"

One Chromosome, No chromatids

One Chromosome, with 2 sister chromatids

One Chromosome in each cell, No chromatids

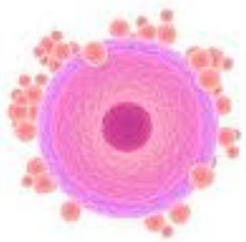




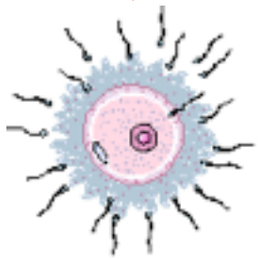
23

Meiosis

23



Meiosis



Fertilization

Mitosis

46

Two cell cleavage

Mitosis

46 in each cell

Blastula

Mitosis

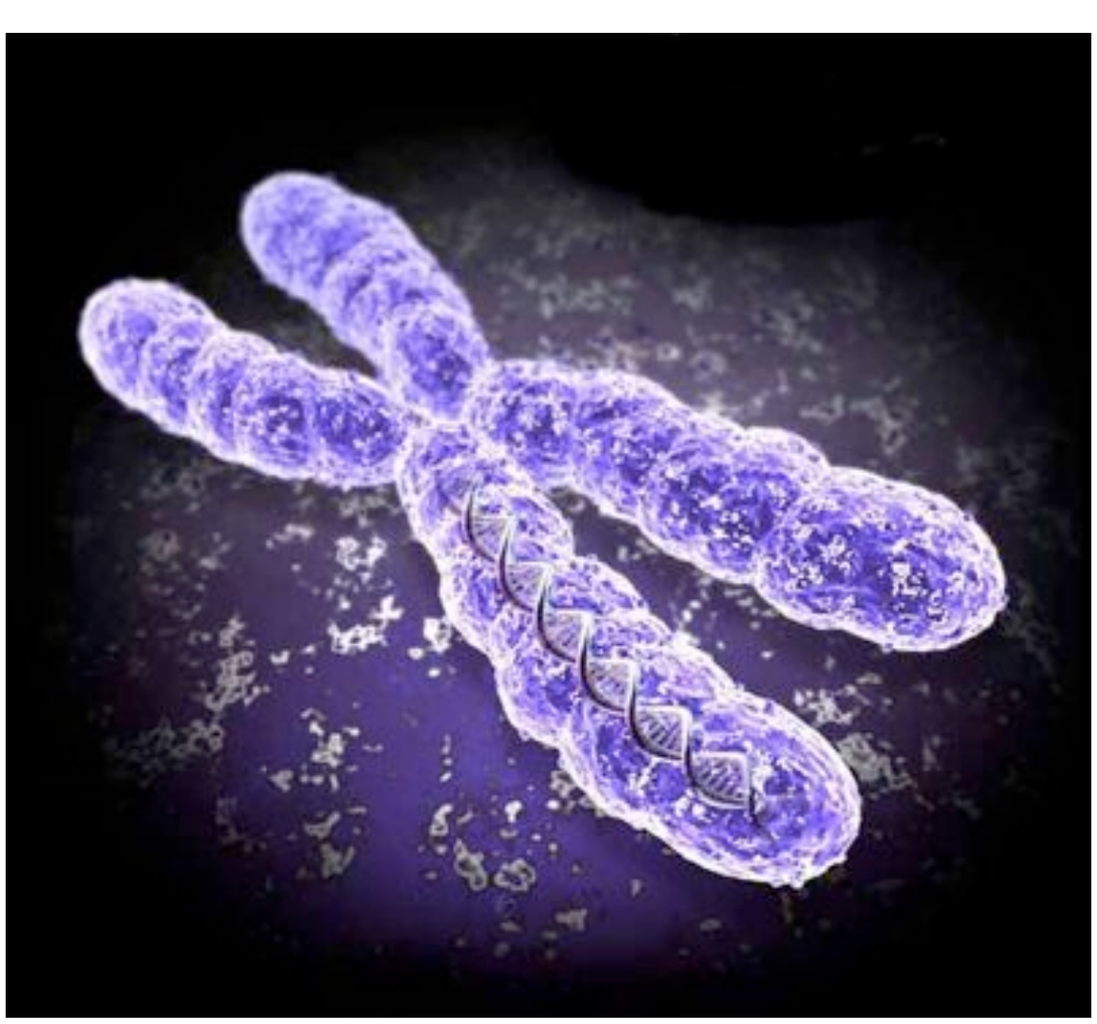
46 in each cell

An adult human has roughly 200 trillion cells that all started as a single cell zygote. Cell division (mitosis) is responsible for this growth and development.

The Cell Cycle

II.

Main Idea: A cells life can be divided into three phases: interphase, mitosis and cytokinesis.

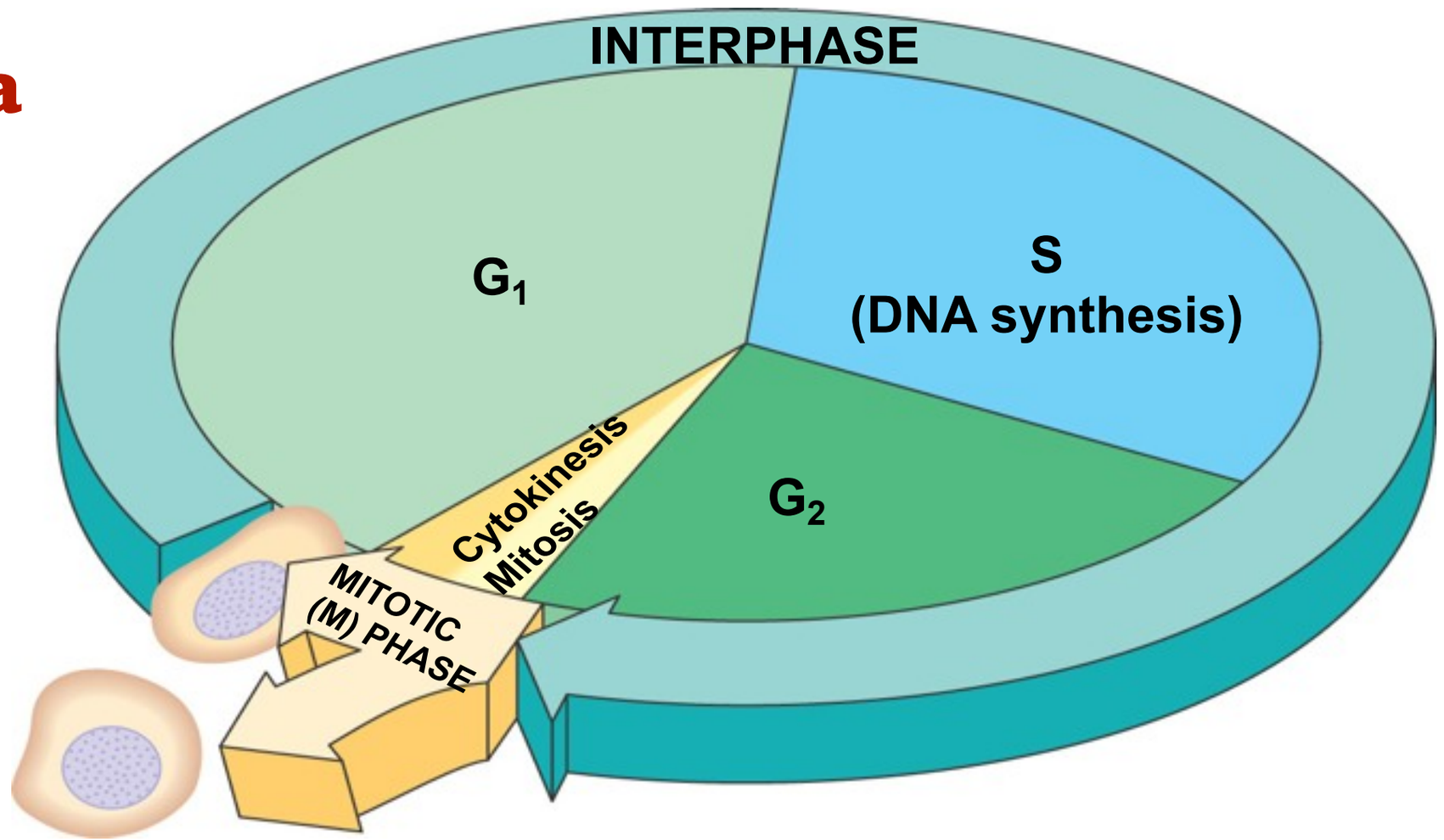


Phases of the Cell Cycle

- **Interphase**- growth and DNA replication but mostly the cell is functioning in in its genetically determined capacity
- **Mitosis**- division of the nucleus
- **Cytokinesis**- division of the cytoplasm

We will assume a cell cycle of 24 hours.

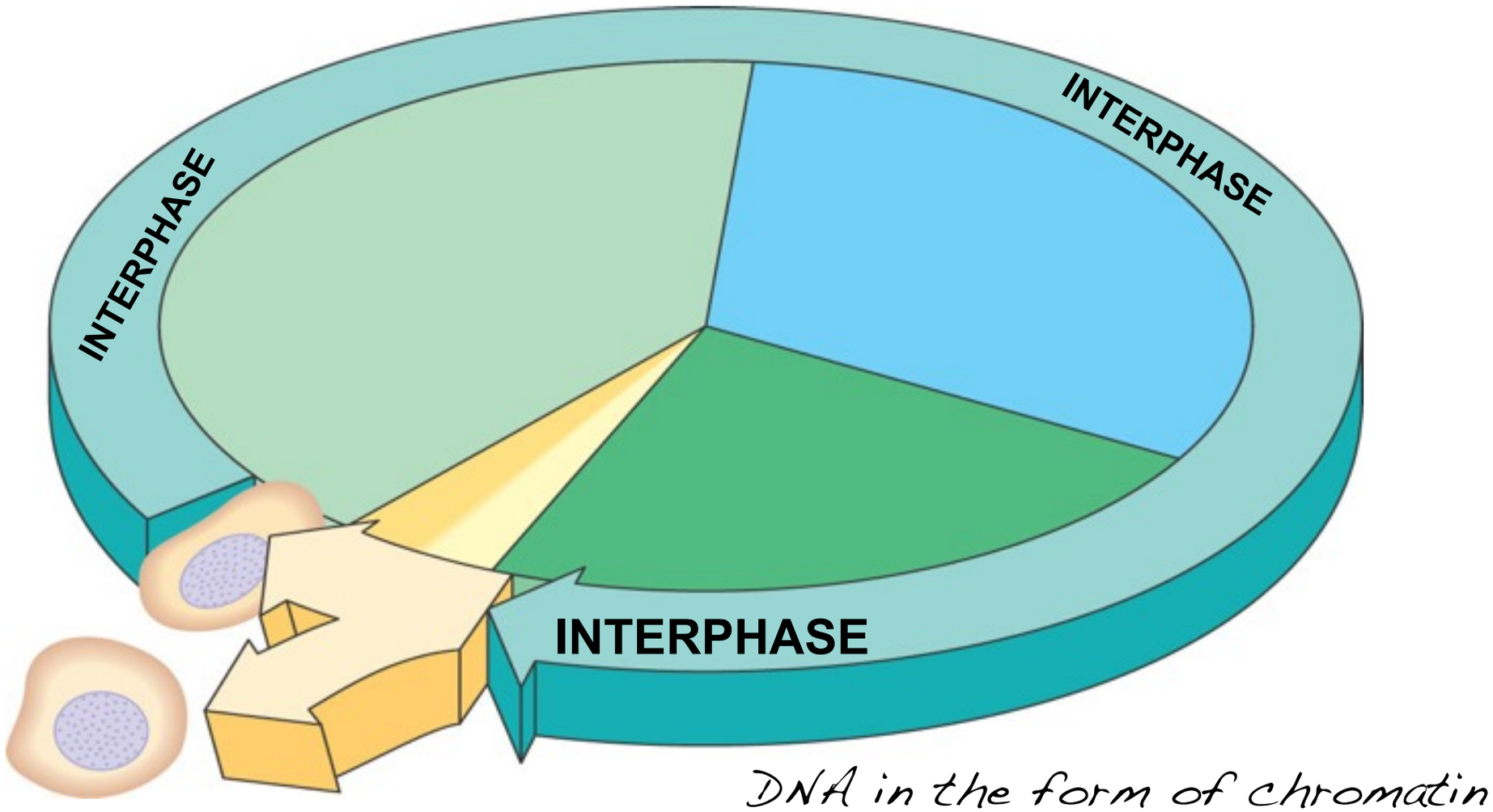
The goal, is to develop a relative sense of time for each phase.



Interphase

- Cells spend about 90% of their life in interphase
- **For the most part, unique cells "do what they do"**
- Interphase is split into three sub phases due to some specific activities that take place in a sequential manner

~23 Hours

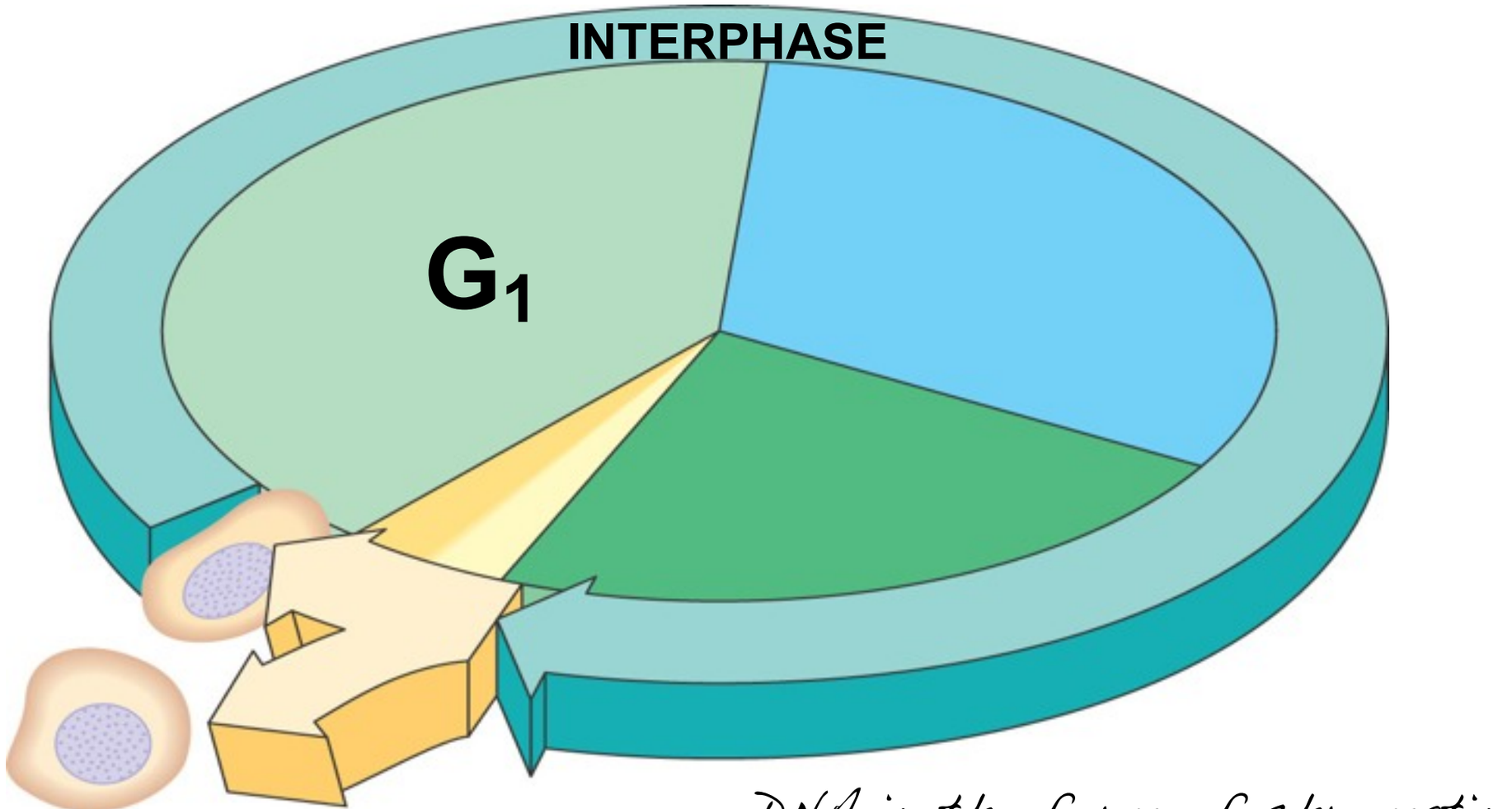


DNA in the form of chromatin

Interphase: G_1

- New daughter cells are smaller than than parental cells.
  - **..thus new cells experience tremendous growth (this includes the generation of more organelles)**
- And again cells continue to "do what they do"

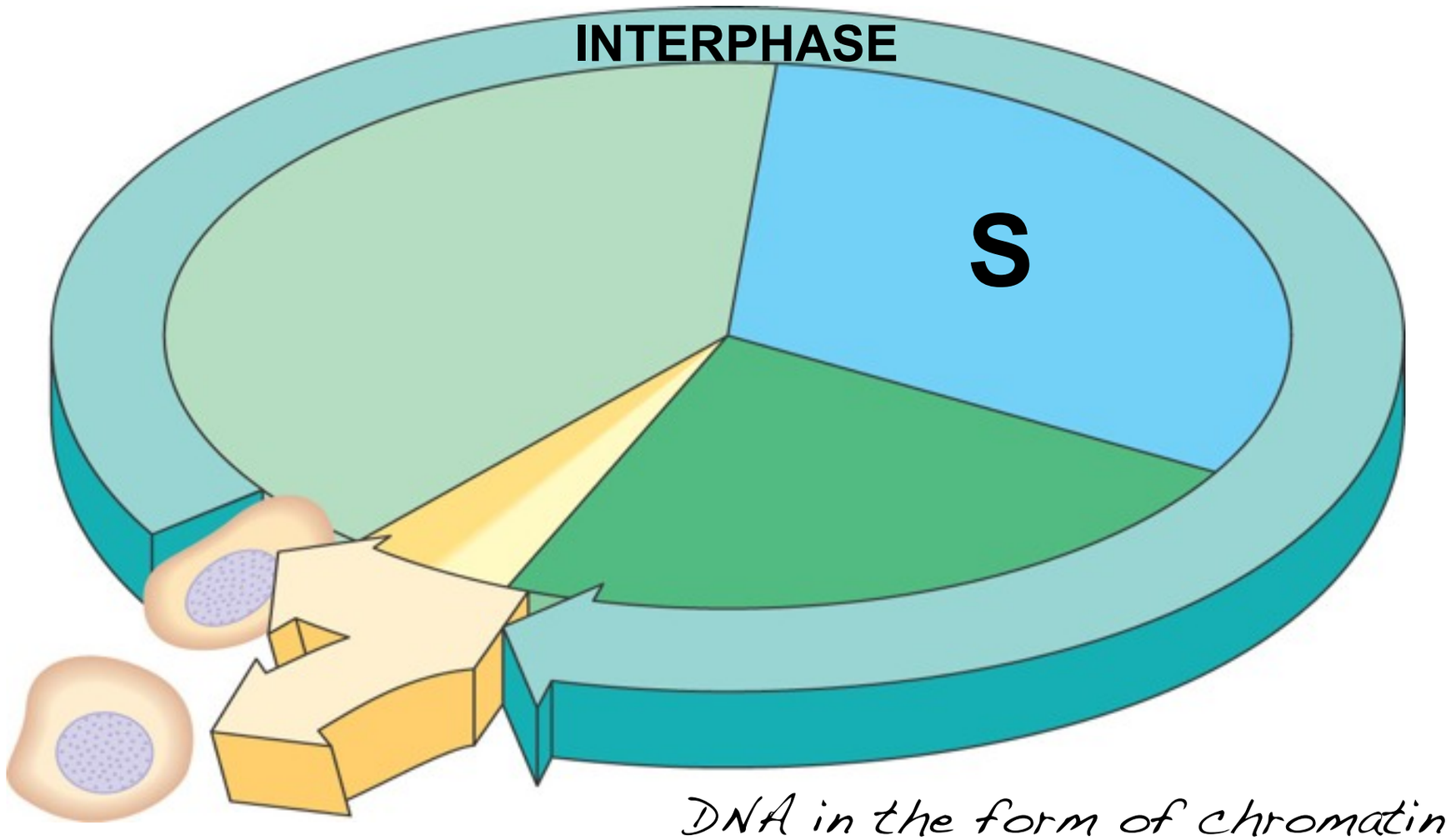
~6 Hours



Interphase: S

- Anticipating and preparing for the next cell division...
  - **DNA is replicated**
  - And again cells continue to "do what they do"
  - And they continue to grow

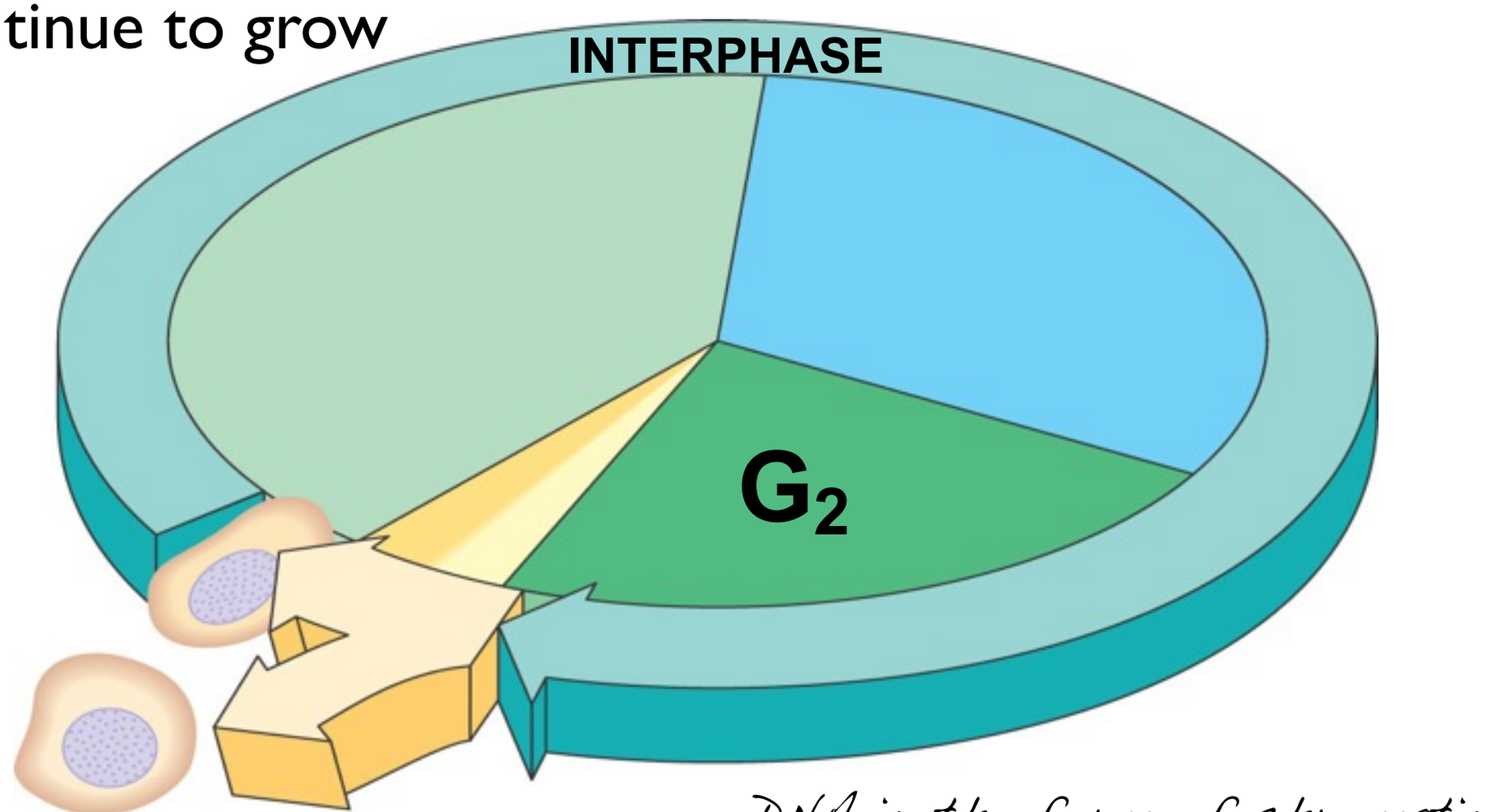
~11 Hours



Interphase: G_2

- **Cells prepare for cell division.**
  - **ex. at the end of G_2, chromatin condenses into chromosomes**
- And again cells continue to "do what they do"
- They even continue to grow

~6 Hours

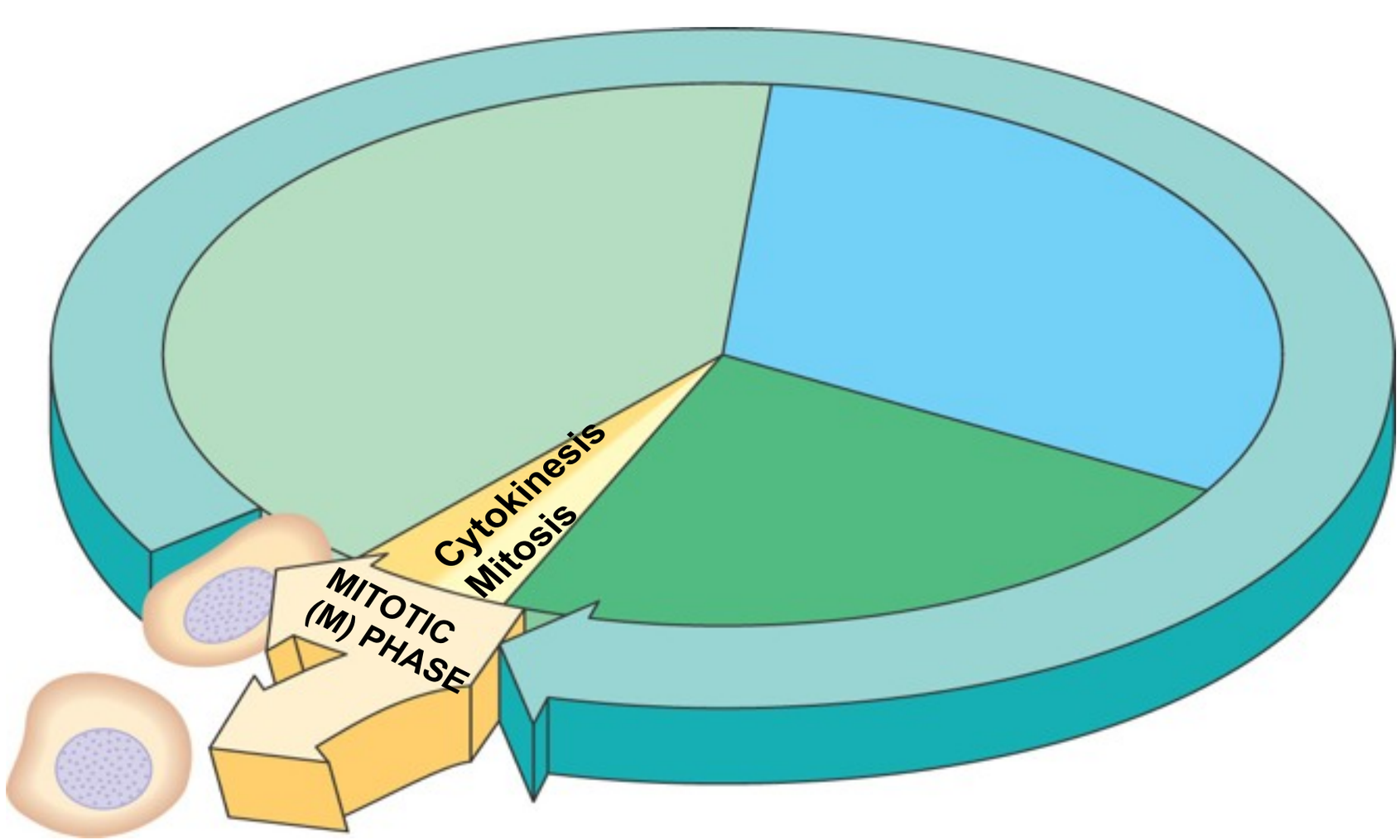


DNA in the form of chromatin

Mitotic Phase: M

- The mitotic phase includes two divisional phases:
  - **Nuclear Division = Mitosis**
  - **Cytoplasmic Division = Cytokinesis**

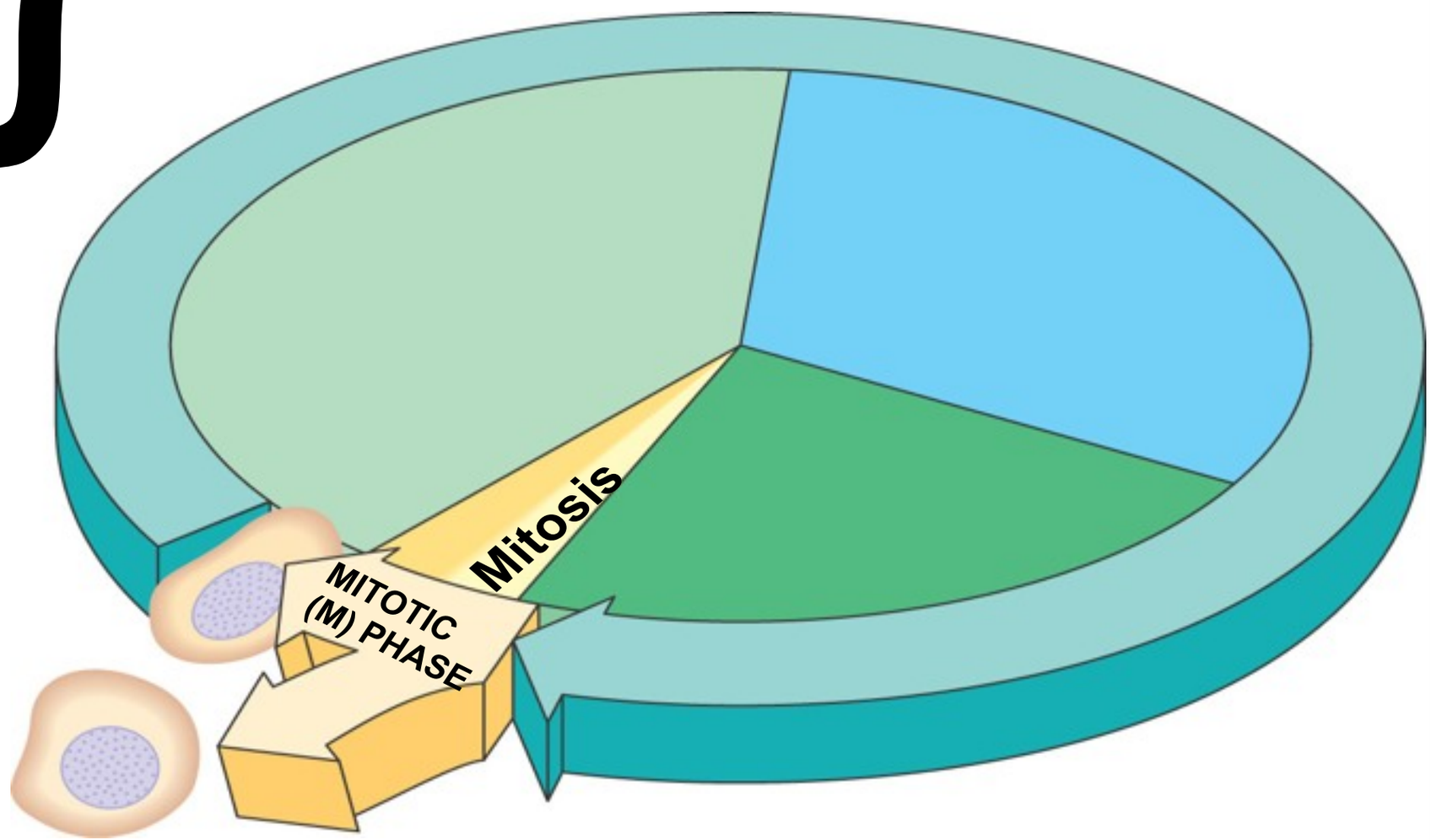
~1 Hour



Mitosis

- Mitosis is a fluid and dynamic process but to teach and better understand the process it is divided into 4 or more sub-phases:
  - **Prophase**
  - **Metaphase**
  - **Anaphase**
  - **Telophase**

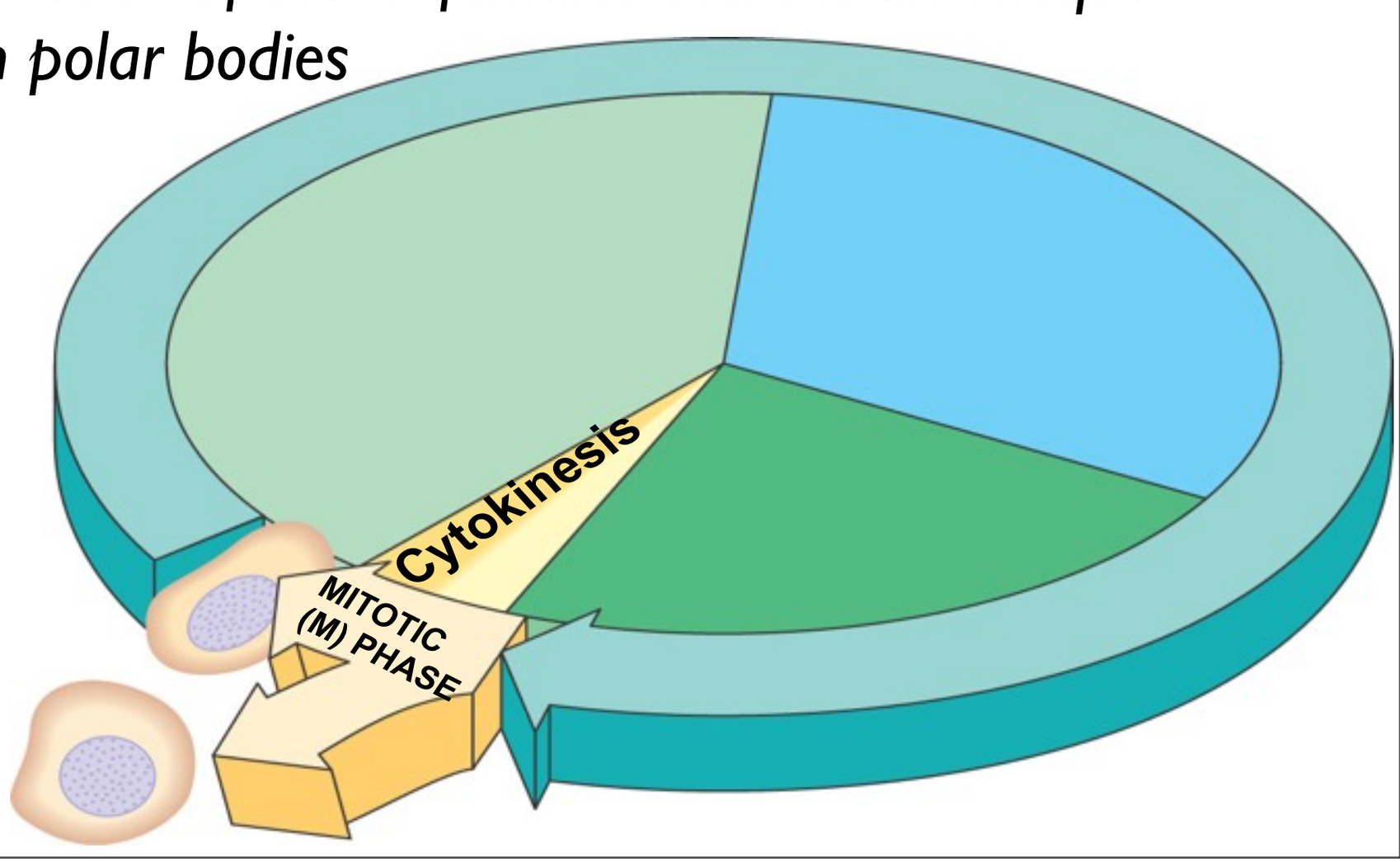
We will look these stages more closely in slides to follow



Cytokinesis

- **Splits the cytoplasm into *equal halves, creating 2 new daughter cells.**
  - Cytokinesis begins while mitosis (telophase) is finishing.
  - Differs in cells with and without cell walls.
    - **during the formation of ova in females there is an unequal split resulting in polar bodies*

We will look cytokinesis more closely in slides to follow

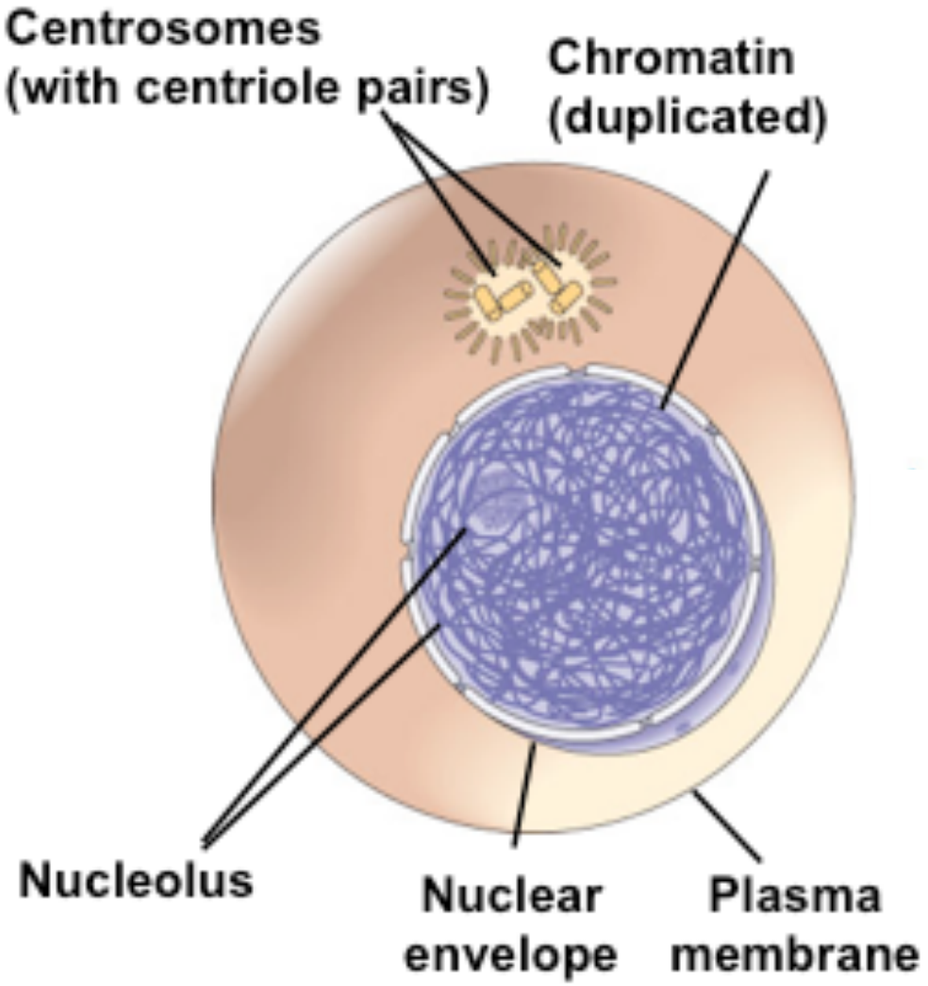


A Cell's Biography

- **Interphase G_1**
  - cell grows
  - organelles replicate
  - carries out destined functions
- **Interphase S**
  - replicates DNA
  - replicates centrosomes
  - cell grows
  - organelles replicate
  - carries out destined functions

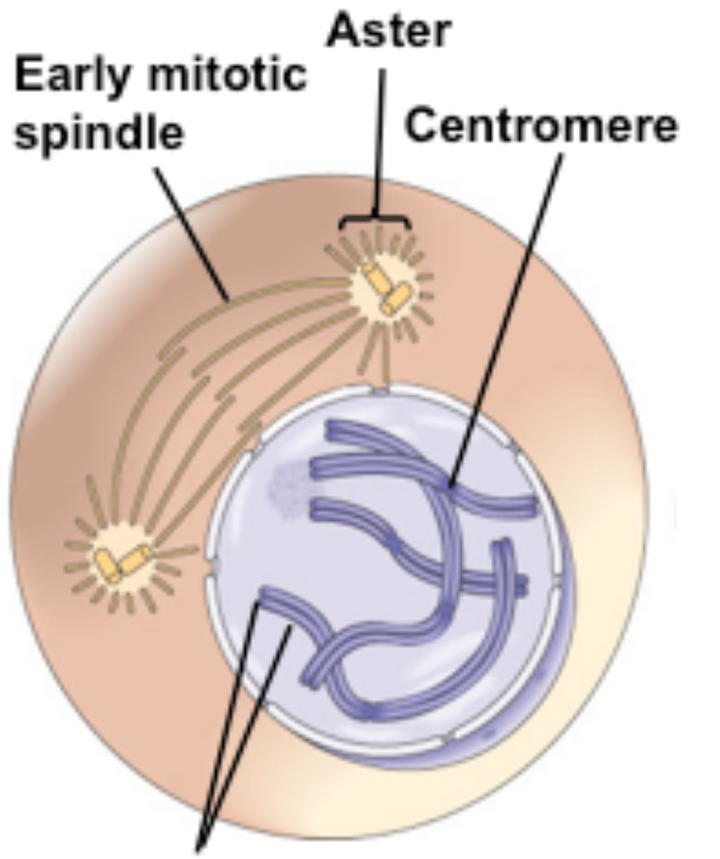
A Cell's Biography

- **Interphase G_2**
  - cell grows
  - organelles replicate
  - carries out destined functions
  - prepares for divisions
  - condenses chromatin into chromosomes (at the very end of G_2 or start of prophase)
- **Mitosis (prophase)**
  - chromatin condensed into chromosomes (by start of prophase)



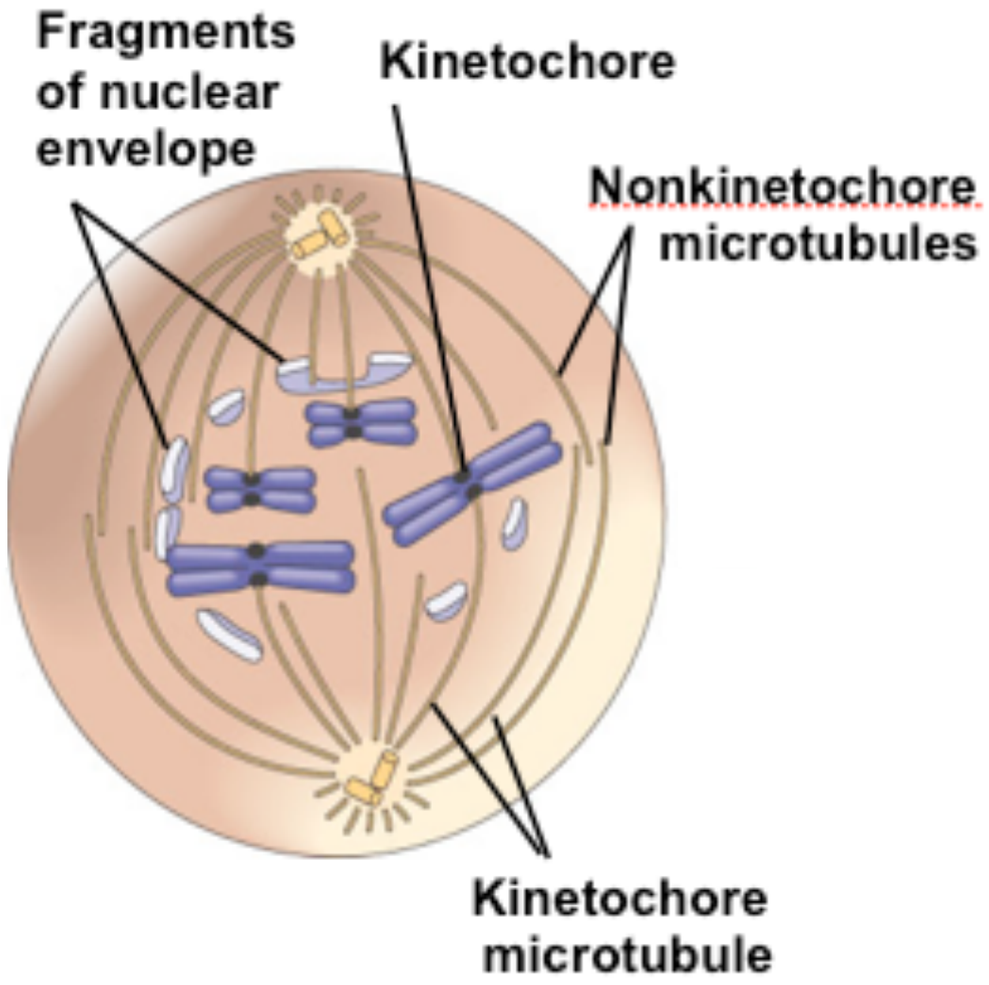
A Cell's Biography

- **Mitosis (prophase)**
  - nucleoli disappear
  - sister chromatids joined at centromeres and visible
  - mitotic spindle forms
    - *made of centrosomes and microtubules*
  - mitotic spindle begins moving the opposite poles
  - nuclear envelope begins to fragments



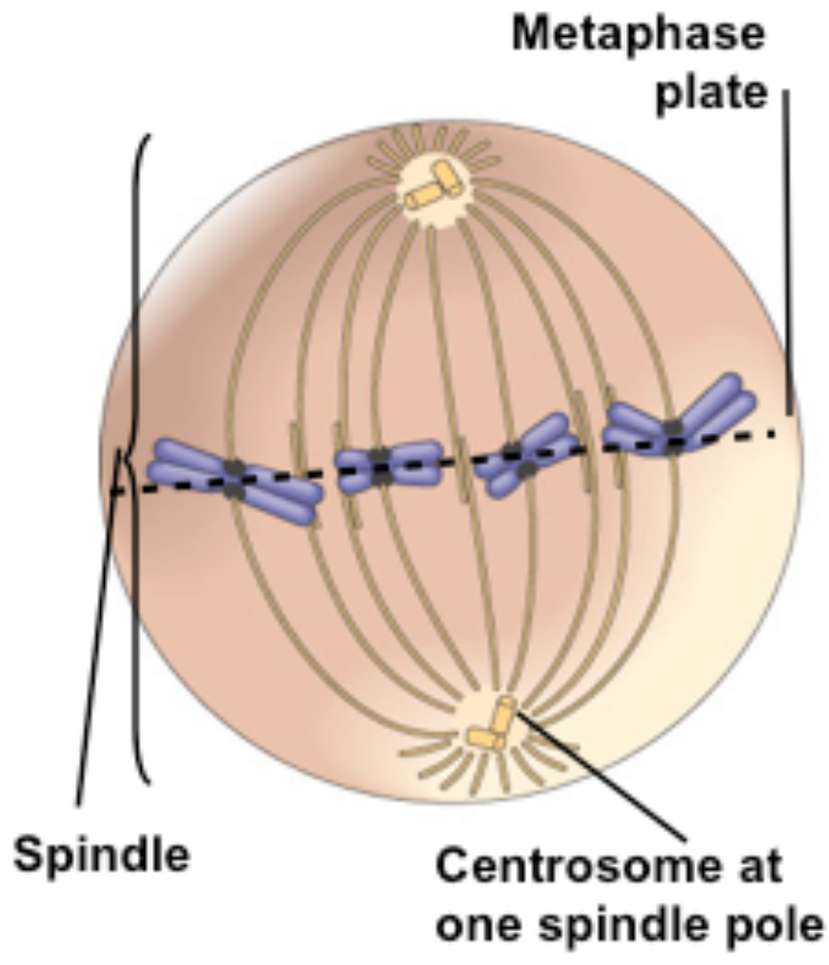
A Cell's Biography

- **Mitosis (prometaphase)**
  - nuclear envelope continues to fragment
  - microtubules starting to reach nuclear area
  - chromosomes continue to condense
  - each sister chromatid now has a kinetochore
  - microtubules begin attaching to the kinetochores
  - other microtubules overlap each other



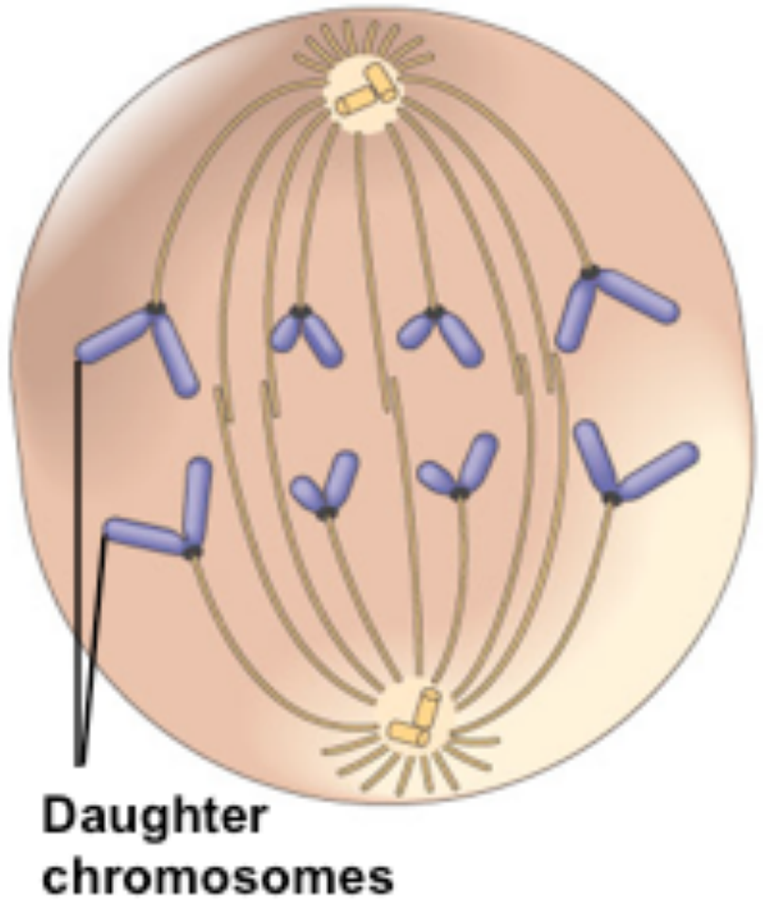
A Cell's Biography

- **Mitosis (metaphase)**
  - centrosomes are now at cell's poles
  - chromosomes are aligned at the cell's center
  - all kinetochores are attached to microtubules



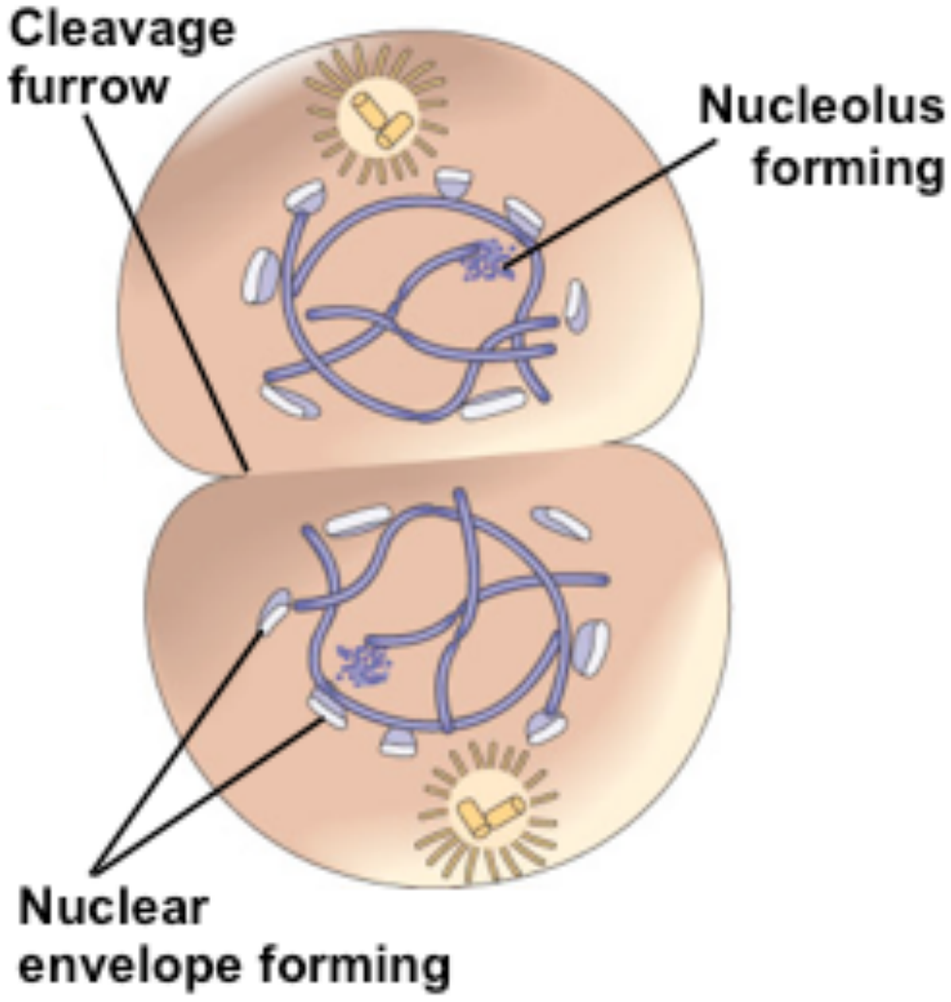
A Cell's Biography

- **Mitosis (anaphase)**
  - cohesin proteins cleave and sister chromatids separate
  - kinetochore microtubules shorten
  - chromosomes migrate away from each other move closer to the poles
  - nonkinetochores microtubules lengthen and elongate cell
  - each end of the cell have equivalent and complete collection of chromsomes



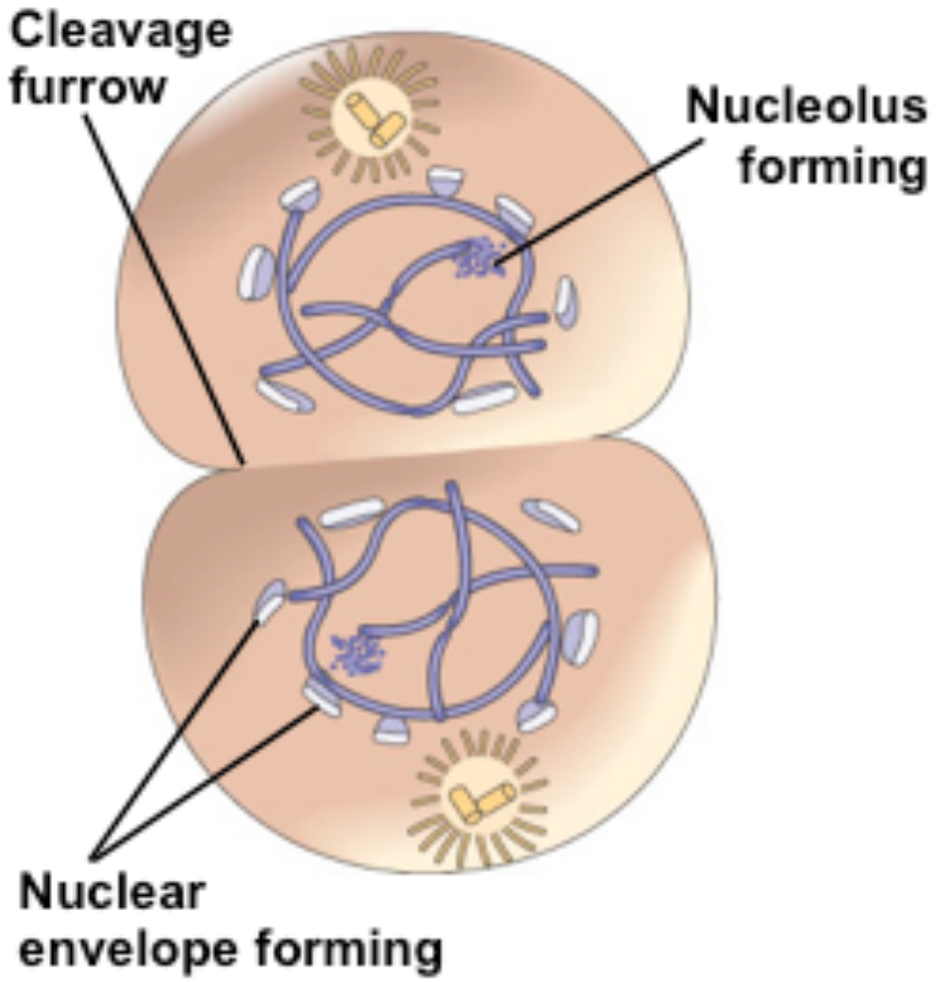
A Cell's Biography

- **Mitosis (telophase)**
  - nuclear envelope begins to form
  - nucleolus begins to form
  - chromosomes begin to unravel into chromatin
  - all microtubules are starting to depolymerize
  - nuclear envelope are intact and chromatin is most abundant

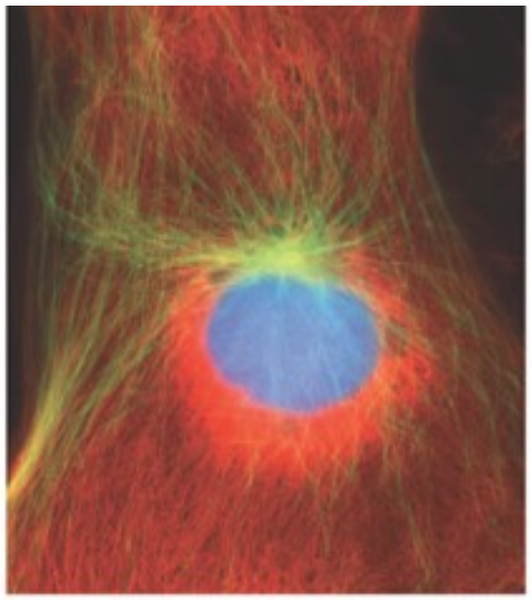


A Cell's Biography

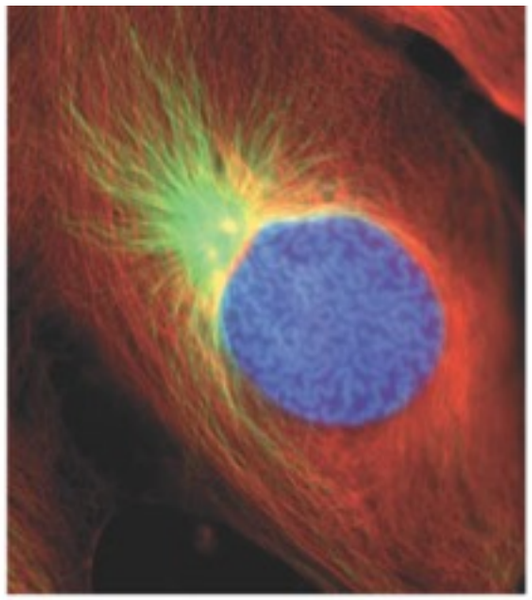
- **Cytokinesis**
  - cell begins to pinch in half (animals) before mitosis is done
  - cell begins to grow new cell wall (plants) through the middle of the cell even before mitosis is done



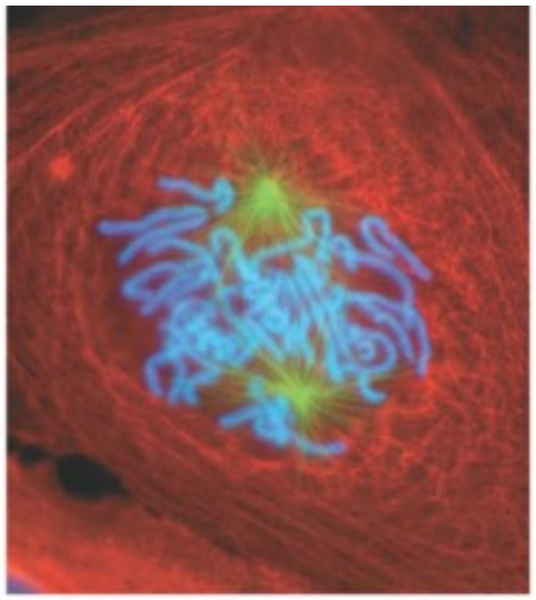
Visual Tour of Mitosis



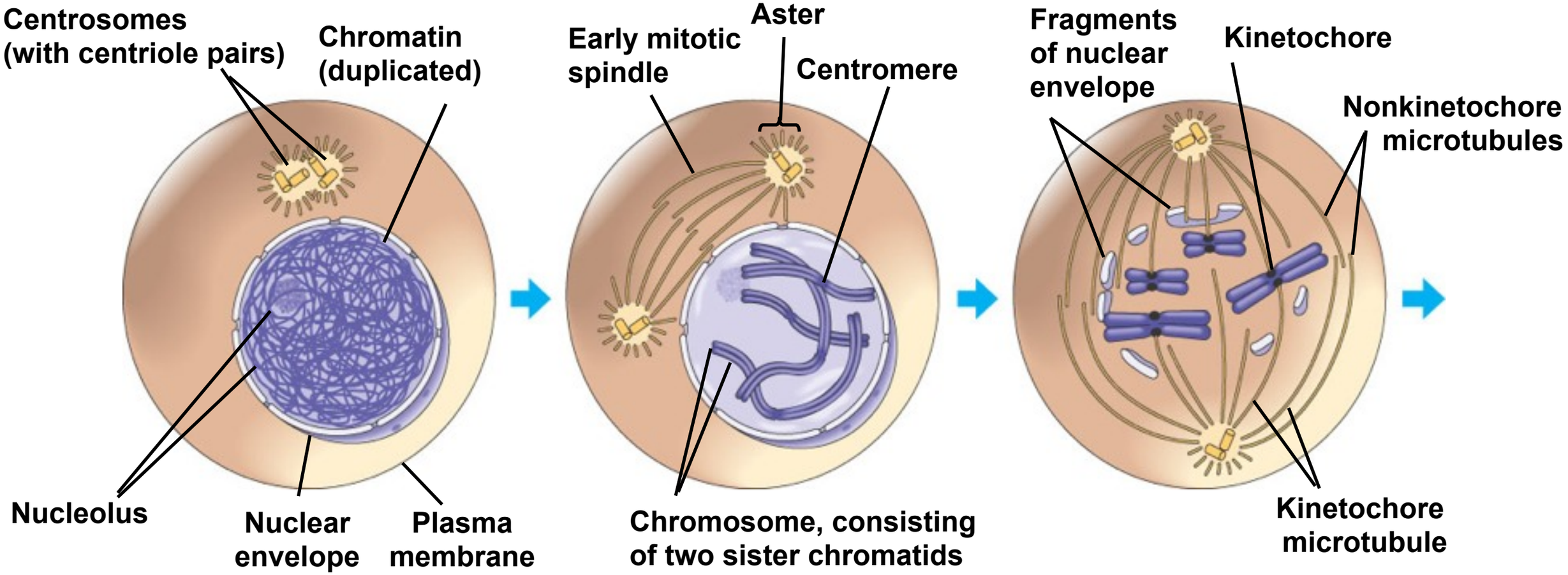
G_2 OF INTERPHASE



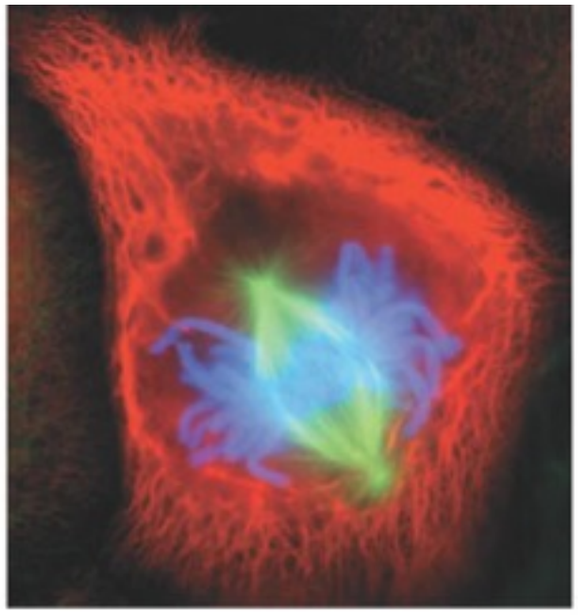
PROPHASE



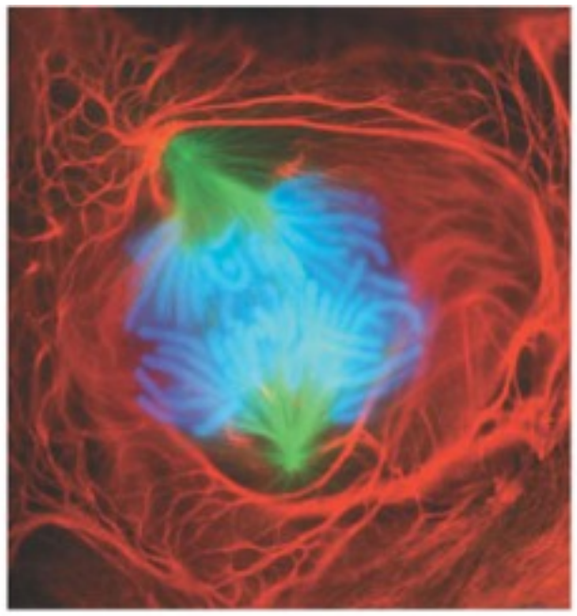
PROMETAPHASE



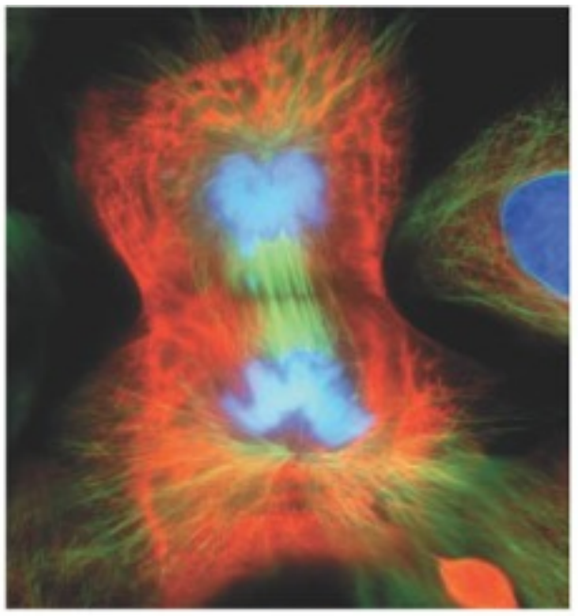
Visual Tour of Mitosis



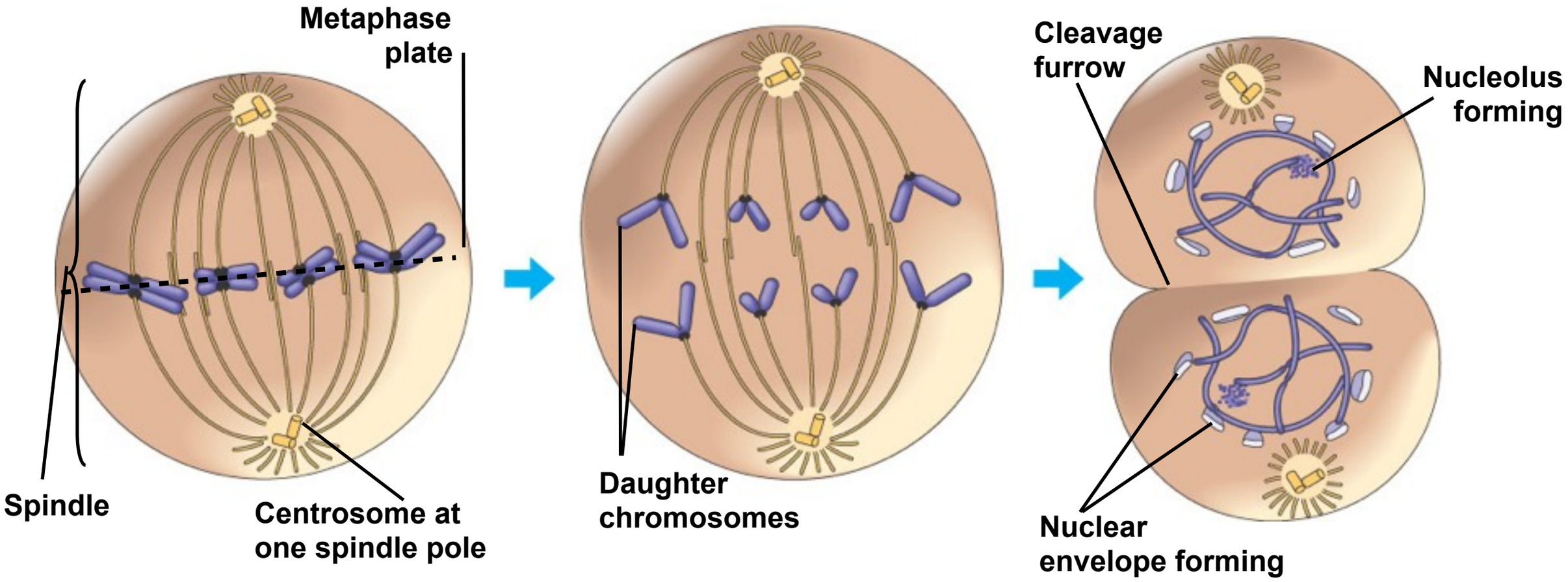
METAPHASE



ANAPHASE

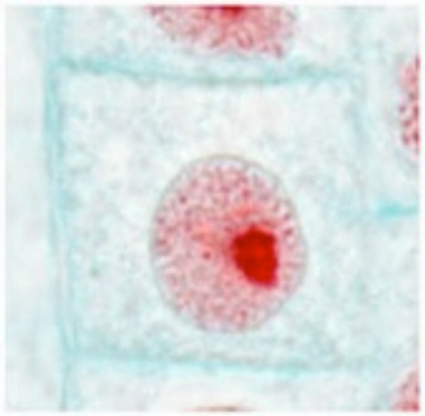


TELOPHASE & CYTOKINESIS

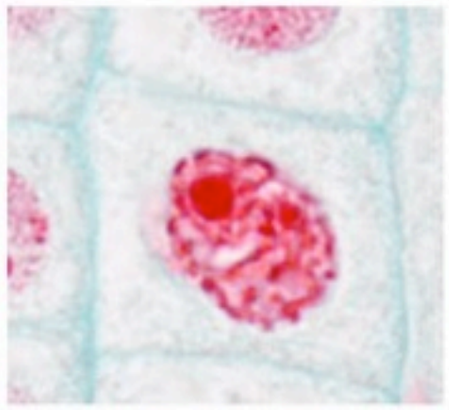


Plant Cells

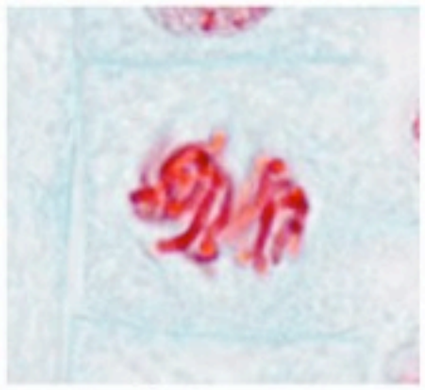
Mitosis - *Allium* Root Tip



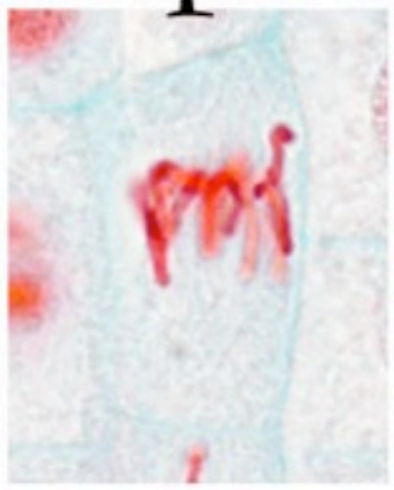
Interpahase



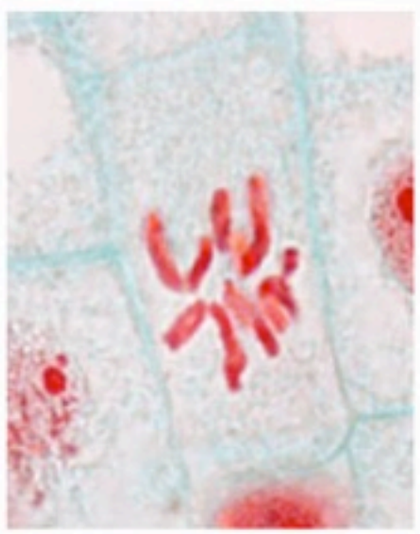
Prophase



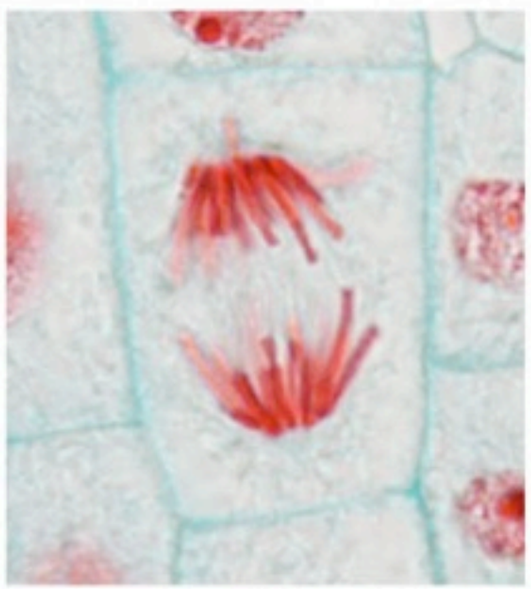
Later Phrophase



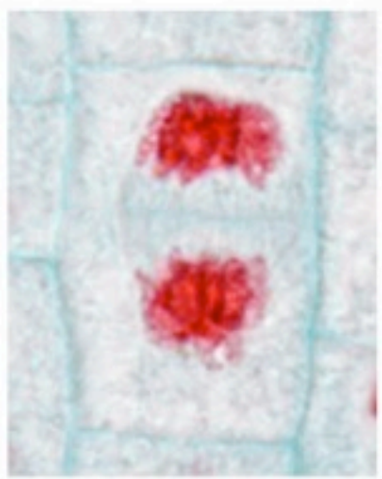
Metaphase



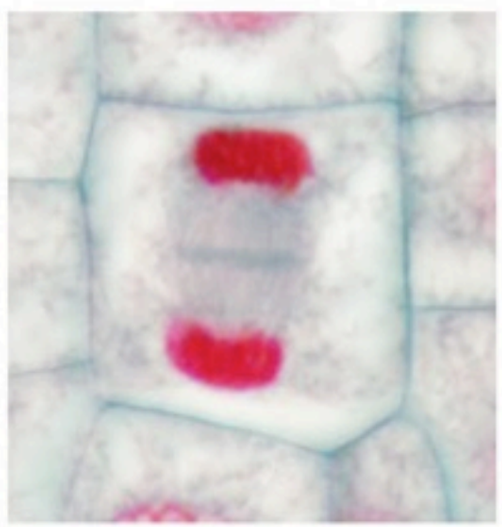
Early Anaphase



Anaphase

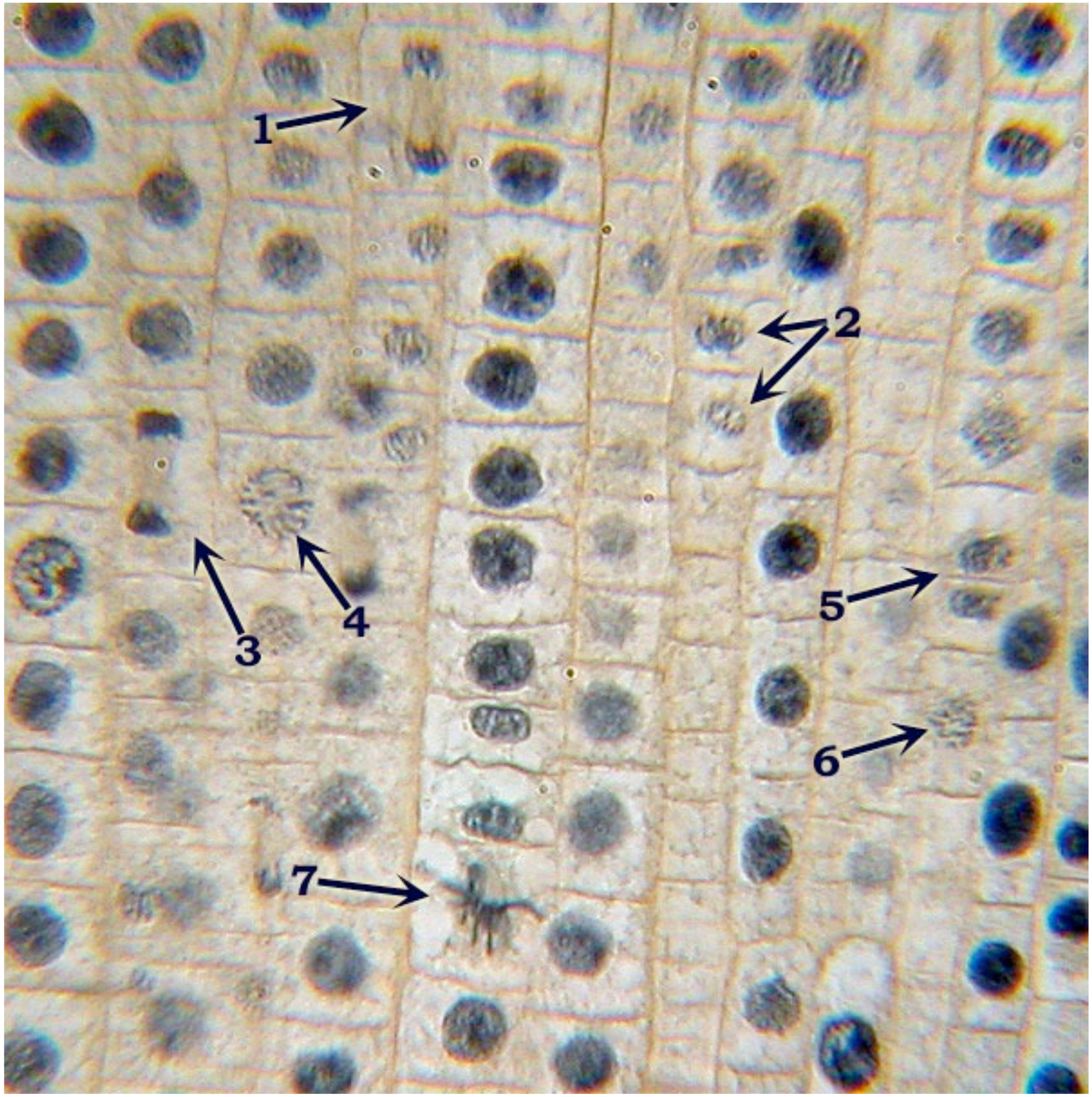


Telophase

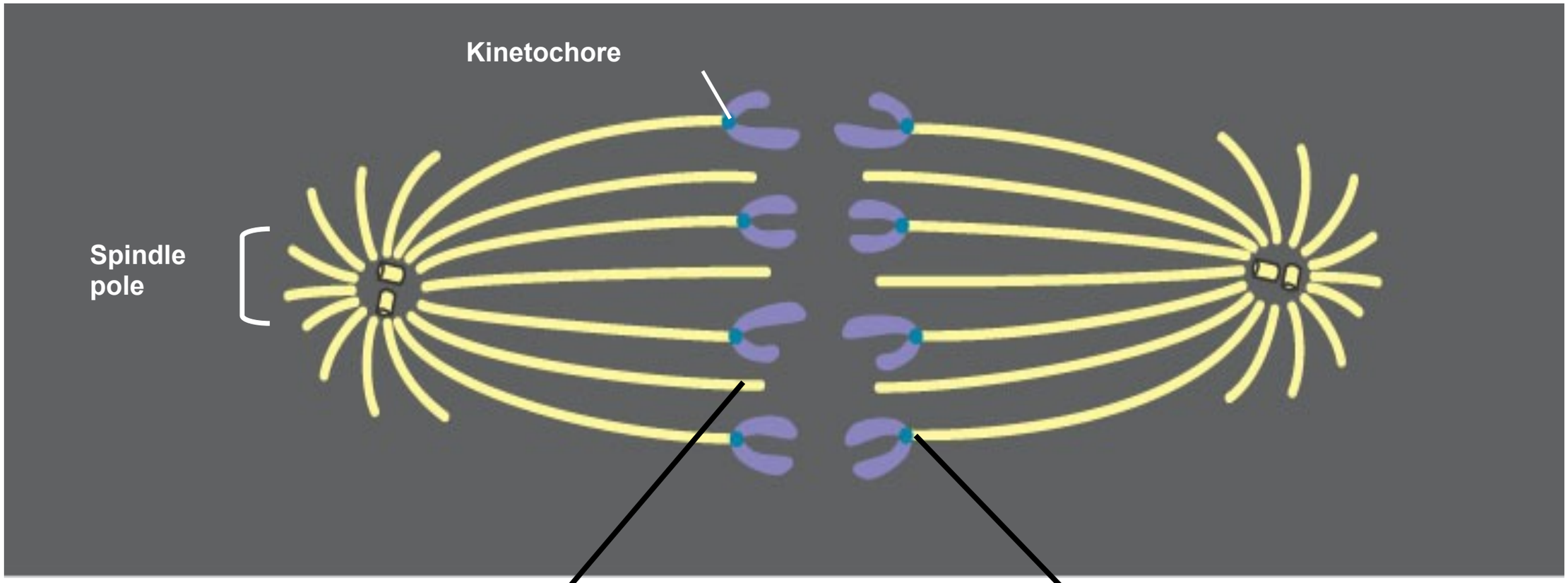


Later Telophase

Can you identify these stages?



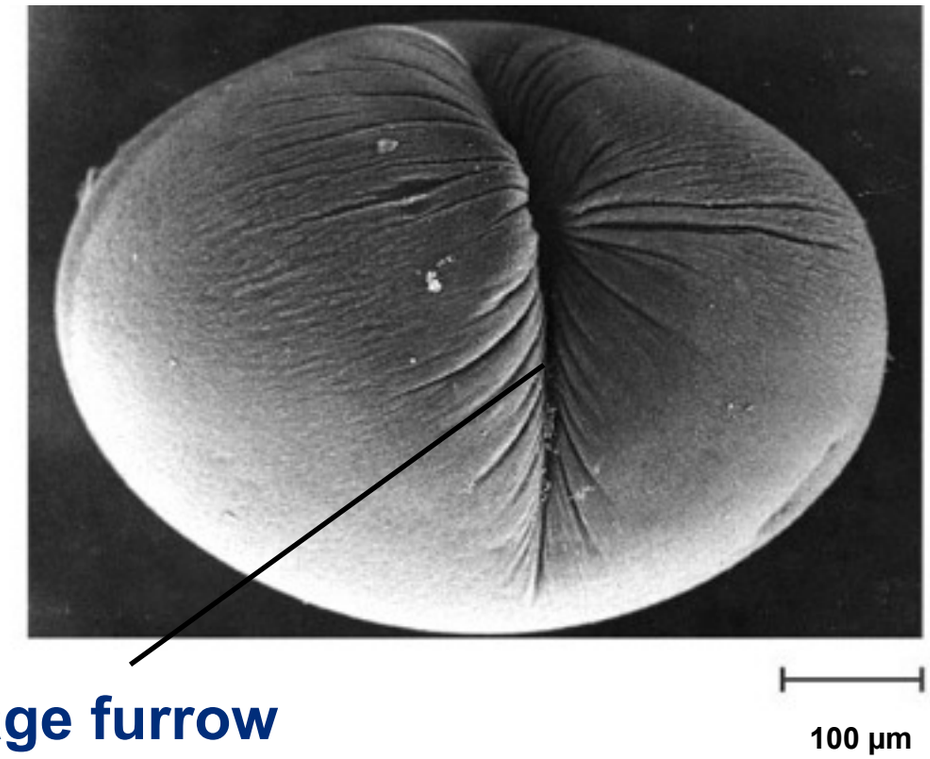
A Closer Look at Cytokinesis

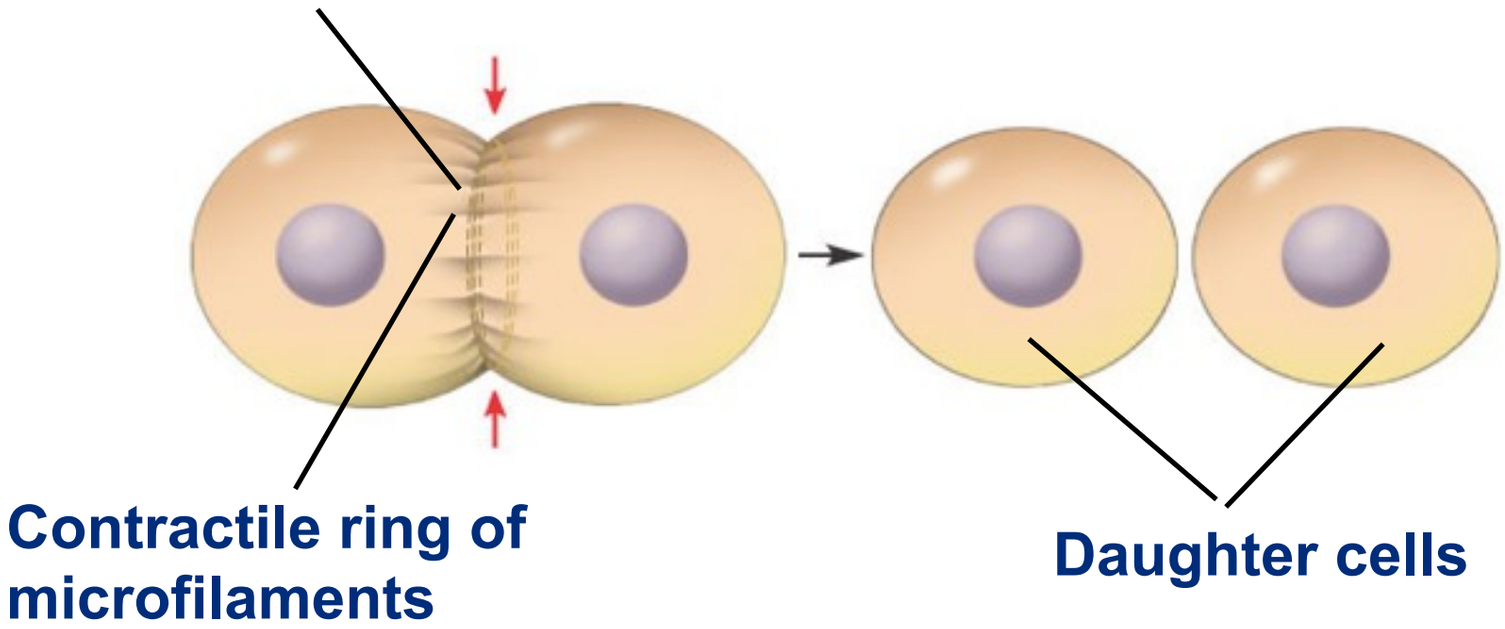


These spindles "polymerize" they grow and thus elongate the cell

These spindles "depolymerize" they shorten at the kinetochore thus separating the sister chromatids

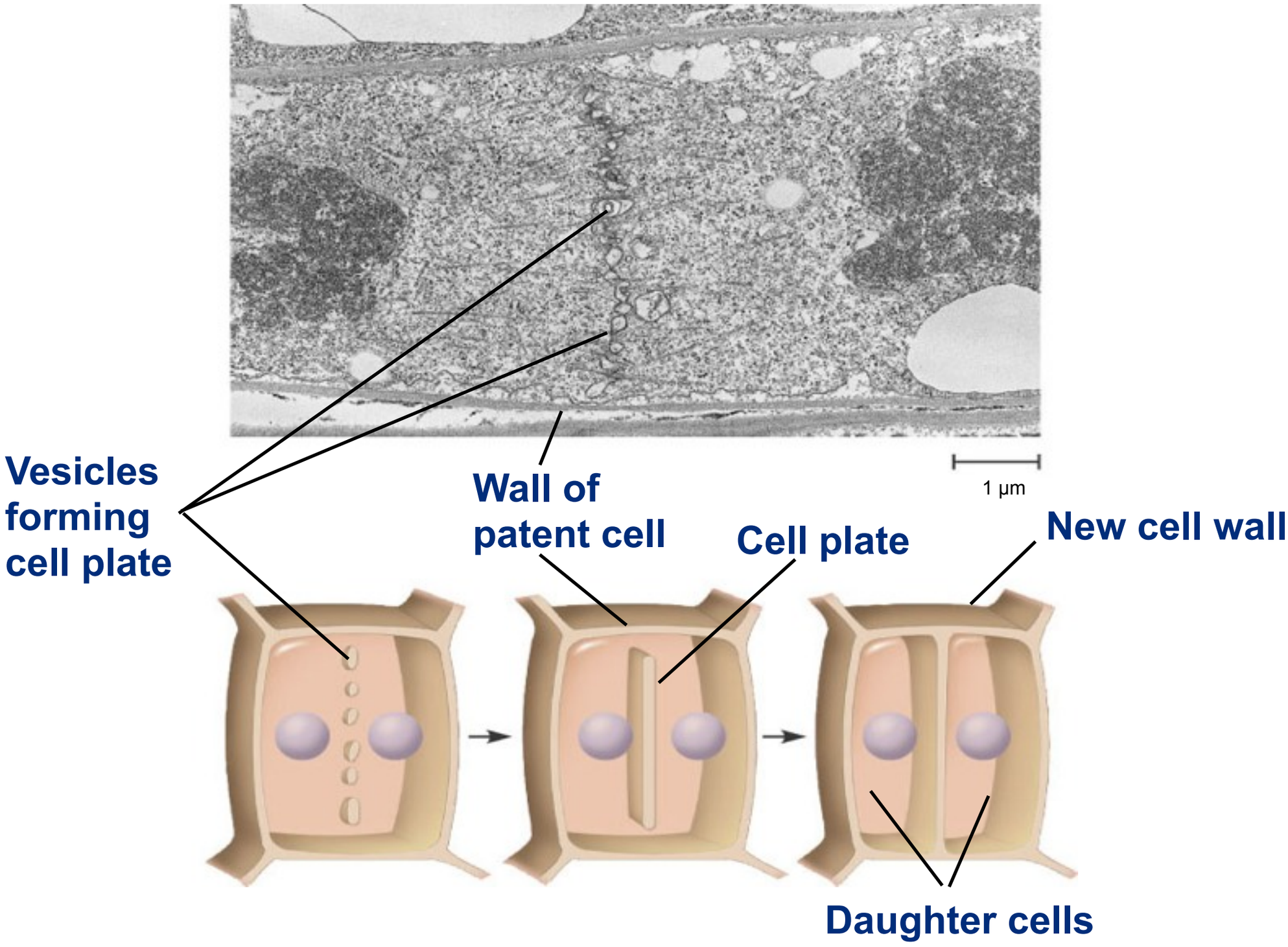
A Closer Look at Cytokinesis





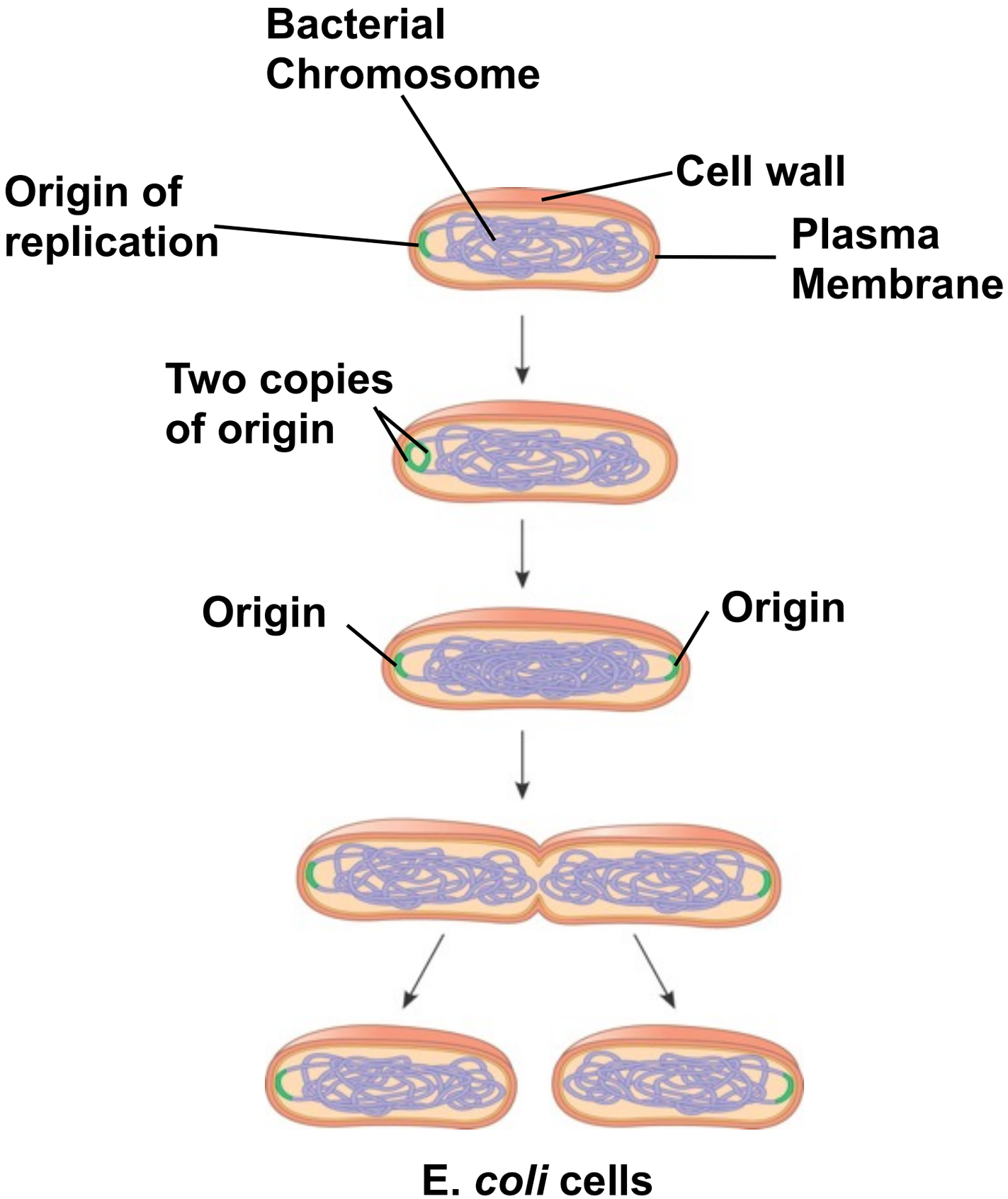
Cleavage of an animal cell (SEM)

A Closer Look at Cytokinesis



Cell plate formation in a plant cell (SEM)

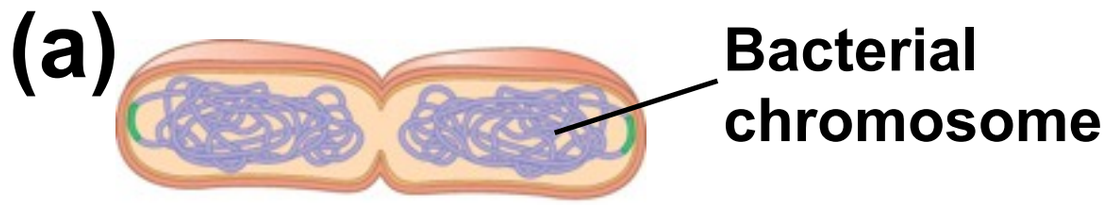
Evolution of Cell Division



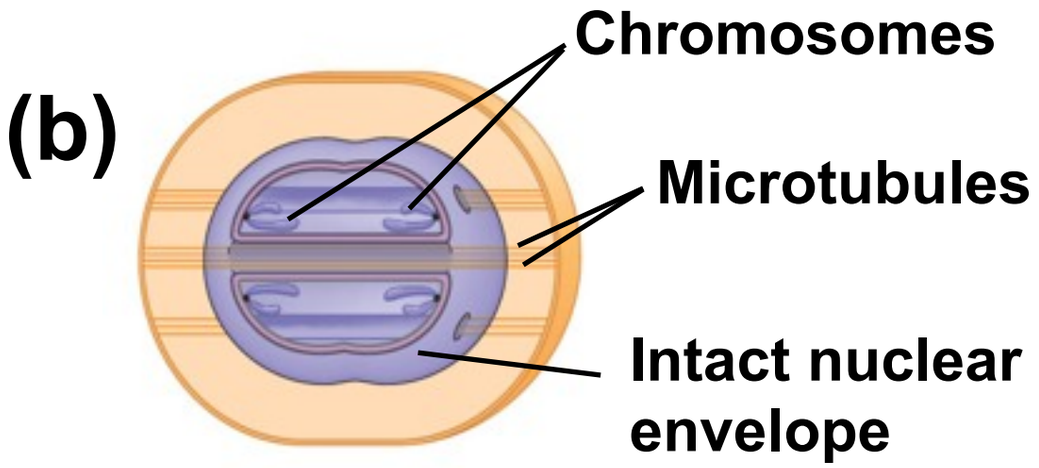
E. *coli* cells

Prokaryotes are the most ancient cells, they preceded eukaryotic cells therefore eukaryotic cell division should share common structures and processes

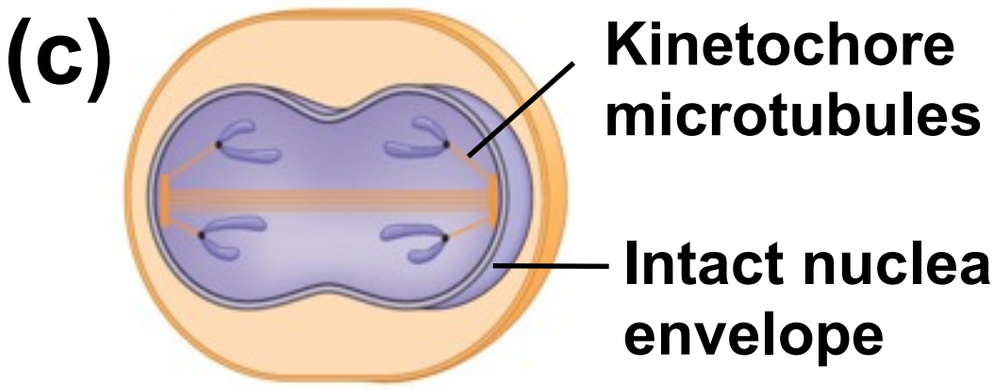
Prokaryotes. During binary fission, the origins of the daughter chromosomes move to opposite ends of the cell. The mechanism is not fully understood, but proteins may anchor the daughter chromosomes to specific sites on the plasma membrane.



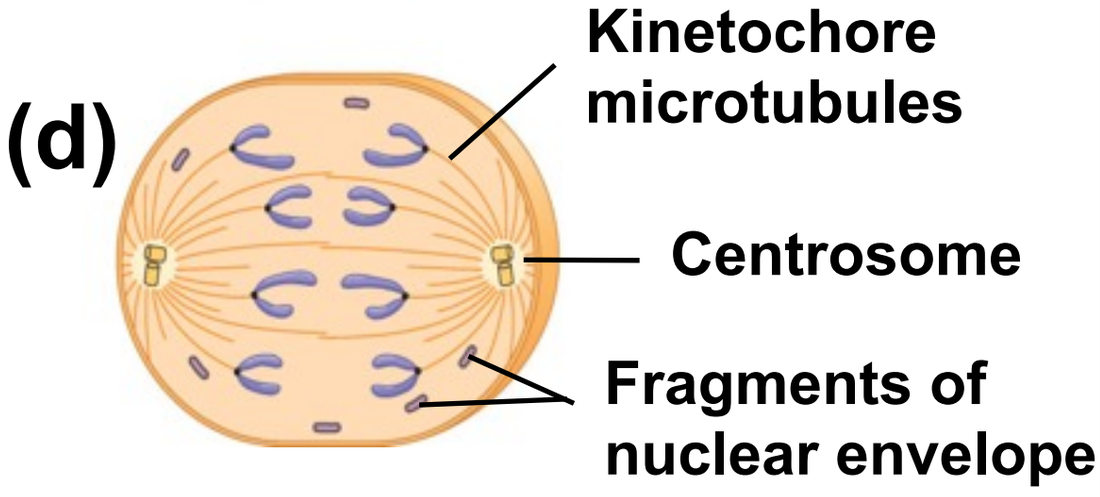
Dinoflagellates. In unicellular protists called dinoflagellates, the nuclear envelope remains intact during cell division, and the chromosomes attach to the nuclear envelope. Microtubules pass through the nucleus inside cytoplasmic tunnels, reinforcing the spatial orientation of the nucleus, which then divides in a fission process reminiscent of bacterial division.



Diatoms. In another group of unicellular protists, the diatoms, the nuclear envelope also remains intact during cell division. But in these organisms, the microtubules form a spindle *within* the nucleus. Microtubules separate the chromosomes, and the nucleus splits into two daughter nuclei.



Most eukaryotes. In most other eukaryotes, including plants and animals, the spindle forms outside the nucleus, and the nuclear envelope breaks down during mitosis. Microtubules separate the chromosomes, and the nuclear envelope then re-forms.



The Cell Cycle

III.

Main Idea: The timing, rate and number of cell divisions in an organism is crucial to normal growth, development and maintenance.

Regulation of Cell Division

- For multicellular organisms to function properly cell division must be regulated and controlled, this includes
  - when cells divide
  - how fast they divide
  - how many times they will divide
- Consider the following cells...
  - once fully formed nerves and muscles NEVER divide
  - epithelial cells (skin) divide most of the time
  - liver cells only divide when they have to (if they are damaged)

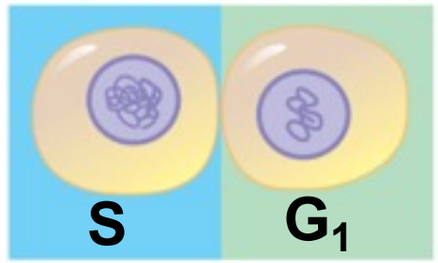
But how?, How is this cell division regulated?

Evidence for Regulation

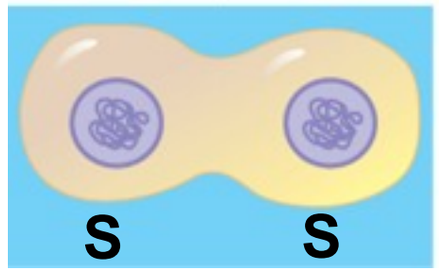
In each experiment, cultured mammalian cells at two different phases of the cell cycle were induced to fuse.

EXPERIMENTS

Experiment 1

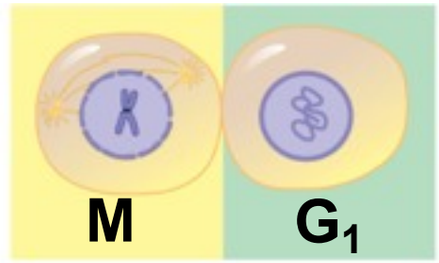


RESULTS

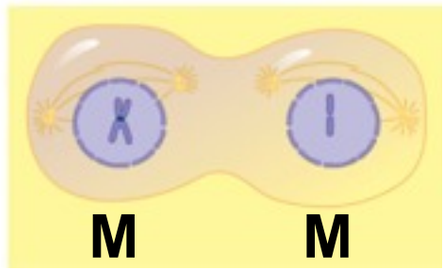


When a cell in the S phase was fused with a cell in G_1, the G_1 cell immediately entered the S phase—DNA was synthesized.

Experiment 2



RESULTS



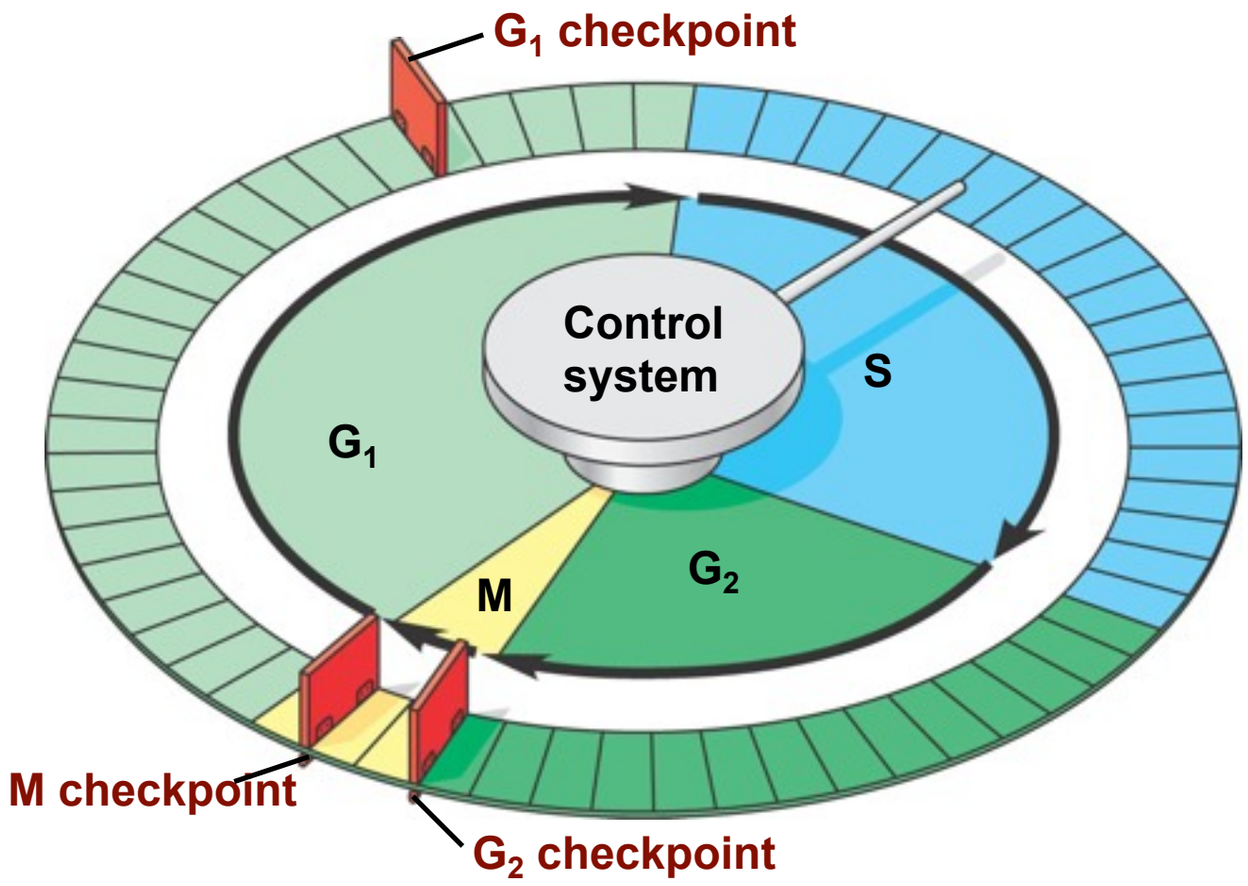
When a cell in the M phase was fused with a cell in G_1, the G_1 cell immediately began mitosis— a spindle formed and chromatin condensed, even though the

CONCLUSION(S)

The results of fusing cells at two different phases of the cell cycle suggest that molecules present in the cytoplasm of cells in the S or M phase control the progression of phases.

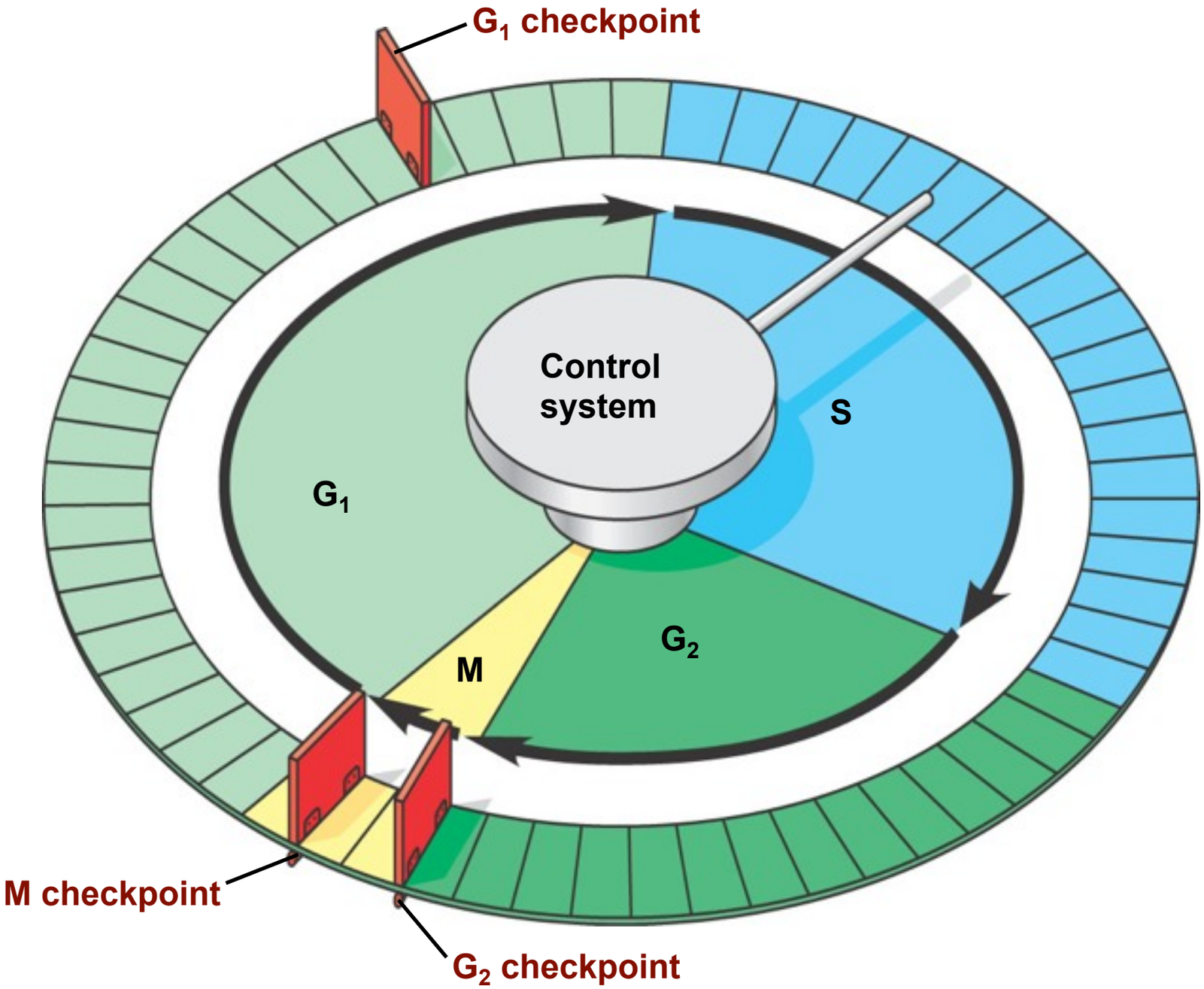
Controlling the Cell Cycle

- **Cell Cycle Control System**- is a set of cyclical molecules that start and coordinate key sequential events in the cell cycle.
- Key **checkpoints** in the cell cycle stop the cycle at that point in the cycle.
  - The cycle only continues if "Go" signals override the stop checkpoints.

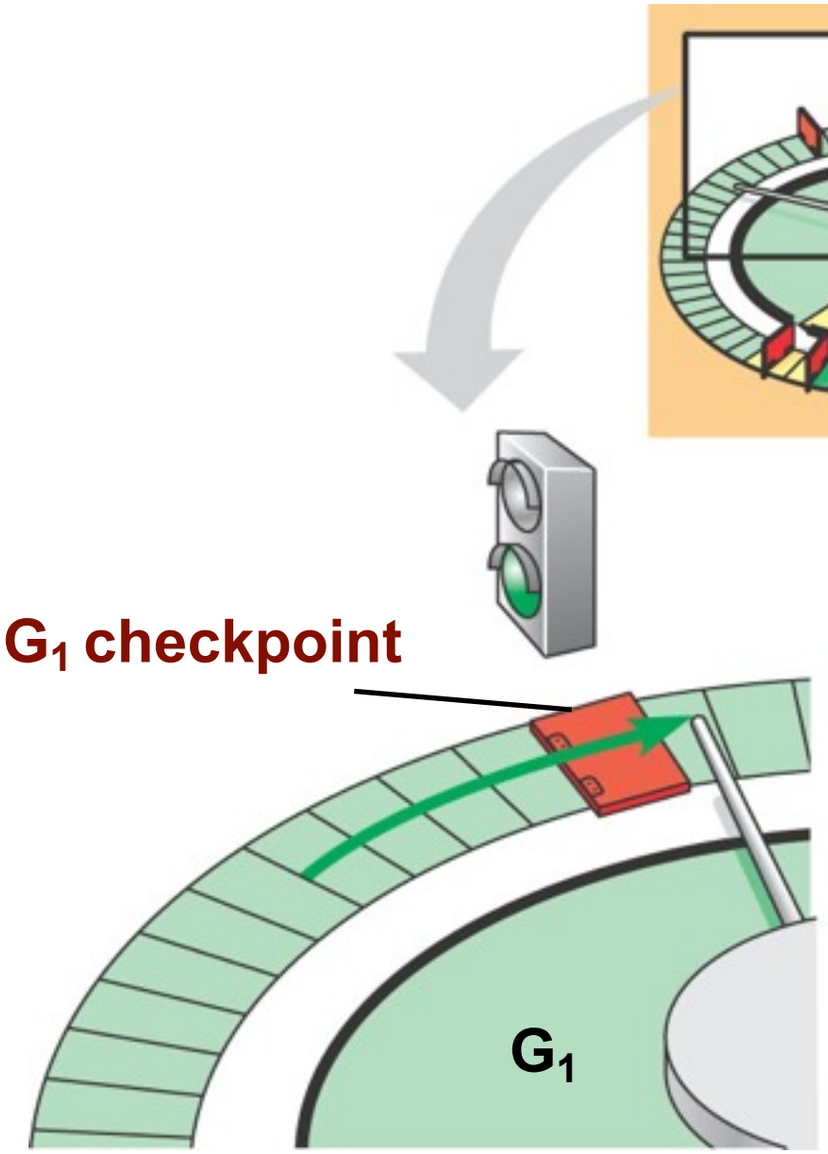


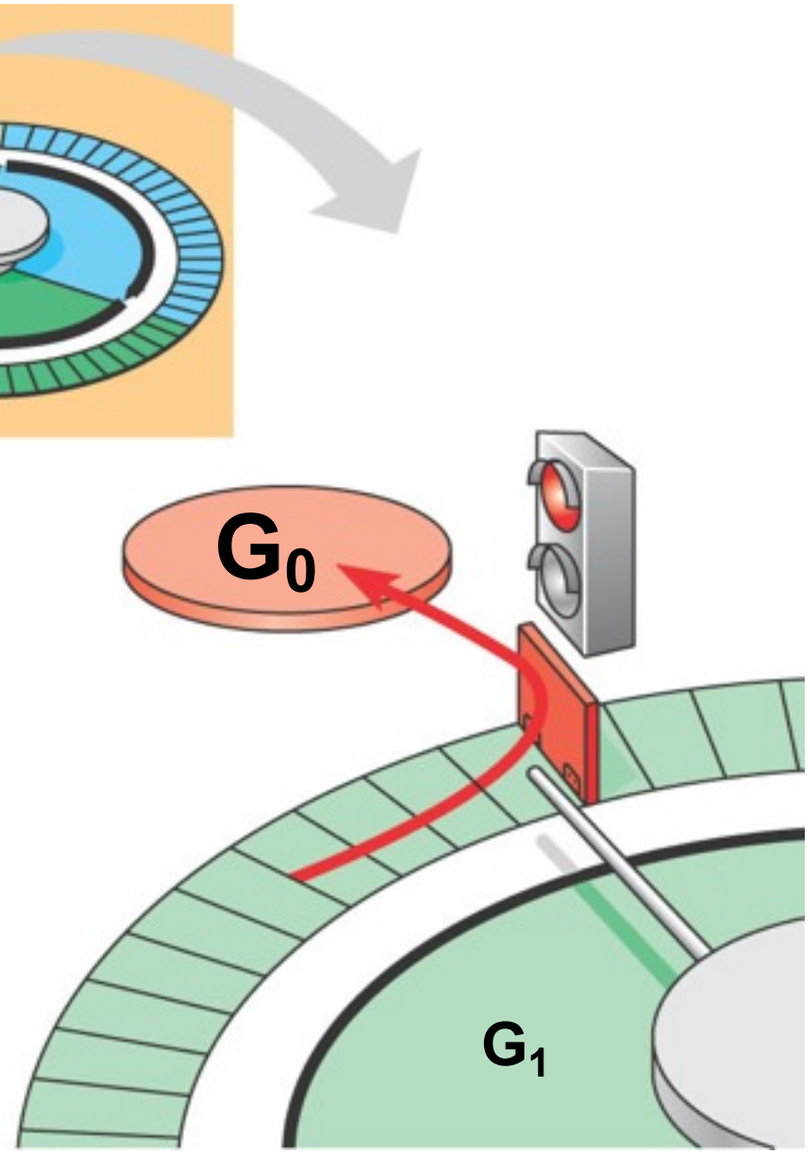
These checkpoints can be regulated from internal mechanisms or from external signals. *Think of washing machine that internally coordinates the different cycles but you can externally override the wash cycles by adjusting the dial as you choose.*

The checkpoints allow the cell to make sure all crucial cellular processes that should have taken place, did indeed take place.



The G_1 checkpoint appears to be the most important, when cells override this checkpoint almost all will continue through the entire cycle.





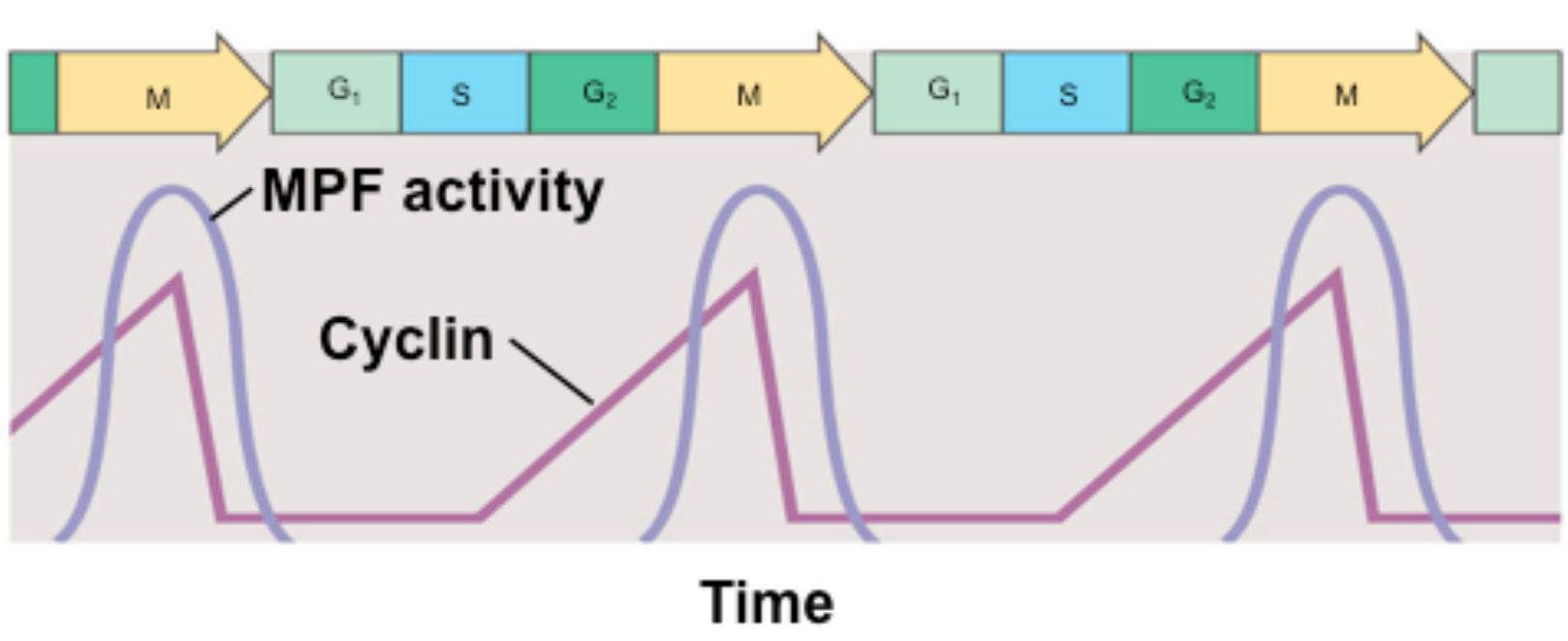
Most cells exist in the G_0 state, the variability comes from the fact that some cells never leave the G_0 state, some leave it only when necessary and yet some override the G_0 state all the time.

If a cell receives a go-ahead signal at the G_1 checkpoint, the cell continues on in the cell cycle.

If a cell does not receive a go-ahead signal at the G_1checkpoint, the cell exits the cell cycle and goes into G_0, a nondividing state.

A Closer Look at Cell Cycle Control

- *Cell Cycle Control System*- specifically involves the <u>fluctuations</u> in the <u>amount</u> and <u>activity</u> of certain <u>regulatory molecules</u> that "pace" sequential events in the cell.
  - These regulatory molecules are primarily **Kinases** and **Cyclins**.



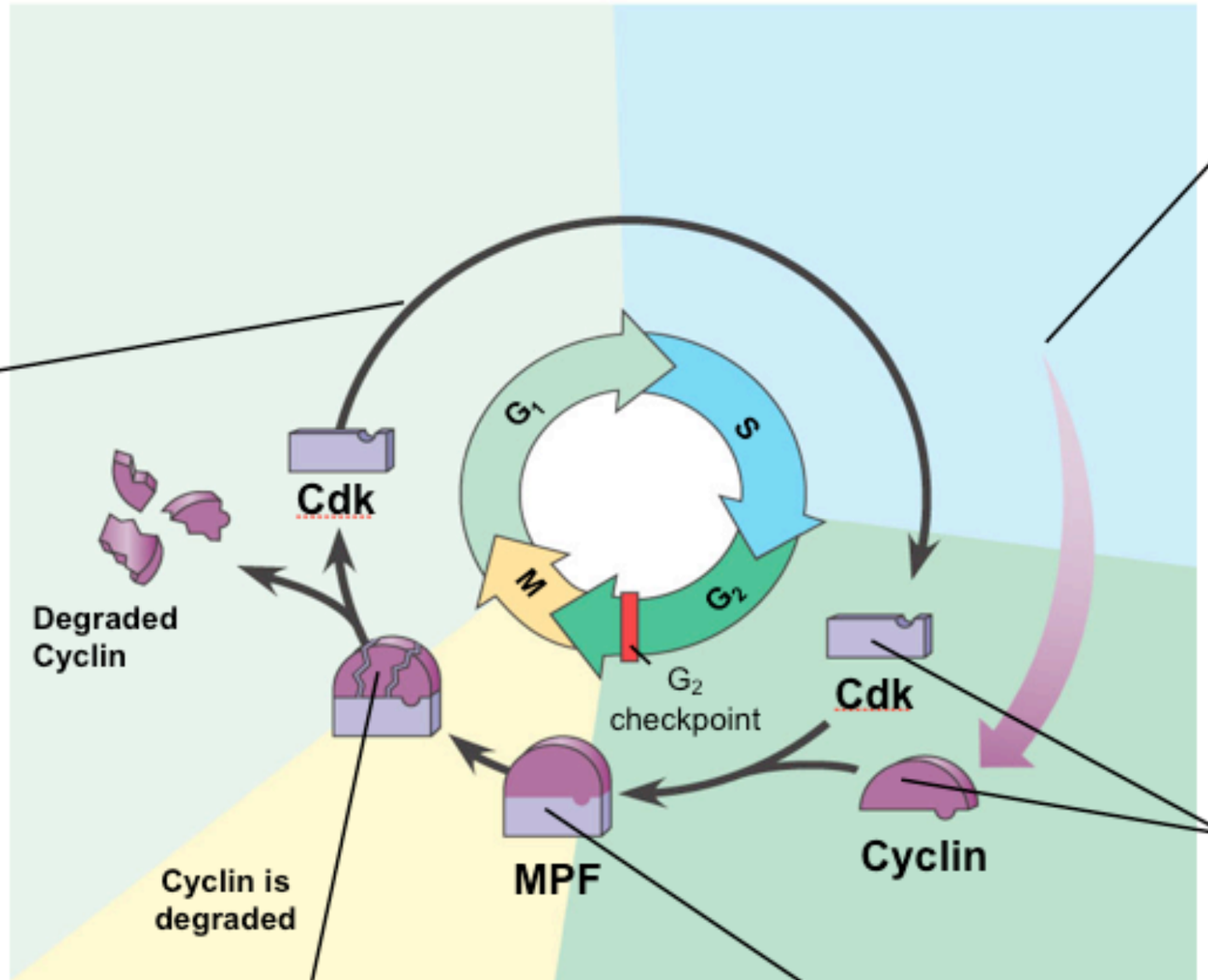
MPF is the specific kinase in the active form

MPF- maturation-promoting factor made of both cyclin and kinase

Cdk- is a cyclin dependent kinase

1.

Synthesis of cyclin begins in late S phase and continues through G_2. Because cyclin is protected from degradation during this stage, it accumulates.



2.

Accumulated cyclin molecules combine with recycled Cdk molecules, producing enough molecules of MPF to pass the G_2 checkpoint and initiate the events of mitosis.

3. **MPF promotes mitosis by phosphorylating various proteins. MPF's activity peaks during metaphase.**

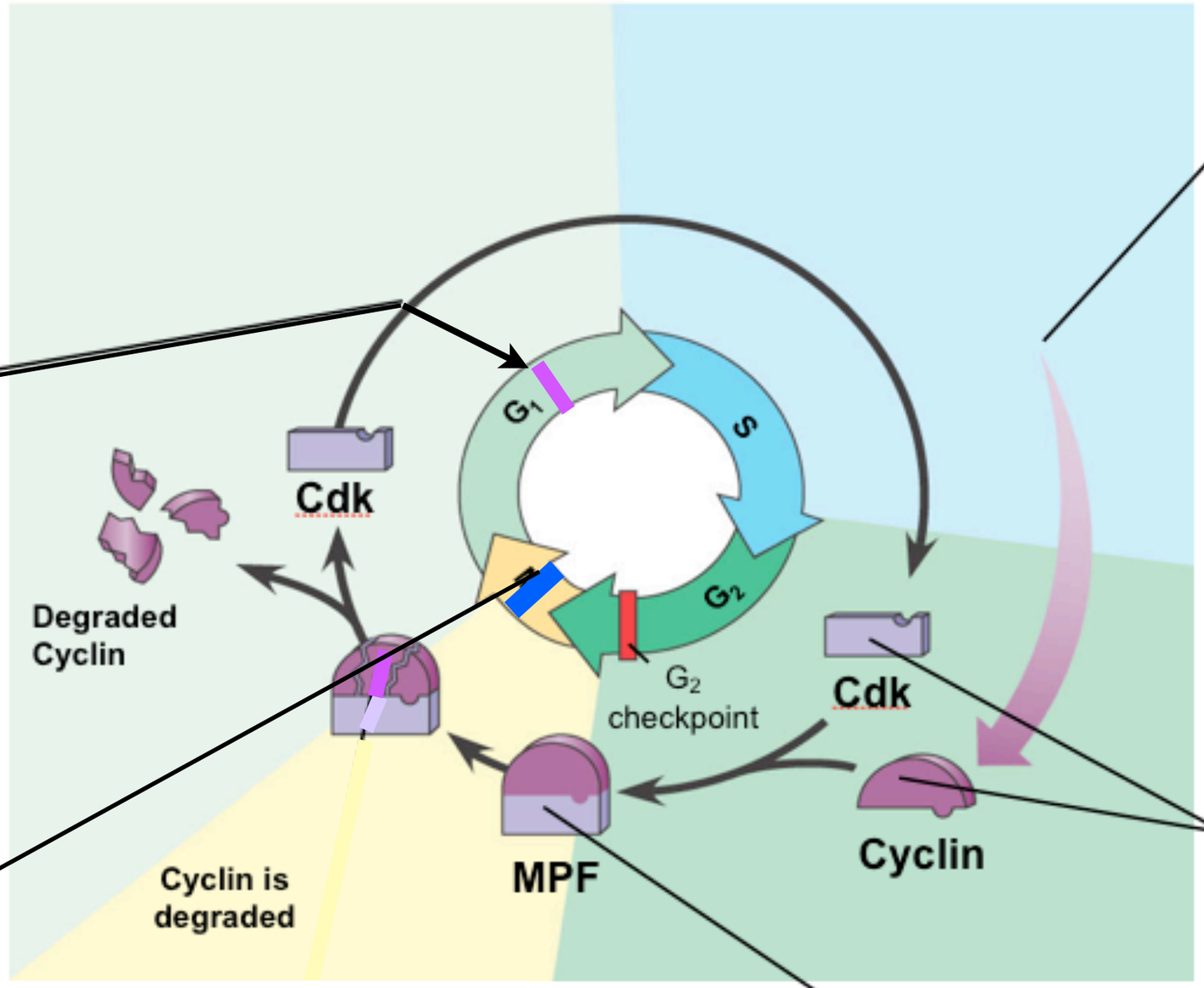
4. **During anaphase, the cyclin component of MPF is degraded, terminating the M phase. The cell enters the G_1 phase.**

5.

During G_1, conditions in the cell favor degradation of cyclin, and the Cdk component of MPF is recycled.

Additional Points

The G_1 checkpoint is controlled a very similar manner using multiple Cdk's and cyclins.



Cyclin is always active but its concentration fluctuates.

Cdk is actually always present, its activity fluctuates.

M checkpoint occurs in anaphase using unique regulatory proteins. All spindles must attach to kinetochores before the "go" signal activates *seperase* which cuts cohesin proteins and pulls apart the sister chromatids

MPF also initiates the catabolism of the nuclear membrane and the condensation of chromatin into chromosomes.

External Signals

- Recall that *Cell Cycle Control Systems* can be regulated internally as well as externally.
  - The G_1, G_2, and M checkpoints described at the last couple slides are involve internally regulated mechanisms.
- Three examples of externally regulated *Cell Cycle Control Systems* include **platelet derived growth factors (PDGF's), density-dependent inhibition**, and **anchorage dependence**.
  - PDGF's stimulate cell division
  - While D.D.I and A.D. inhibit cell division

What kind of receptor do PDGF's bind to?

Tyrosine Kinase Receptors

Platelet Derived Growth Factors

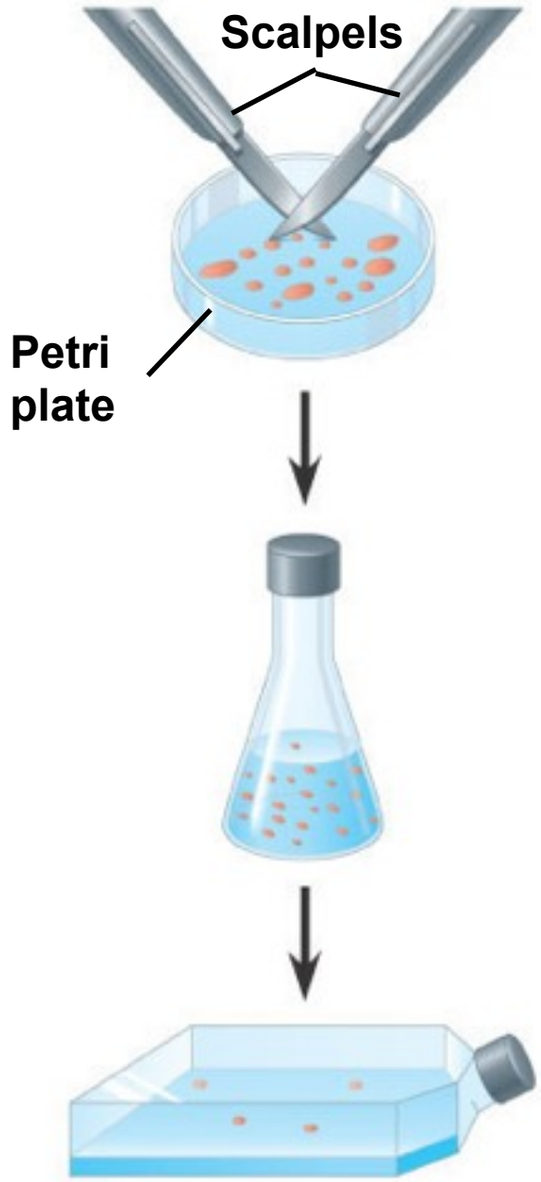
EXPERIMENT

A sample of connective tissue was cut up into small pieces.

Enzymes were used to digest the extracellular matrix, resulting in a suspension of free fibroblast cells.

Cells were transferred to sterile culture vessels containing a basic growth medium consisting of glucose, amino acids, salts, and antibiotics (as a precaution against bacterial growth).

PDGF was added to half the vessels. The culture vessels were incubated at 37°C.



Without PDGF = NO Growth

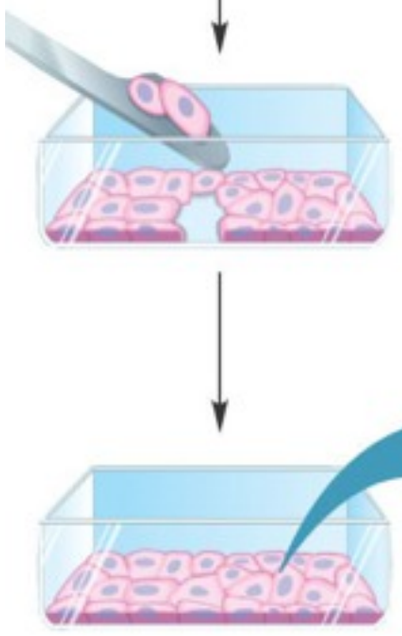
With PDGF = Growth

Density-Dependent Inhibition & Anchorage Dependence

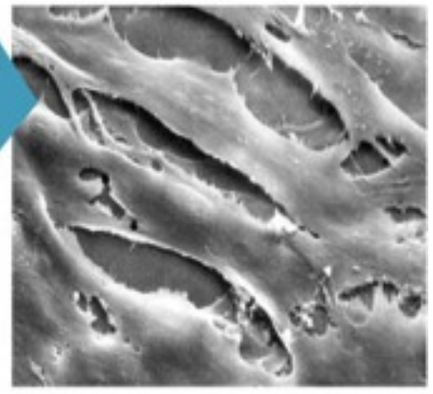
Many cells exhibit A.D., they must be attached to other cells or a surface of some kind in order to reproduce.

Cells anchor to dish surface and divide (anchorage dependence).

When cells have formed a complete single layer, they stop dividing (density-dependent inhibition).



If some cells are scraped away, the remaining cells divide to fill the gap and then stop (density-dependent inhibition).



Normal mammalian cells. The availability of nutrients, growth factors, and a substratum for attachment limits cell density to a single layer.

Anchorage Dependence

- Recall that *Cell Cycle Control Systems* can be regulated internally as well as externally.
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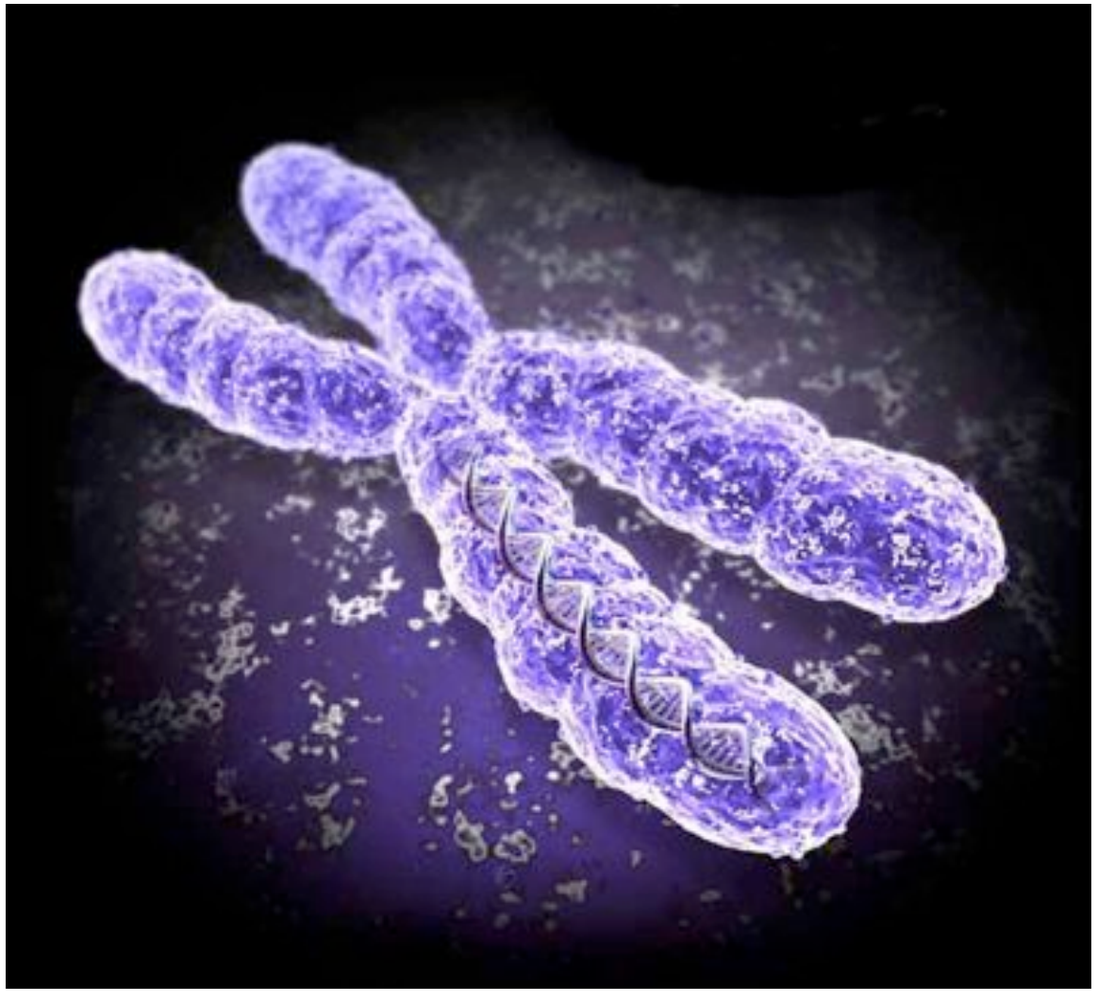
  - PDGF's stimulate cell division
  - While D.D.I and A.D. inhibit cell division

The Cell Cycle

IV.

Main Idea: The loss of cell cycle control can result in cancer (uncontrolled cell growth).



Cancer

- **Cancer is uncontrolled cell growth.**
  - **Molecular control mechanisms/signals have no effect on cancerous cells.** 1.
  - Hypotheses include:
    - *they do not need growth factors*
    - *they may make their own growth factors internally*
    - *they may have an abnormal pathway that is activated from something other than growth factors*

There is more to cancer than faulty cell control mechanisms...

Cancer

- **Cancerous cells are also immortal**. 2.
  - Normal cells divide 20-50 times, age and die.
  - In 1951 scientists removed cancerous cells from tumor found in woman named Henrietta Lacks, scientists started a cell culture from these cells.
  - The "Hela Cell line" as it is known today is still dividing!
- **Cancerous cells are also immortal**. 3.
  - Lastly cancerous cells evade the apoptotic pathways that normally destroy cells that have damaged or infected cells

Whatever the specific cause, faulty genes, and their protein products are are the blame.

Cancer

- **Transformation-** the process that converts a normal cell to a cancerous cell
  - The bodies normal immune response kills cancerous cells.
  - If the transformed cell evades destruction it replicates into a mass cancerous cells called a **tumor**.
- **Benign Tumors** remain at the original location and as a result are easily treated with surgical removal.
- **Malignant Tumors** spread to new locations (**metastasis**) and as a result are much more difficult to treat.

Breast Cancer

A tumor grows from a single cancer cell.

1.

Tumor

Glandular tissue

2.

Cancer cells invade neighboring tissue.

Cancer cells spread through lymph and blood vessels to other parts of the body.

3.

Lymph vessel

Blood vessel

Cancer cell

Metastatic Tumor

4.

A small percentage of cancer cells may survive and establish a new tumor in another part of the body.

Cancer

- **Malignant Tumors-** are characterized by more than just cellular proliferation.
  - Malignant cancer cells often have abnormal number of chromosomes.
  - Malignant cancer cells often lose constructive functions.
  - Malignant cancer cells often detach from neighboring cells.
  - Malignant cancer cells can release signal molecules that cause the growth of blood and lymph vessels to feed the growing tumor.
- Treating malignant tumors before they spread to new locations (**metastasis**) greatly increases the success rate.

Cancer Treatment

- Cancer treatment may begin with the detection and **surgical removal** of the tumor.
  - Malignant cancer treatment also involves **radiation**, applying high energy wavelengths to the area of the tumor to damage the DNA of cancerous cells.
  - Malignant cancer treatment also involves **chemotherapy**, the administration of toxic chemicals that disrupt cellular division.
    - Unfortunately both radiation and chemotherapy kill normal healthy cells as well, resulting in some negative side effects.
    - *nausea, hair loss and increased susceptibility to infections*

Cancer Treatment

- Cancer treatment is becoming more personalized and effective.
    - The progress stems from technological advancements but most importantly from our increased knowledge of normal cell functions.
- Consider breast cancer
    - 1 in 8 women will develop breast cancer
    - The incidence of breast cancer (worldwide) grows each year
    - BUT the mortality rate is falling

Title

I.

Main Idea:.

PREFACE

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Title

I.

Main Idea:.

PREFACE

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