Reproduction is a fundamental property of life. Cells are the fundamental unit of life. Reproduction occurs at the cellular level with one mother cell giving rise to two daughter cells.

Cellular reproduction consists of making copies of all internal components of the cell, positioning those components, and then dividing the cell so that the new cells receive a copy of each of the important internal components.

Prokaryotic cells reproduce by **binary fission**. They grow to a size sufficient to divide into two cells, replicate their DNA (so that they have two DNA molecules) and then build a new cell membrane between the two DNA molecules.
DNA replication in prokaryotes begins at a single point on the circular double stranded DNA molecule, the replication origin.

DNA is replicated in both directions from the replication origin, until there are two complete double stranded DNA molecules. Each of the double stranded molecules consists of one of the original strands and one new strand.

Each strand is attached to neighboring attachment points on the cell membrane and then a new cell membrane is built to separate the molecules into different cells.

The FtsZ protein is required for proper cell division. The protein accumulates where the septum forms between the cells. The FtsZ protein is chemically similar to the microtubules that form the spindle fibers in eukaryotes.
Cell division in eukaryotic cells is more complex. The DNA of eukaryotes is distributed among many chromosomes and the chromosomes are contained within the nucleus. The chromosomes must be replicated and then organized in a way that ensures that each of the daughter cells receives one copy of each chromosome. The process of organizing and distributing chromosomes is called **mitosis**.

Humans have 46 chromosomes, that carry approximately 25,000 genes. If mitosis happens properly, each daughter cell gets one copy of each chromosome.
Before DNA replication, a chromosome consists of one continuous double stranded DNA molecule.

After replication, each chromosome consists of two double stranded DNA molecules attached at a single point - the **centromere**.

Each of the double stranded DNA molecules is an exact copy of the other. Each of the copies is called a **chromatid**.

Each of the 46 chromosomes of humans has a centromere. The centromere can be located in a central position, a terminal position, or somewhere in between.

- **Metacentric**
- **Submetacentric**
- **Acrocentric**
- **Telocentric**

Chromosome size also varies greatly.
Most organisms have between 10 and 100 chromosomes in their cells. There is no relationship between chromosome number and evolutionary progress.

<table>
<thead>
<tr>
<th>Group</th>
<th>Total Number of Chromosomes</th>
<th>Group</th>
<th>Total Number of Chromosomes</th>
<th>Group</th>
<th>Total Number of Chromosomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>FUNGI</td>
<td></td>
<td>PLANTS</td>
<td></td>
<td>VERTEBRATES</td>
<td></td>
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<tr>
<td>Neurospora (yeast)</td>
<td>7</td>
<td>Hop baptis</td>
<td>3</td>
<td>Orpiment</td>
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<td>Saccharomyces (yeast)</td>
<td>16</td>
<td>Garden pea</td>
<td>14</td>
<td>Frog</td>
<td>26</td>
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<tr>
<td>INSECTS</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mosquito</td>
<td>6</td>
<td>Bread wheat</td>
<td>42</td>
<td>Human</td>
<td>46</td>
</tr>
<tr>
<td>Drosophila</td>
<td>8</td>
<td>Sugar cane</td>
<td>80</td>
<td>Chimpanzee</td>
<td>98</td>
</tr>
<tr>
<td>Honeybee</td>
<td>17</td>
<td>Horse tail</td>
<td>316</td>
<td>Horse</td>
<td>64</td>
</tr>
<tr>
<td>Silkworm</td>
<td>36</td>
<td>Adder's tongue fern</td>
<td>1262</td>
<td>Chicken</td>
<td>70</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Dog</td>
<td>70</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Cell division in eukaryotes can be viewed as part of a larger process in the life of a cell - the **cell cycle**. In the cell cycle, cells are either dividing or preparing to divide.

- **G₁** - (first gap) - normal growth and metabolism
- **S** - synthesis of DNA
- **G₂** - (second gap) - normal growth and metabolism and replication of organelles - spindle fiber formation begins

**G₁, S, and G₂** are collectively called **interphase**.
M - mitosis - chromosomes are organized and chromatids are moved to opposite sides of the cell.

Mitosis has 4 named phases - **prophase**, **metaphase**, **anaphase**, and **telophase**.

C - cytokinesis - the division of the cell into two cells.

The entire cell cycle can be very short in some cells - especially in early embryos where cells are large and divide to produce smaller and smaller cells - or it may take years for a single cell to grow to a sufficient size to allow it to divide.

Some cells enter a resting stage - called **$G_0$** - where they don’t grow and aren’t preparing for another cell division. Most cells in the human body are in **$G_0$**. Some can reenter **$G_1$** to prepare for cell division, but some, like nerve and muscle cells, never do.
Mitosis
Cells leave $G_2$ and enter mitosis with their chromosomes in a replicated state. During interphase the chromosomes are not tightly coiled - they exist as chromatin fibers.

During prophase - chromosomes condense, the spindle fibers form, nuclear membrane disintegrates, and the spindle fibers attach to either side of each centromere.

Spindle fibers (microtubules) attach to the **kinetochore** which is part of the centromere.

Each chromatid has a kinetochore.

After the spindle fibers attach the kinetochores begin shortening of the microtubules. This positions the chromosomes in the center of the cell.
During metaphase, the chromosomes are aligned at the equator of the cell - at the **metaphase plate.**
Anaphase begins with division of the centromeres. Sister chromatids are pulled to opposite poles of the cells.

Kinetochore microtubules depolymerize microtubules to shorten them. This moves the chromosomes.

Telophase - chromosomes arrive at the poles of the cell, a nuclear membrane forms around them, chromosomes decondense.
In plant cells, a cell plate forms between the two nuclei, creating two daughter cells.

In animal cells, the cell membrane constricts between the poles, creating two daughter cells.
The end product of mitosis and cytokinesis is two daughter cells each with an exact copy of the DNA that was in the original parent cell. These cells can enter $G_1$ and begin the process again.

With the exception of sperm and egg cells, all the cells in any multicellular eukaryote are produced by mitosis. All possess all the genetic information contained in the original cell from which they came.

Cells in some tissues (e.g. skin) go through the cell cycle twice each day. Others may cycle on a monthly basis. Other cells may be in an indefinite $G_0$ stage and will never divide again.

How is cell division regulated?
Control of the Cell Cycle

Not all cells grow and divide at the same pace. Cells decide to proceed to the next stage in the cell cycle by assessing their state at three different checkpoints in the cell cycle.

**G₁/S checkpoint** - a cell assesses its size and nutritional state. If it can support cell division it proceeds to S.

**G₂/M checkpoint** - at the end the cell assesses the DNA synthesis. If OK, it proceeds to Mitosis.

**M (Spindle) checkpoint** - during metaphase the cell assesses the alignment of chromosomes. If OK, it proceeds to cytokinesis.

In single celled organisms the prime determiner of advance past the G₁ checkpoint is cell size and nutritional state.

In multicellular organisms, a growth factor or combination of growth factors present at the G₁ checkpoint signals the cell to proceed to S if size and nutrition are sufficient.

<table>
<thead>
<tr>
<th>Growth Factor</th>
<th>Range of Specificity</th>
<th>Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epidermal growth factor (EGF)</td>
<td>Broad</td>
<td>Stimulates cell proliferation in many tissues; plays a key role in regulating embryonic development;</td>
</tr>
<tr>
<td>Erythropoietin</td>
<td>Narrow/Permissive</td>
<td>Required for proliferation of red blood cell precursors and their maturation into erythrocytes (red blood cells);</td>
</tr>
<tr>
<td>Epidermal growth factor (EGF)</td>
<td>Broad</td>
<td>Induces the production of many cell types; inhibits immunoregulation of many types of immune cells; acts as a signal for embryonic development;</td>
</tr>
<tr>
<td>Inhibitors-like growth factor</td>
<td>Broad</td>
<td>Stimulates proliferation of many cell types; promotes the effects of other growth factors in promoting cell proliferation;</td>
</tr>
<tr>
<td>Interleukin 2 (IL-2)</td>
<td>Narrow/Permissive</td>
<td>Triggers the division of activated T lymphocytes; starts the immune response;</td>
</tr>
<tr>
<td>Mitogens-priming factor (MIF)</td>
<td>Broad</td>
<td>Enhances entrance of the cell cycle into the M phase;</td>
</tr>
<tr>
<td>Neurotrophic growth factor (NGF)</td>
<td>Narrow/Permissive</td>
<td>Stimulates the growth of neuron processes during neural development;</td>
</tr>
<tr>
<td>Platelet-derived growth factor (PDGF)</td>
<td>Broad</td>
<td>Promotes the proliferation of many connective tissues and some non-dividing cells;</td>
</tr>
<tr>
<td>Transforming growth factor b (TGF-b)</td>
<td>Broad</td>
<td>Accretes or inhibits the responses of many cell types to other growth factors; plays an important role in cell differentiation</td>
</tr>
</tbody>
</table>
Mammalian cells grown in tissue culture will multiply to form a layer one cell thick and then stop dividing.

If a group of cells is removed from the culture, the surrounding cells begin dividing and fill in the gap created and then stop.

How do they know when and when not to grow?

The cells in the tissue culture are constantly producing small amounts of growth factor. Each cell and its neighbors are also constantly taking up growth factor and breaking it down. Cells will only grow if the concentration of growth factor exceeds a threshold amount. It only does so when there is a gap in the cells, where the growth factor can accumulate.

After the cells fill the gap, all growth factor produced is degraded by neighboring cells and further growth stops.
Cancer is the uncontrolled growth of cells. Uncontrolled cell growth consumes resources needed by noncancerous cells. When this occurs noncancerous cells die and are replaced by cancerous cells that continue to grow unchecked.

Cancerous cells in culture do not stop growing once they cover the surface of the growth medium.

Cancerous growth can be caused by
- growth in the absence of a normally required growth factor
- excessive production of the growth factor by cells
- lack of a growth inhibitor

All conditions that lead to cancer are ultimately the product of a gene that is not functioning normally. Genes can fail to function normally if they are damaged - if they mutate.

Genes that have mutated and as a result cause cancerous growth are called oncogenes. Genes that have not mutated, but that can mutate to become oncogenes are called proto-oncogenes. Most proto-oncogenes have important functions in the development or maintenance of tissues.

Cancer is a genetic disease caused by mutations. Mutations are caused by many things. Some chemicals are powerful agents of mutation.
Cancer usually develops after many mutations have accumulated in cells.

**Mutations Commonly Leading to Colorectal Cancer**

<table>
<thead>
<tr>
<th>MUTATED GENE</th>
<th>Oncogene</th>
<th>Tumor suppressor</th>
</tr>
</thead>
<tbody>
<tr>
<td>APC</td>
<td>K-ras</td>
<td>DCC</td>
</tr>
<tr>
<td>Loss of APC</td>
<td>Mutation of K-ras and DCC</td>
<td>Mutation of p53</td>
</tr>
<tr>
<td>Normal epithelium</td>
<td>Early benign polyp</td>
<td>Late benign polyp</td>
</tr>
<tr>
<td>Hyperproliferative epithelium</td>
<td>Intermediate benign polyp</td>
<td>Carcinoma</td>
</tr>
<tr>
<td>Other mutations</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Mutations in cells accumulate over time. The incidence of cancer increases with age.
Q: What causes cancer?
   a. Everything causes cancer
   b. Cancer is unavoidable
   c. Inherited genetic problems
   d. Anything that causes mutations

Smoking causes cancer.

Lung cancer was a very rare disease before cigarette smoking became common.
Lung cancer is still a **very rare disease** among **non-smokers**.

Pollution, in air, water, and food, causes cancer.

**Potential Carcinogen — Pollution**

- Above U.S. average
- Highest cancer rates
High consumption of red meat (as in US) causes cancer.

How are cancer causing substances discovered?
By their ability to cause mutations. The Ames test is the standard test of a substance’s ability to cause mutation.

Any substance that causes mutation (a **mutagen** in bacteria is labeled as cancer causing (a **carcinogen**).
The list is large, but not everything causes cancer.

Cancer may not be completely avoidable, and some people seem to have greater genetic predispositions to developing cancer, but for most people, reduced exposure to mutagens reduces the risk of cancer.