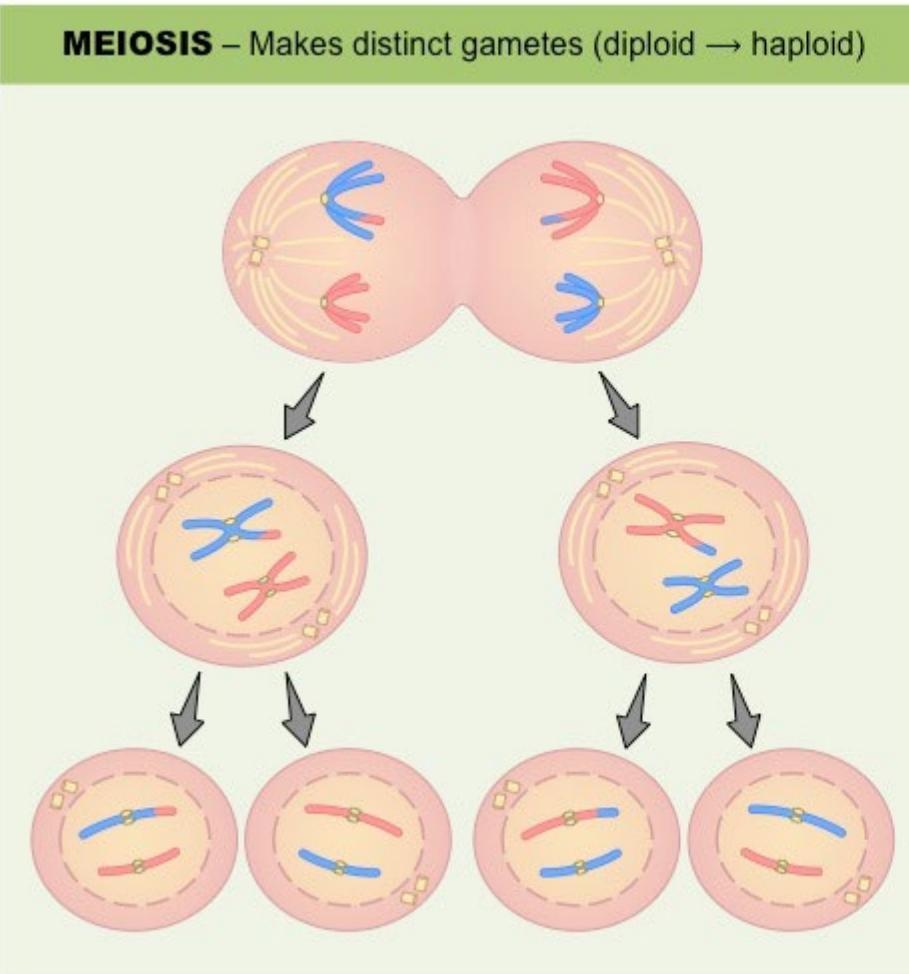


Chapter 4.1

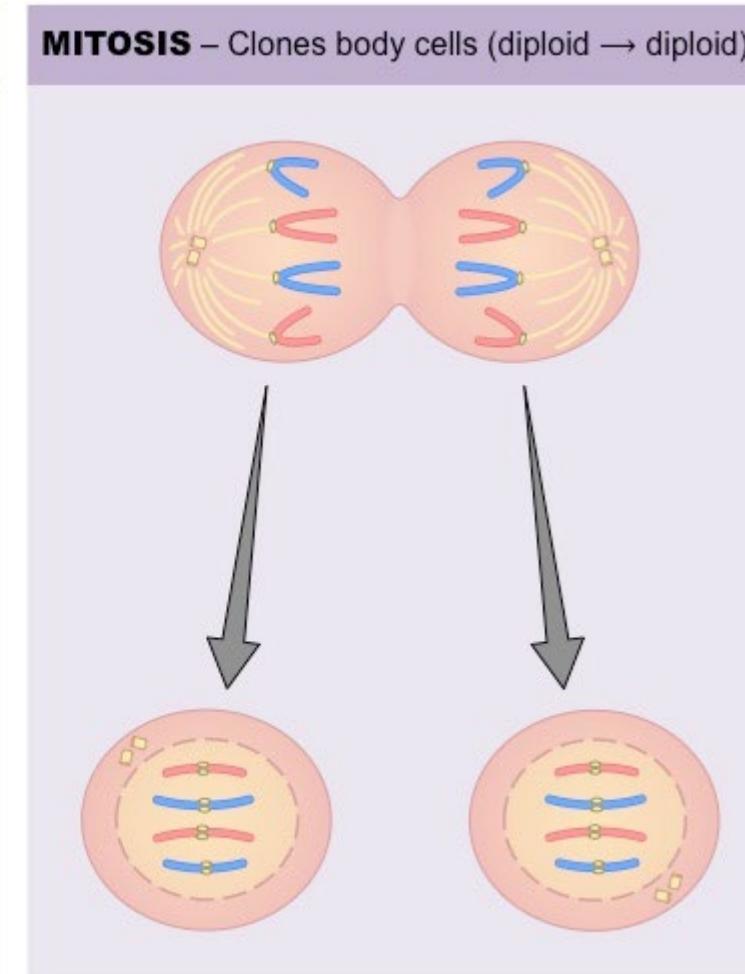
Cell Division – The Cell Cycle - DNA Replication



There are two types of cell division in human physiology.



46 chromosomes to 23 chromosomes



46 chromosomes to 46 chromosomes

About Mitosis

Mitosis: conserves chromosome number (humans = 46)

Mitosis takes place inside the nucleus

Human “somatic cells” divide by mitosis (e.g. skin & liver)

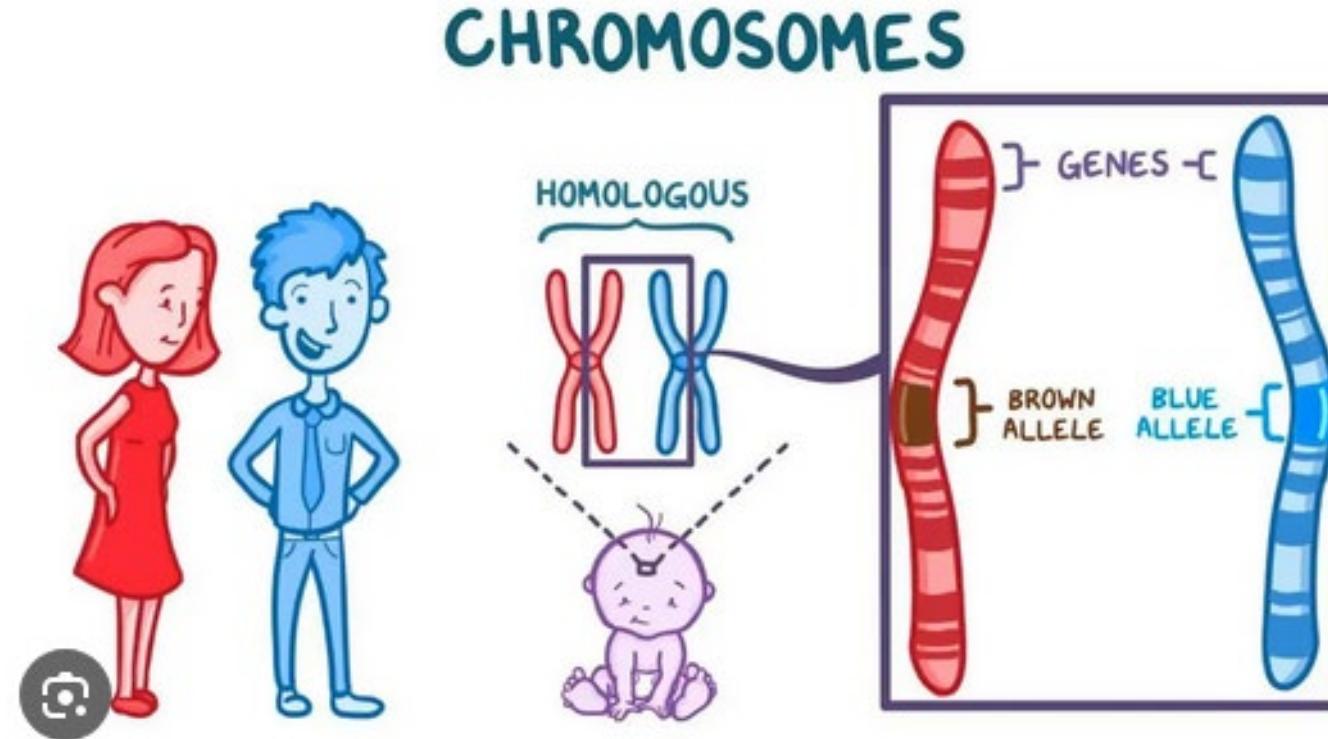
Somatic cells are called “diploid cells” /// 46 chromosomes

Humans have 23 pairs of chromosomes /// total of 46 chromosomes (23 from mother & 23 from father)

Each “chromosome pair” will have a similar gene in the same location on the chromosome

- Two genes for each type of protein
- One gene is recessive, and the other gene is dominate.
- This is called an allele pair

"Allele" is the word that we use to describe the alternative form or versions of a gene. People inherit one allele for each autosomal gene from each parent, and we tend to lump the alleles into categories.. Humans are diploid, meaning they have two alleles for each gene at a given genetic locus (one from each parent).

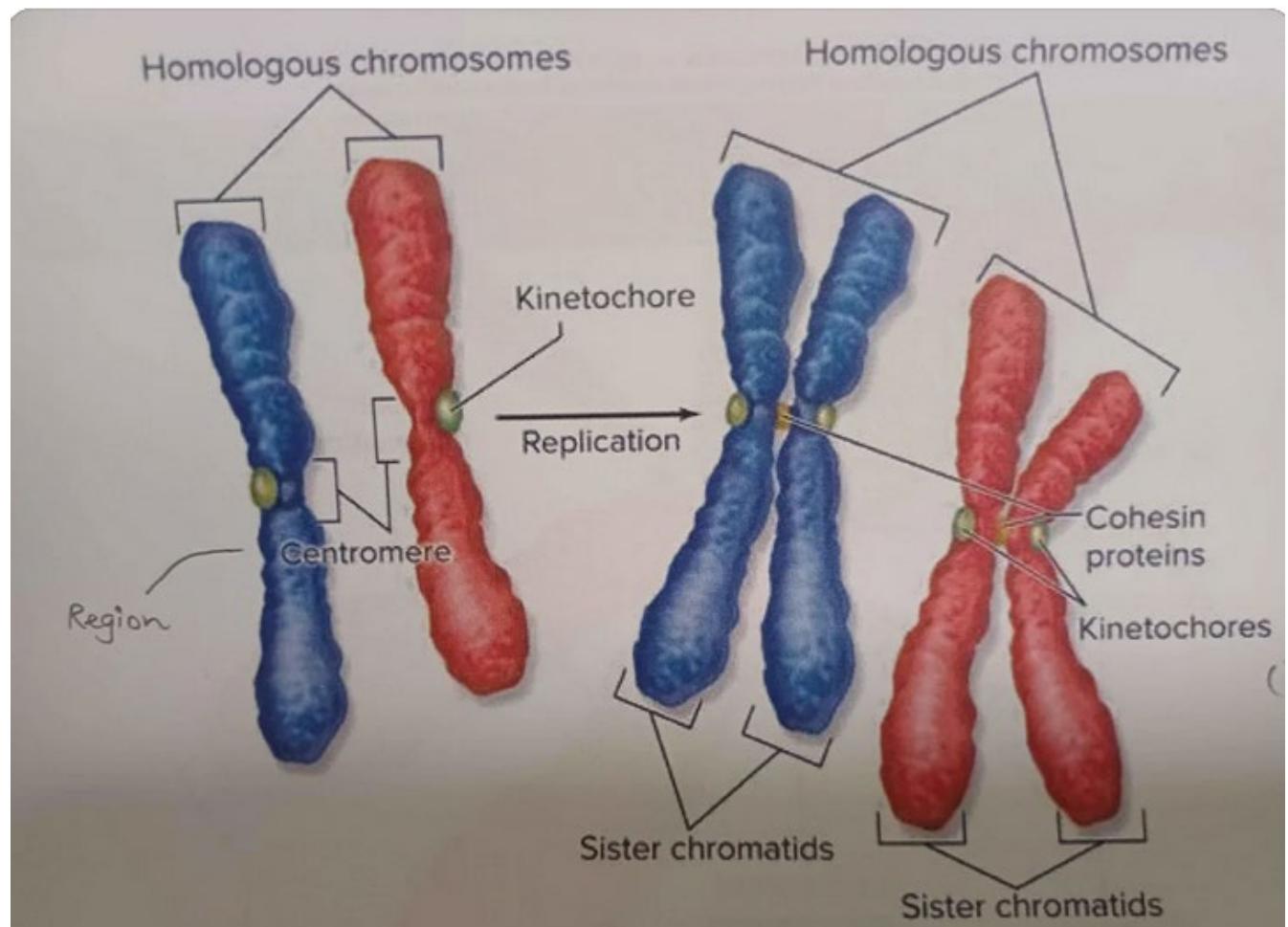


In mitosis, two similar chromosomes are called homologous chromosomes (they code for same genes/proteins). A “father-mother pair” of the same chromosome are called homologous. If one chromosome makes a copy of itself and is joined by a centromere, then this too is called a homologous chromosome. Each strand of this joined homologous chromosome is called a sister chromatid.

A chromosome is the entire structure containing genetic material, while a chromatid is one of the two identical copies of a replicated chromosome that are joined together at a centromere before cell division.

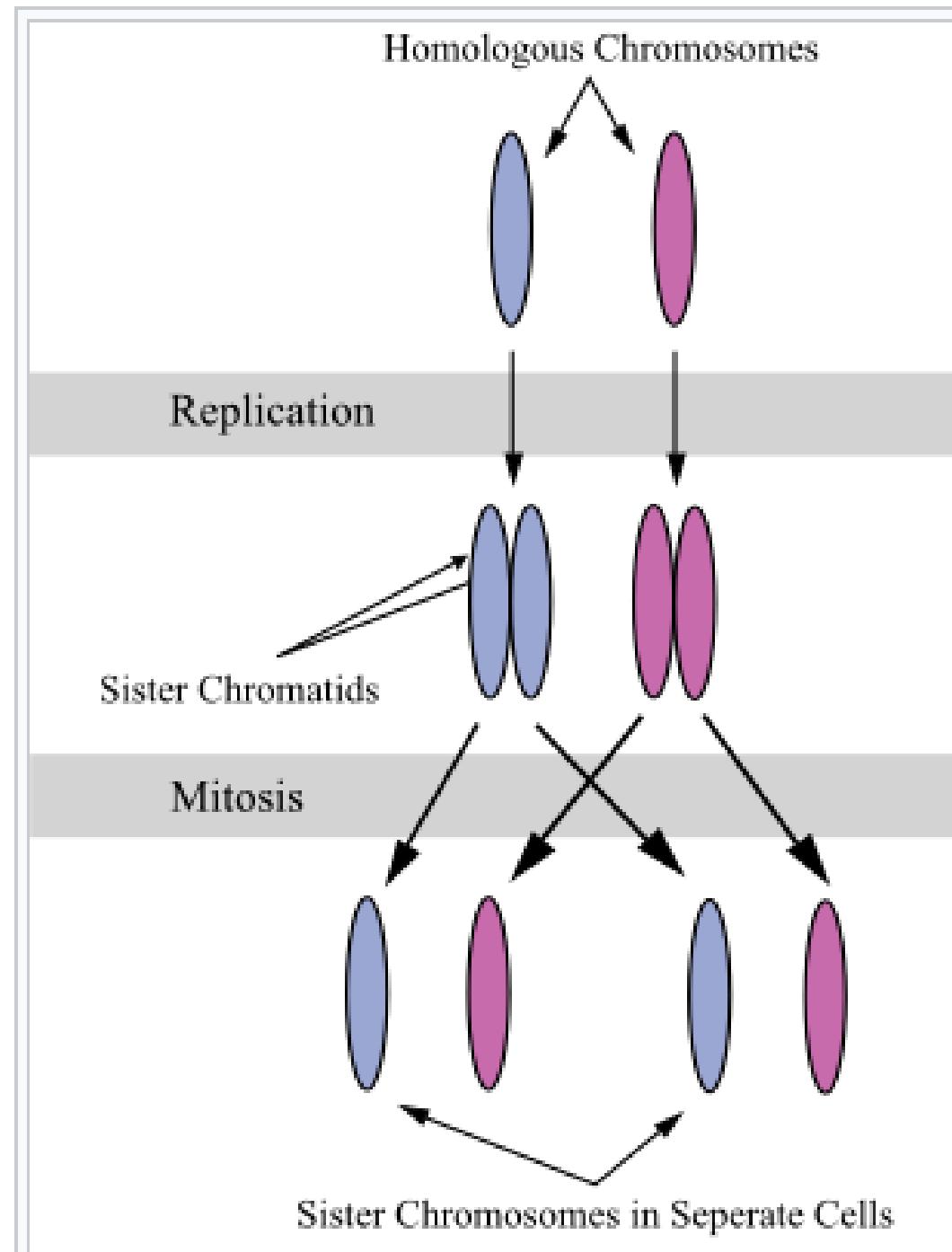
Think of it this way: a chromosome is the complete "X" shape, and each arm of the X is a single chromatid. After cell division, the two sister chromatids separate and become individual, single-chromatid chromosomes in the new daughter cells.

In mitosis, you replicate 46 chromosomes to make 92 sister chromatids then divide them by half to make two new cells. Each new cell has 46 chromosomes.



Sister chromatids are two identical copies of a single, replicated chromosome, joined together at the centromere by a common protein called cohesion.

They are **formed during the S phase of the cell cycle** when a chromosome replicates its DNA. During mitosis cell division, sister chromatids separate and move to opposite ends of the cell, ensuring that each daughter cell receives a complete and identical set of genetic material.



Human Karyotype

Humans Have
46 Chromosomes

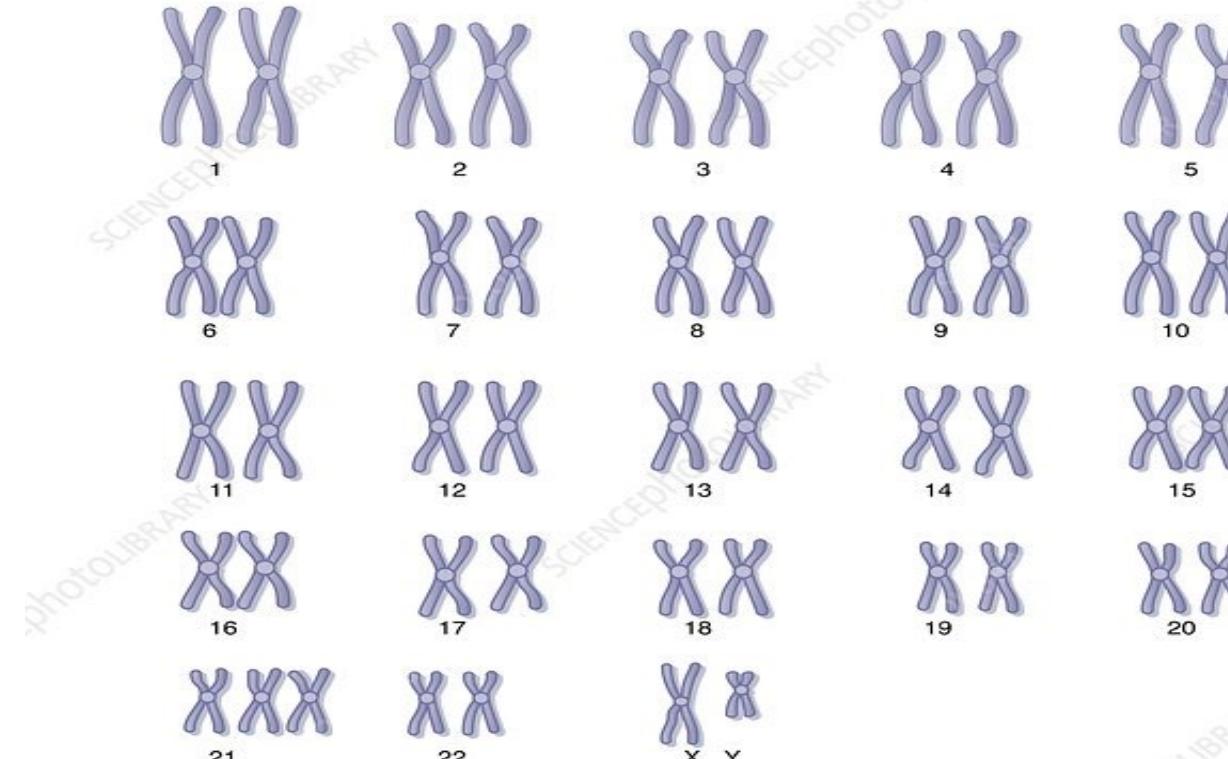
23 Pairs

One Chromosome From
the Father and One
From Mother



Typical karyotype from a somatic cell. Twenty-two **autosome chromosomes** and one pair of **sex chromosomes**

Male Down's Syndrome



Genetic disease caused by an extra chromosome #21.

About Meiosis

Meiosis: cell division that reduces chromosome number by $\frac{1}{2}$

Human gonadal tissue produce gametes by meiosis (**testes produce sperm and ovaries produce eggs**)

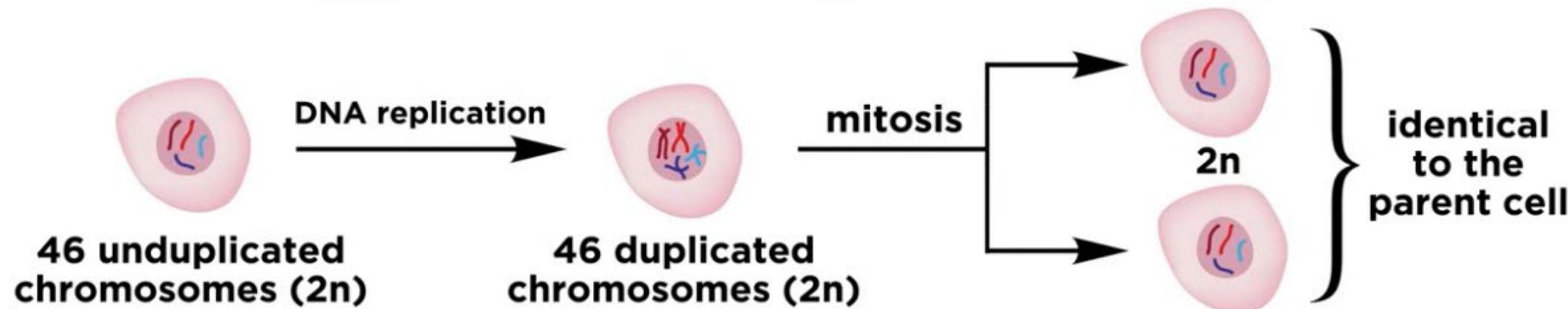
The gametes are **“haploid cells”** (somatic cells are diploid)

Haploid cells have 23 chromosomes

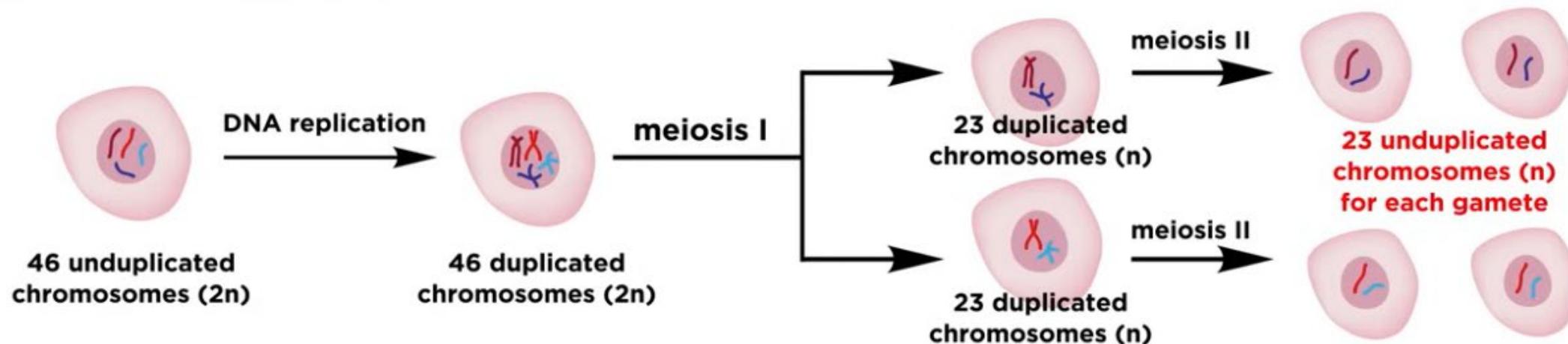
An egg and a sperm combine their chromosomes to create a new diploid cell called the zygote

Everybody start life as a **zygote (a single diploid cell)**

Mitosis Produces Diploid Cells (2n)

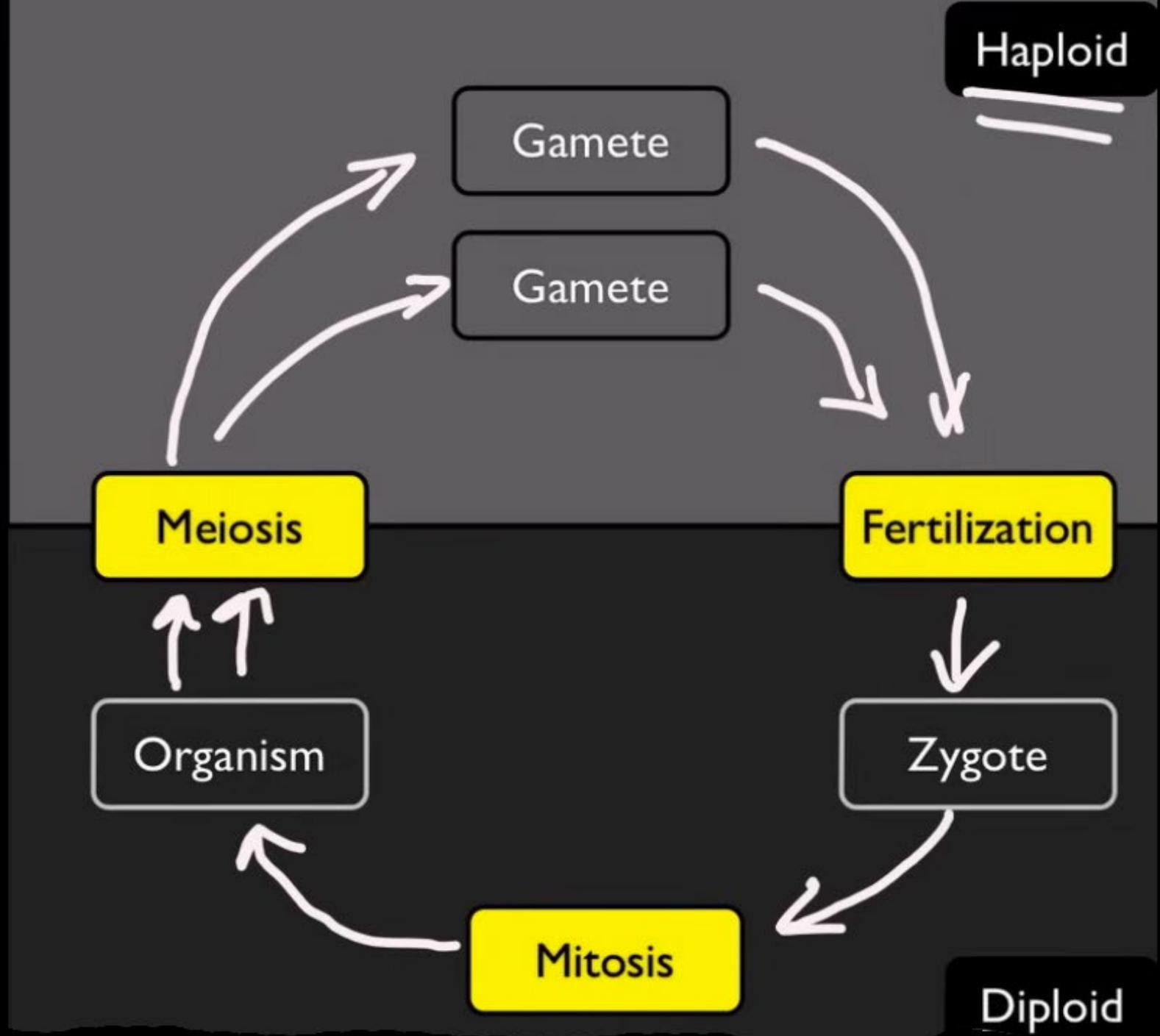


Meiosis Produces Haploid Cells (n)



We will look at the different phases of mitosis and meiosis after a review of the mitotic cell cycle. During meiosis, the cell cycle is repeated twice.

Human Life Cycle





The life of a cell is broken into two phases. In the first phase, the cell carries out the functions predetermined by its genes.

The second phase occurs when the cell prepares to divide to make two identical new cells.

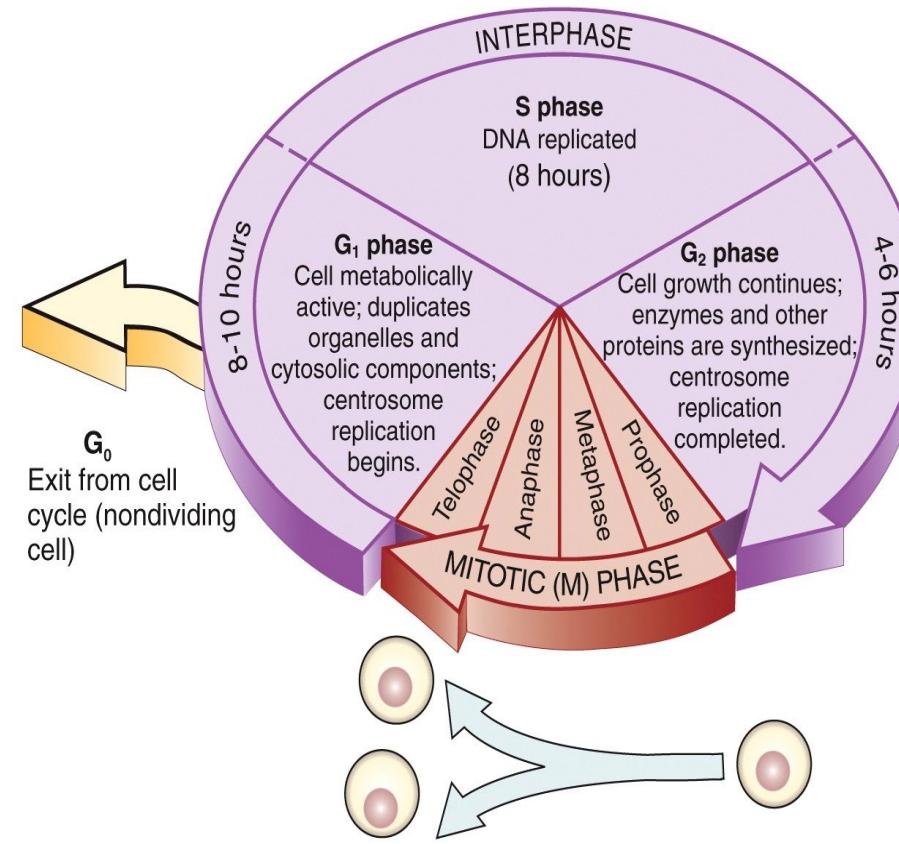
The two phases are called:

- Interphase (first phase)
- mitotic phase (second phase)

Each phase is divided into sub-phases

During interphase, the cell is performing its programmed functions (e.g. make proteins)

Mitosis Cell Cycle



A typical human cell might take about 24 hours to divide, but fast-cycling mammalian cells, like the ones that line the intestine, can complete a cycle every 9-10 hours when they're grown in culture

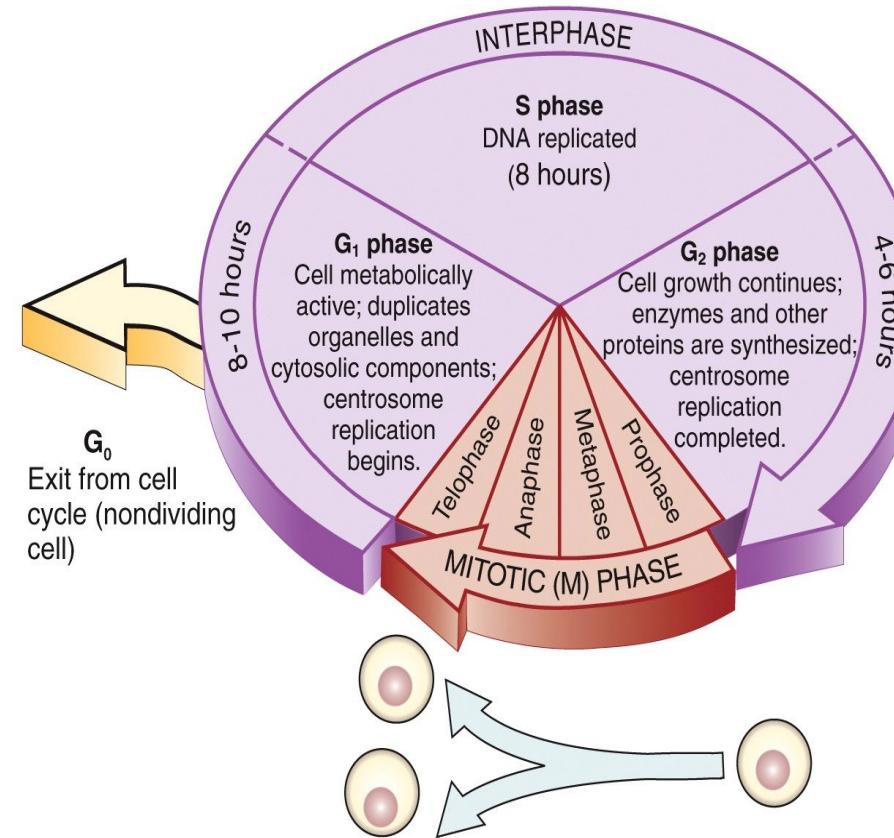
Mitosis Cell Cycle

During embryonic development, different genes are turned on and off to determine what the mature cell will become and what the cell will do.

For example, some epithelial cells become skin tissue and other epithelial cells become liver tissue.

The cell enters the mitotic phase when the cell is ready to form two identical cells.

At the end of the mitotic phase, each new cell will have a nucleus and half of the original cell's organelles and cytoplasm.



A typical human cell might take about 24 hours to divide, but fast-cycling mammalian cells, like the ones that line the intestine, can complete a cycle every 9-10 hours when they're grown in culture

Interphase is divided into three sub-phases /// During interphase the cell will double its nucleic acid content (DNA)

G₁ phase, the first gap phase

Newly formed daughter cells lack sufficient cytoplasm

Make more organelles and cytoplasm as well as nucleotides needed to replicate DNA in S phase

S phase, synthesis phase

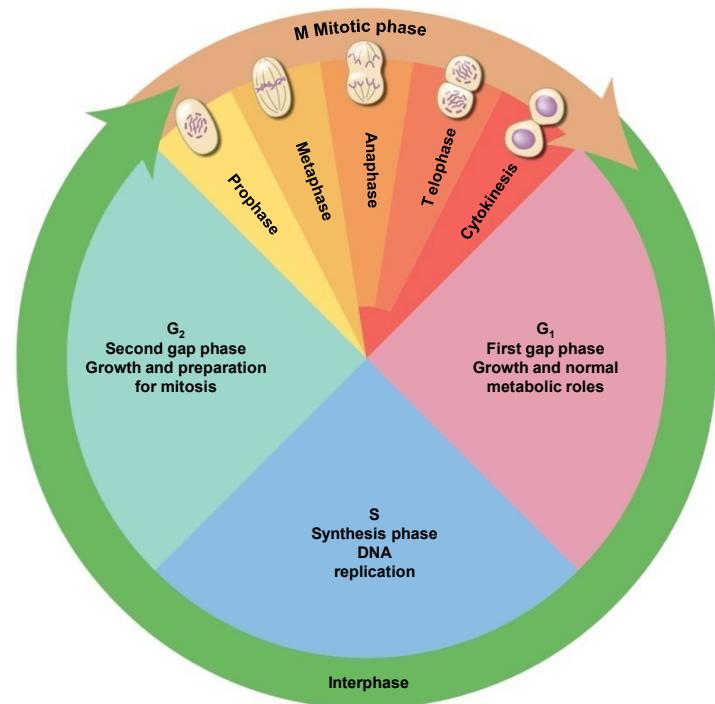
Duplicates centrioles
DNA replication occurs

G₂ phase, second gap phase

Interval between DNA replication and cell division
Finishes centriole duplication

Synthesizes enzymes that control cell division // and repairs DNA replication errors

Mitosis Cell Cycle



G Zero phase

Cell leave the cell cycle to “rest” / temporary pause
Skeletal muscle and almost all nerve cells are examples of cells in G zero

M phase = Mitotic Phase

Mitosis Cell Cycle

At end of M phase, original cell creates two new nuclei, each with 46 chromosomes

Before entering the M Phase, a cell must double its DNA so each daughter cell at the end of M Phase will receive the same number of chromosomes as the parent cell

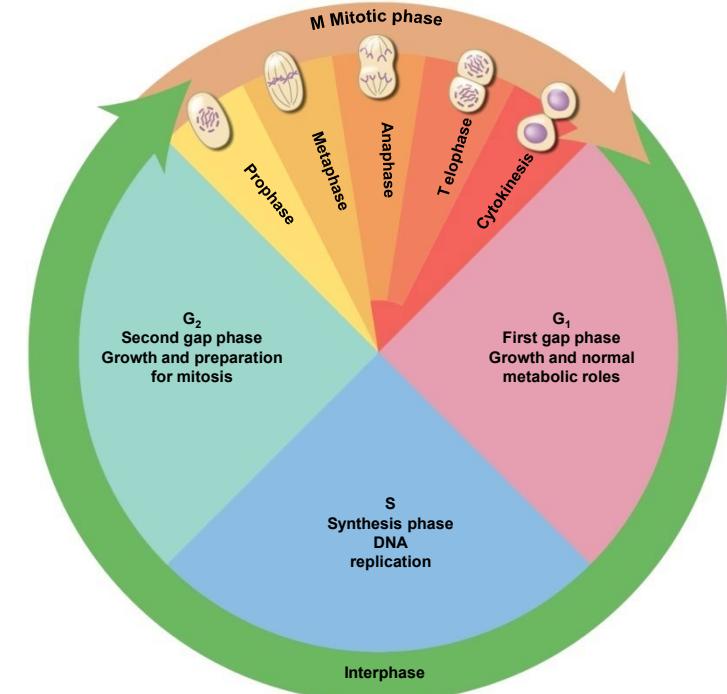
After DNA is duplicated the cell pinches in two to form two new daughter cells

Interphase Major Events

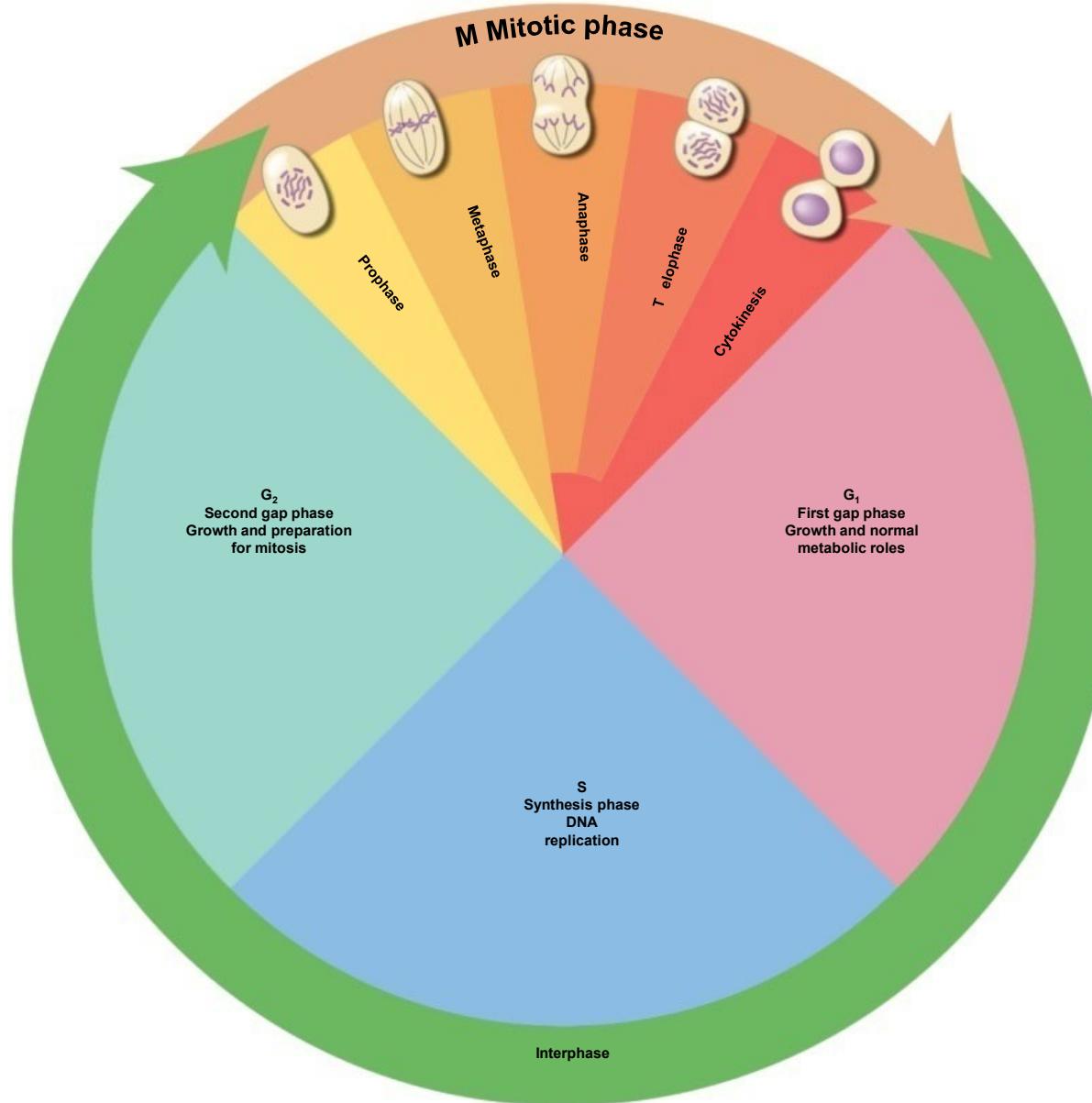
G1, S, and G2 phases

S phase is when a copy of the original DNA is made

Cell cycle duration varies between cell types



Mitosis Cell Cycle



DNA Replication

Before a cell divides by mitosis, the **cell must double the DNA** (the genetic material / the chromosomes) - this occurs in the S Phase of interphase

All 46 **chromosomes** are copied. (46 chromosomes now become 92 sister chromatids.).

During interphase – DNA is an **uncoiled strand** of nucleic acid called **chromatin**. In this form, genes are exposed and may be transcribed.

DNA is **tightly coiled** during the mitotic phase, and the nucleic acids are visible. Now the DNA are called **chromosomes**

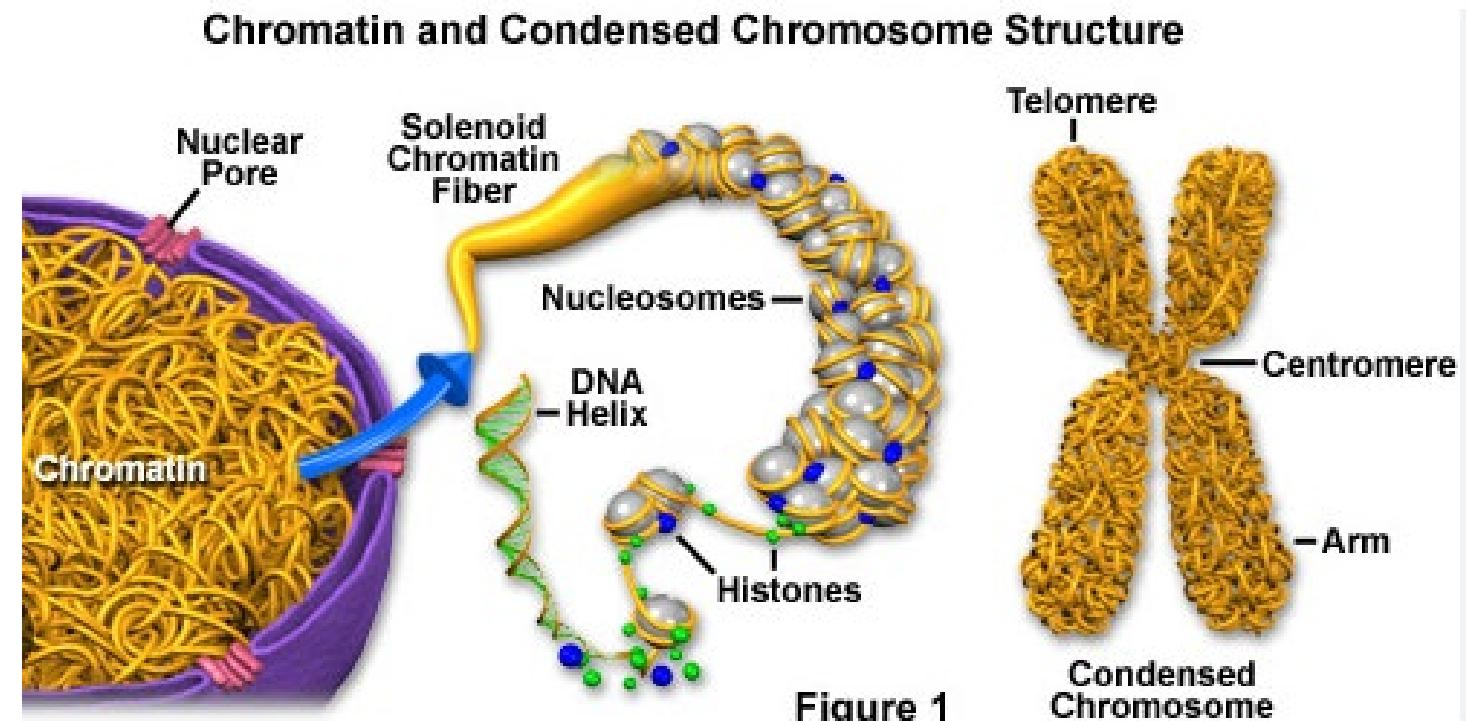


Figure 1

Single chromosome with two sister chromatids

At the end of interphase, the parent cell (i.e. the original cell) has now doubled its DNA (92) /// now the parent cell can give each new cell (the daughter cell) a complete copy of DNA (46 chromosomes)

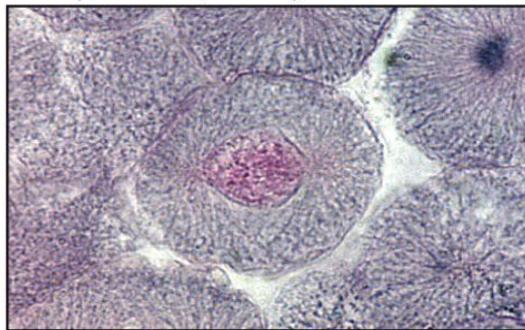
$46 \times 2 = 92$ (or 46 identical chromosomal pairs)

Since DNA controls all cellular function, this replication process must be very exact – no mistakes in duplication process /// a mistake = a mutation

The chromosome's genes are “recipes” for making protein. A gene is a segment on the DNA strand. Proteins may be structural (e.g. hair) or functional (e.g. enzymes).

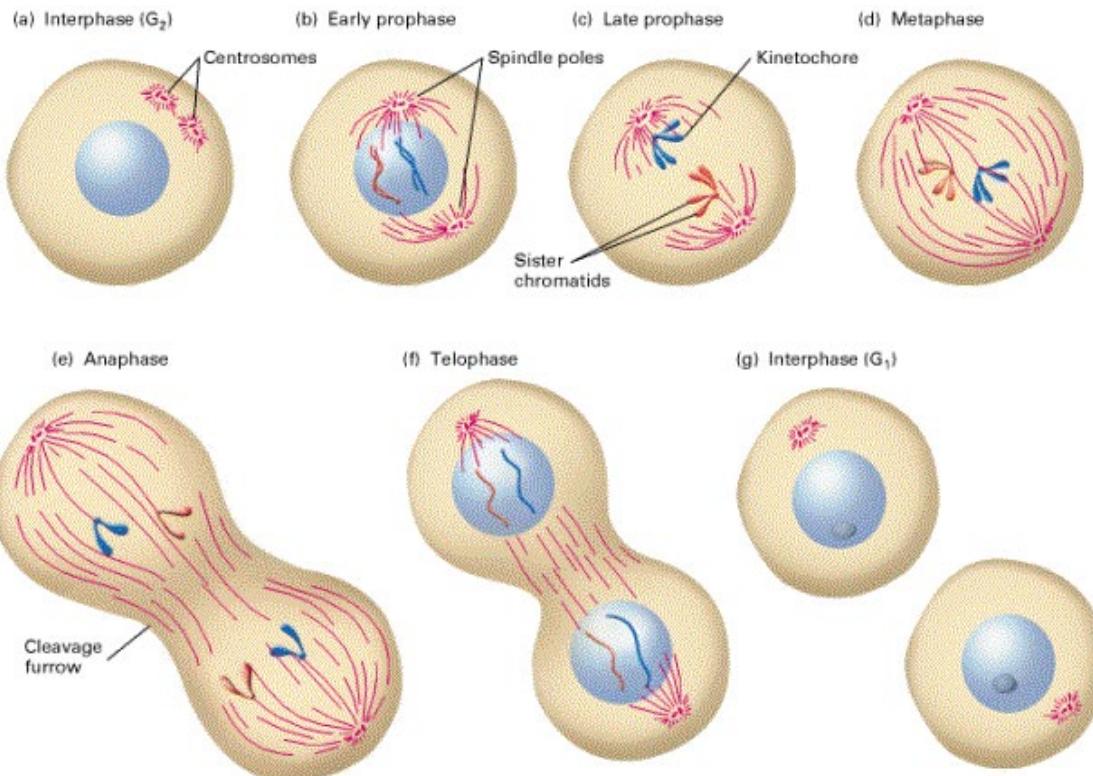
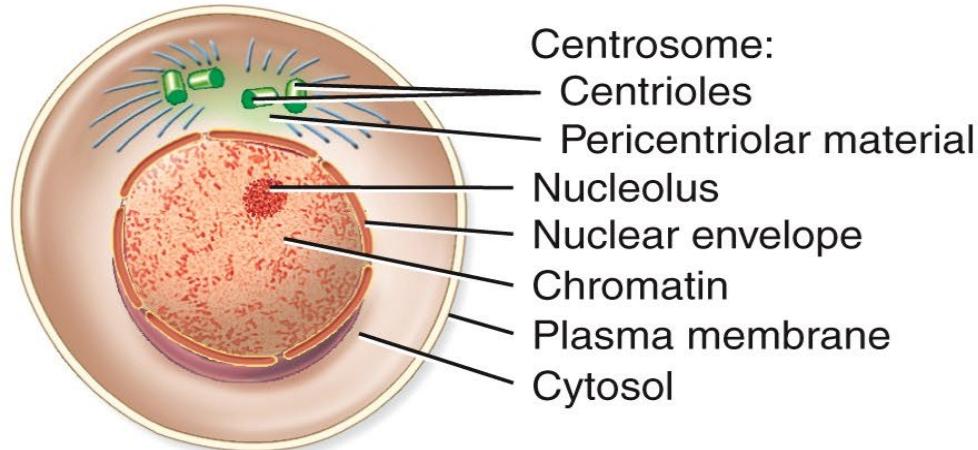
We have 19,900 genes. We have two copies for each gene, one from our father and one from our mother. These are called an allele pair.

Courtesy Michael Ross, University of Florida



LM all at 700x

(a) INTERPHASE



Chromatin condenses to form chromosomes. In a condense state, the nucleic acid strands are visible. This occurs only in the mitotic phase.

During interphase, the DNA is diffused, not visible, and called chromatin.

Cytokinesis

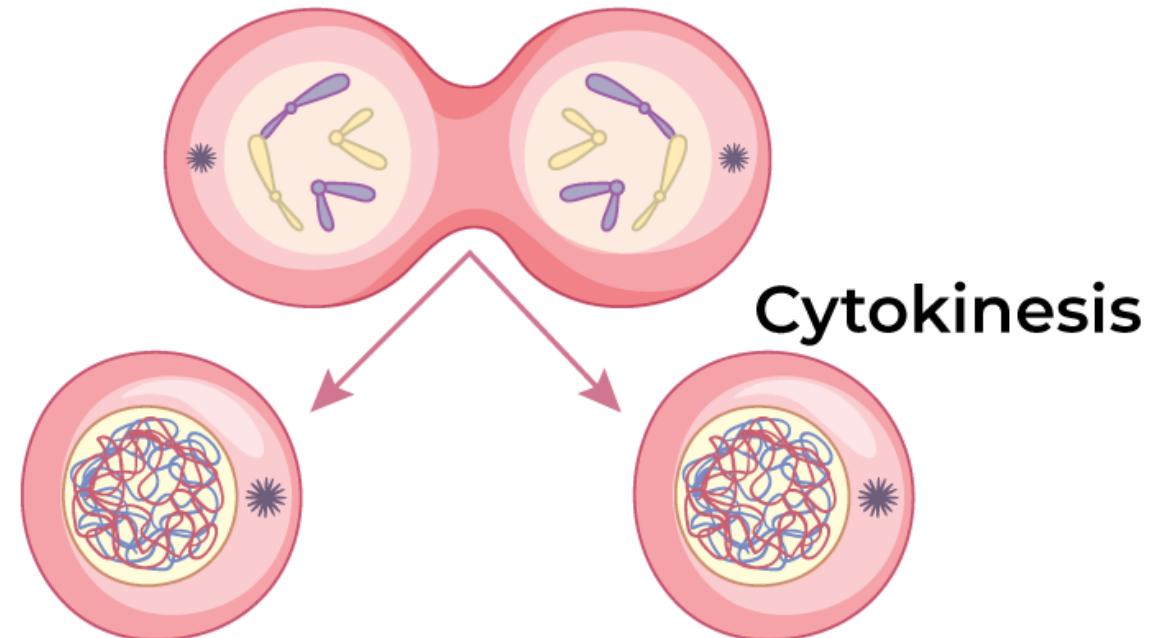
Cytokinesis divides the cytoplasm between the two new cells at the end of the mitotic phase

Creates the **cleavage furrow** around the equator of cell

Telophase is the end of mitosis but overlaps with cytokinesis

Early traces of cytokinesis visible in anaphase

Achieved by motor protein (myosin) pulling on microfilaments of actin in the terminal web of cytoskeleton // Cell eventually pinches in two



Timing of Cell Division

When may cells divide by mitosis?

If they have enough cytoplasm for two daughter cells

If they have doubled their DNA (made complete copy of all chromosomes).

If they have adequate supply of nutrients

If they are stimulated by growth factor

Chemical signals secreted by blood platelets, kidney cells, and other sources

If neighboring cells die. This opens up space in the tissue for new cells and prevents contact inhibition.

What will inhibit mitosis?

When nutrients are not available

Lack of growth factor secreted by cells in region.

Contact Inhibition

The cessation of cell division in response to contact with other cells

If existing cells are too closely packed with neighboring cell, then there is no room for new cells

The Two Laws That Make Accurate DNA Replication Possible

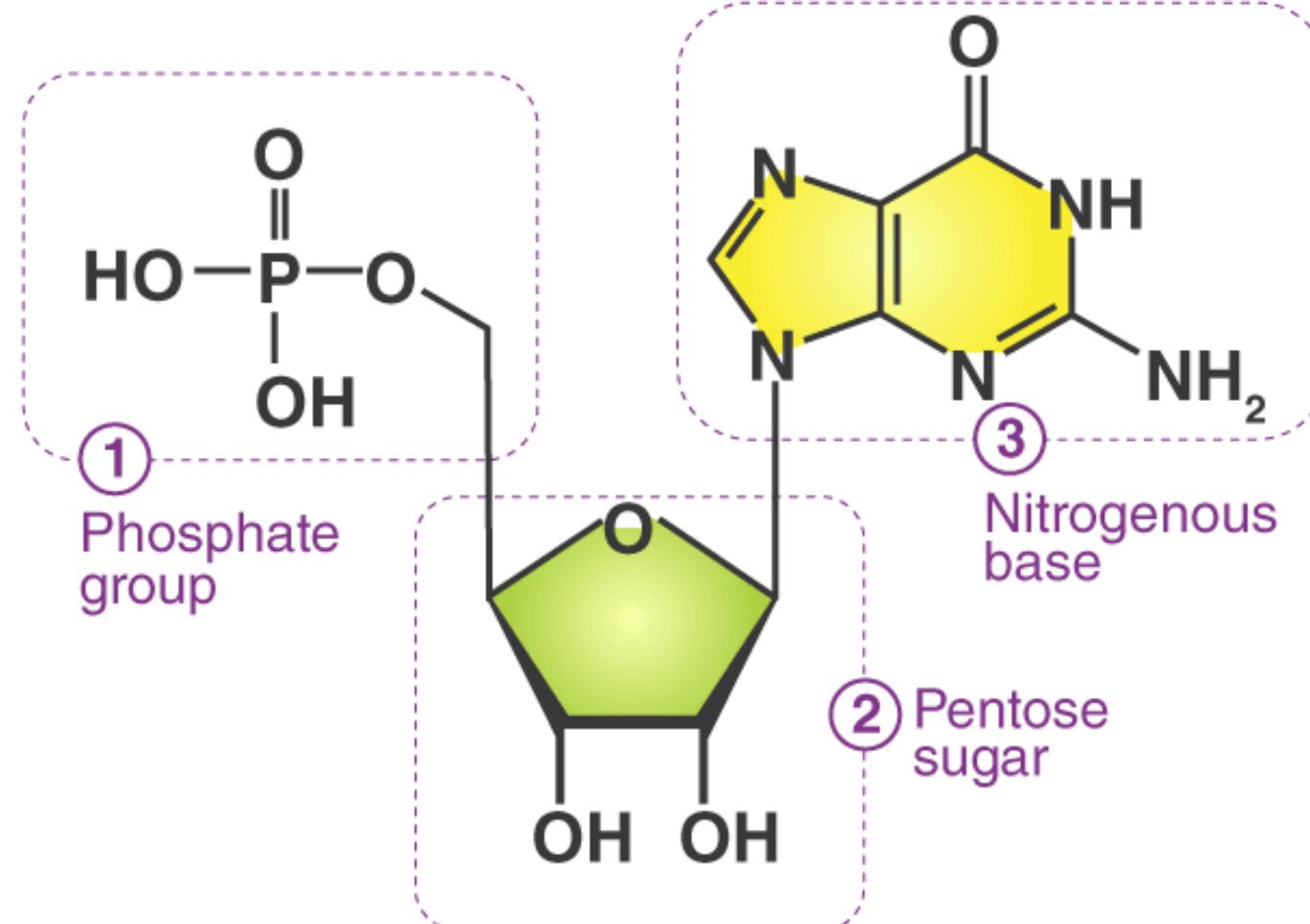
Law of Complementary Base Pairing

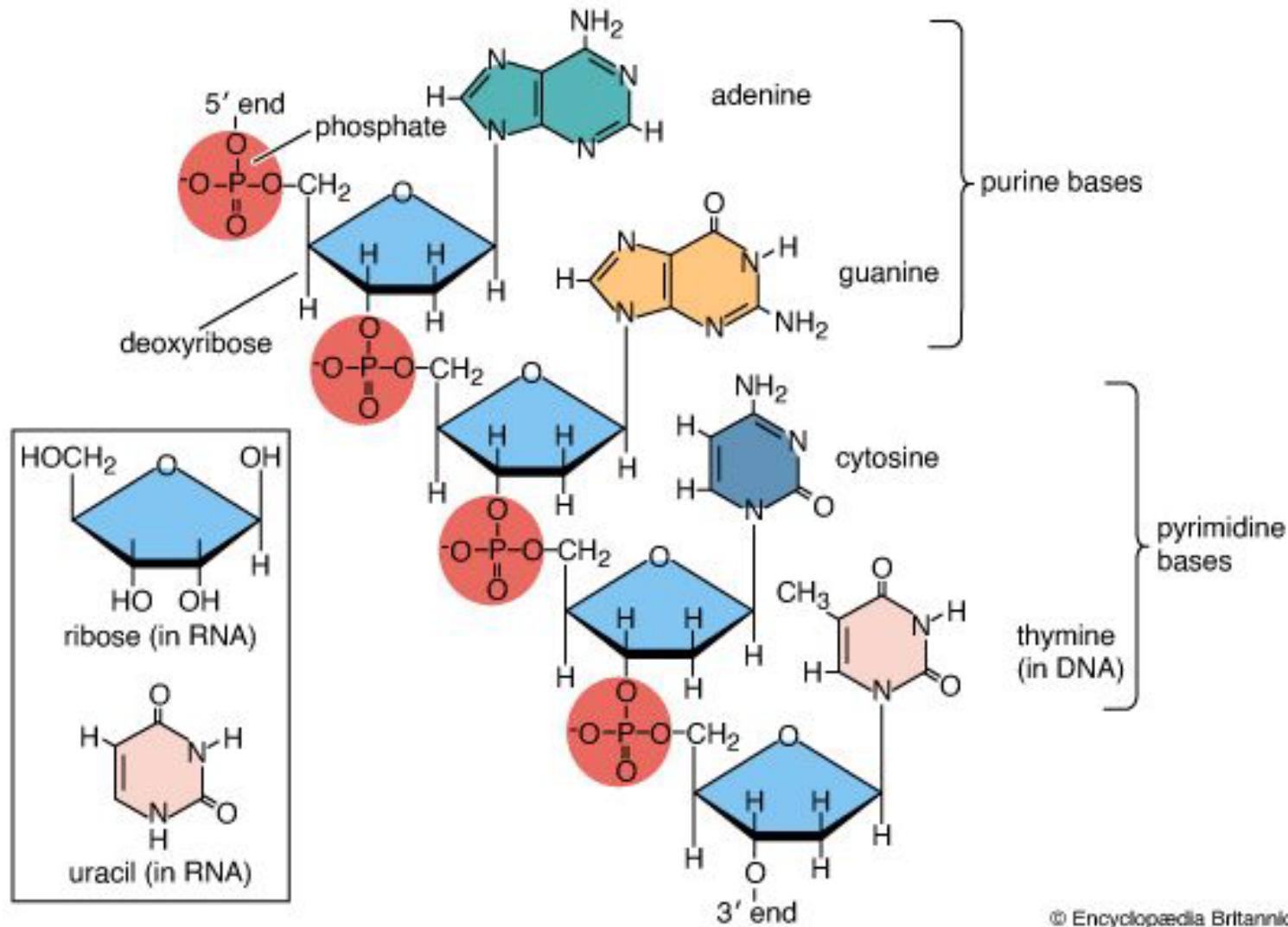
Ability to predict the base sequence of a new DNA strand by using the sequence of the original strand

Law of Semi-Conservative Replication

A duplicated DNA molecule will have one side of the double helix with the original DNA molecule, and the other side of the double helix will be made from new nucleotides.

NUCLEOTIDE



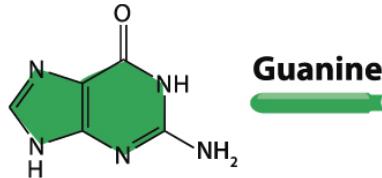
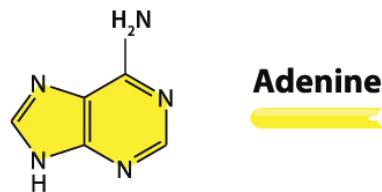
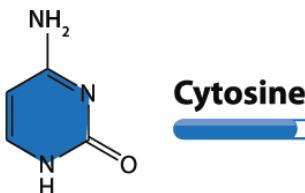
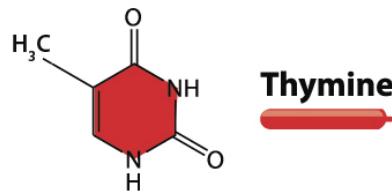


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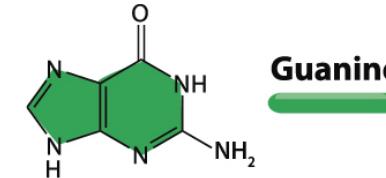
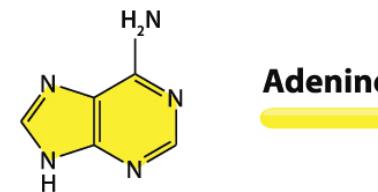
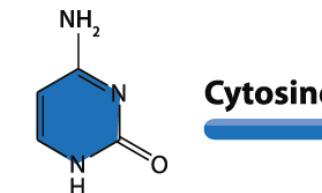
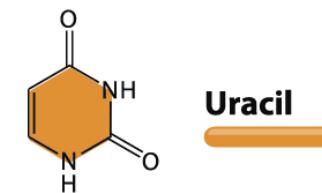
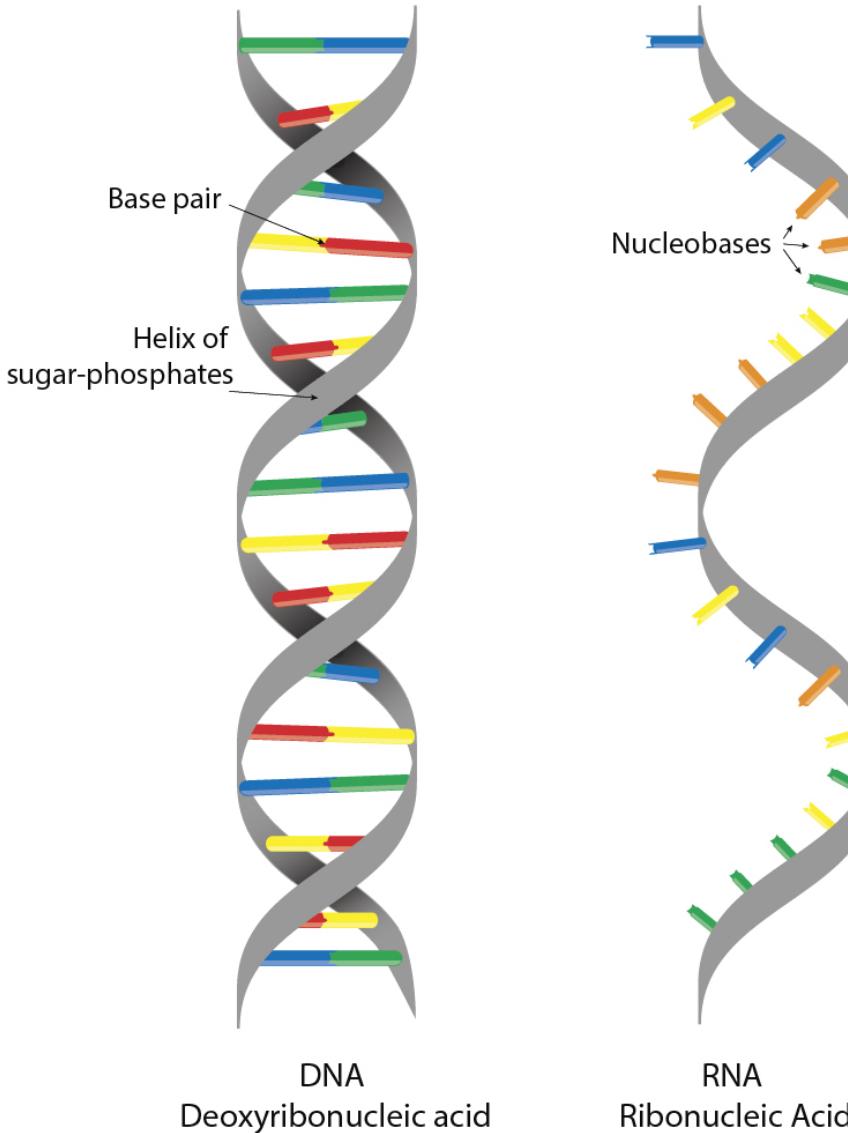
Uracil is substituted for thymine in the RNA molecule.

DNA = A-T and C-G

RNA = A-U and C-G

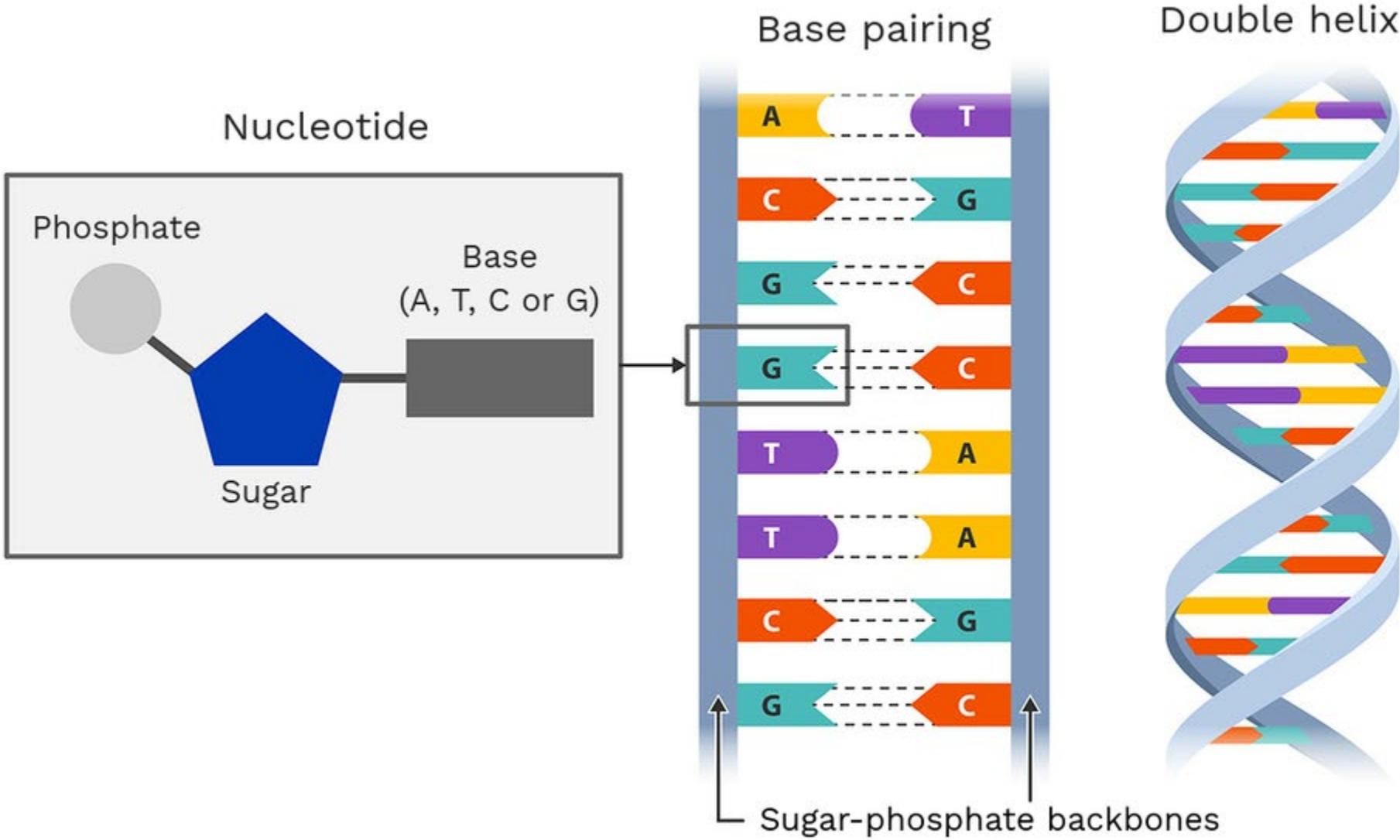


Nucleobases
of DNA

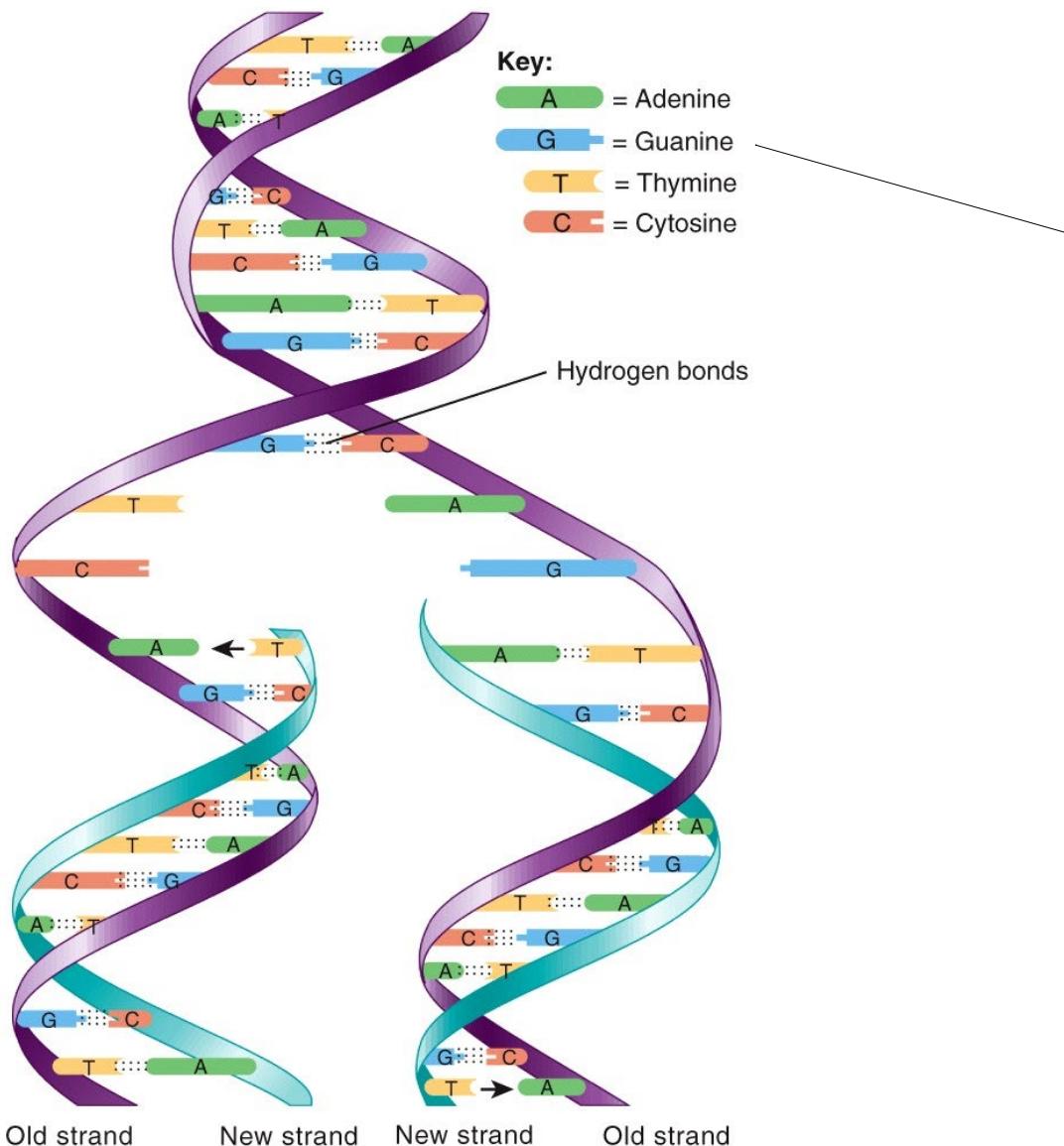


Nucleobases
of RNA

DNA is a double helix formed by two separate nucleic acid molecules hydrogen bonded together. RNA is a single strand of nucleic acid but may fold to make hydrogen forming a globular structure.



Law of Semi-Conservative Replication



DNA is a macromolecule of a nucleic acid polymer. It is constructed by two strands of nucleic acid connected by hydrogen bonds.

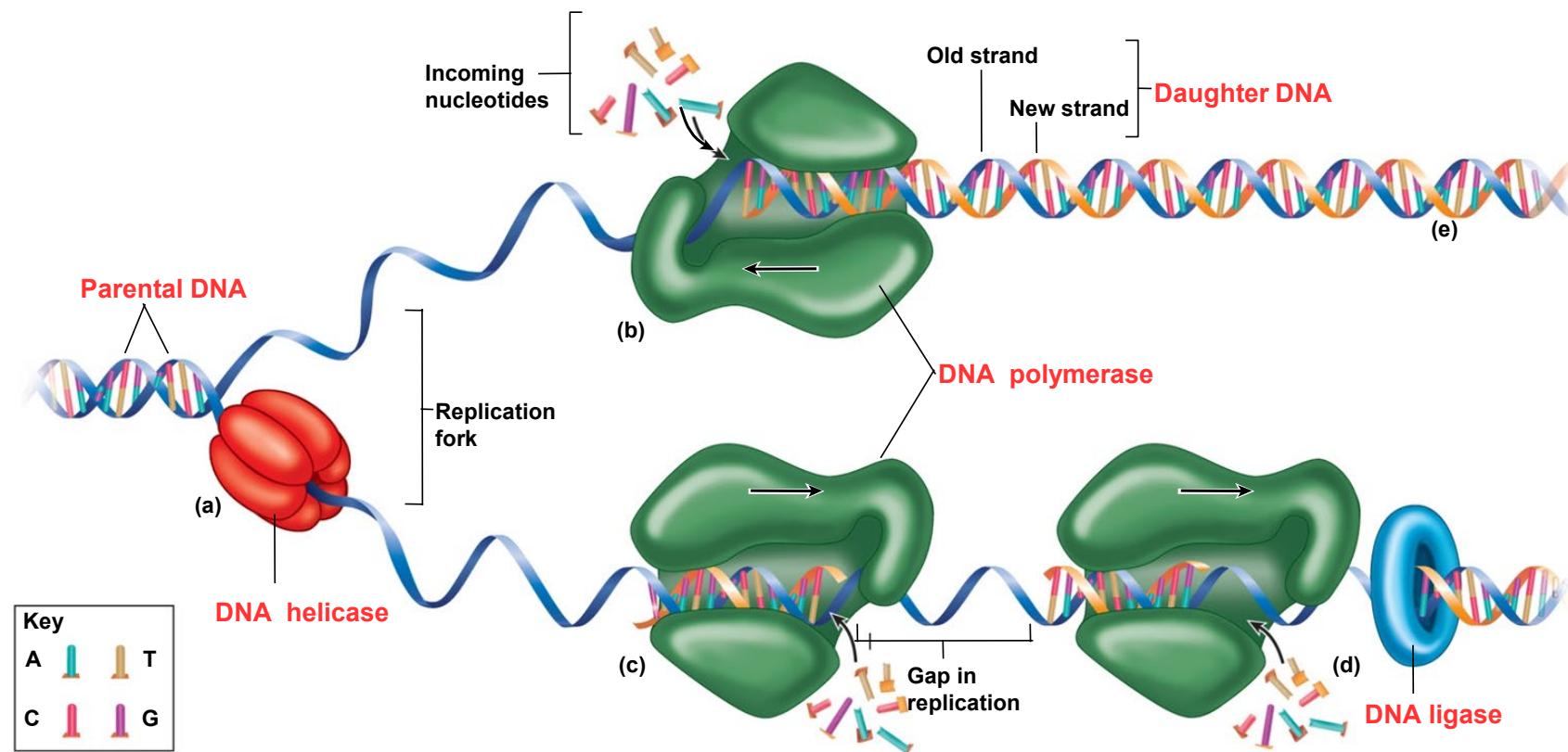
These four nucleotide molecules are used to make a strand of nucleic acid (DNA).

Adenine forms hydrogen bonds only with thymine. (A-T)

Guanine forms hydrogen bonds only with cytosine. (G-C)

If you have only a single strand of nucleic acids and an assortment of free nucleotide, then they will hydrogen bond with only its appropriate nucleotide to make a new double strand DNA molecule.

Enzymes Required for DNA Replication



Steps of DNA Replication

Double helix unwinds from histones

Enzyme **DNA helicase** opens one short segment of helix at a time // exposing its nitrogen bases

Replication fork – the point where the DNA is opened up (like two separated halves of a zipper)

DNA polymerase move along each strand /// read the exposed bases /// matches complementary free nucleotides to the exposed nucleotides

The two separated strands of DNA are copied by two separate polymerase molecules, one on each strand - proceeding in opposite directions

the polymerase molecule moving toward the replication fork makes a long, continuous, new strand of DNA

the polymerase molecule moving away from the replication fork makes short segments of DNA at a time ... **DNA ligase** will later join the segments together

Steps of DNA Replication

From the one old *parental DNA* molecule, **two new *daughter DNA* molecules are made**

Semiconservative replication - each daughter DNA consists of one new helix synthesized from free nucleotides and one old helix conserved from the parental DNA

New histones are synthesized in cytoplasm

Millions of histones are transported into the nucleus within a few minutes after DNA replication

Each newly formed DNA helix will wrap around histones to make a new nucleosome

Each DNA polymerase works at a rate of **100 base pairs per second** // would take weeks if only one polymerase replicated one chromosome

Thousands of polymerase molecules work simultaneously on each DNA molecule // all 46 chromosomes are replicated in 6 - 8 hours

Errors and Mutations

DNA polymerase may make mistakes

multiple modes for correction of replication errors

double checks the new base pair and able to replace incorrect nucleotides

biochemically unstable hydrogen pairs replaced with more stable correct pairs

–result is only 1 error per 1 billion bases replicated

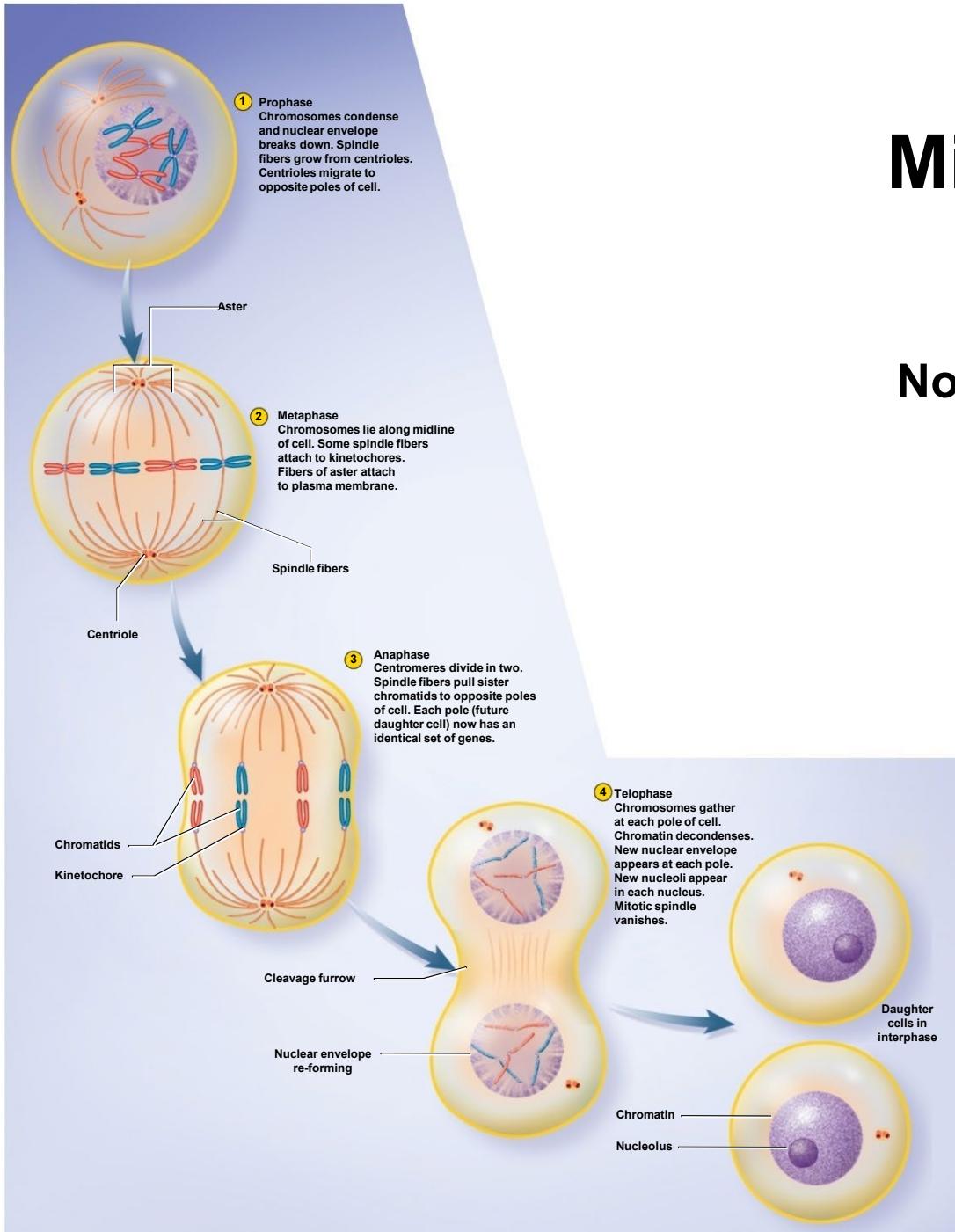
Mutations

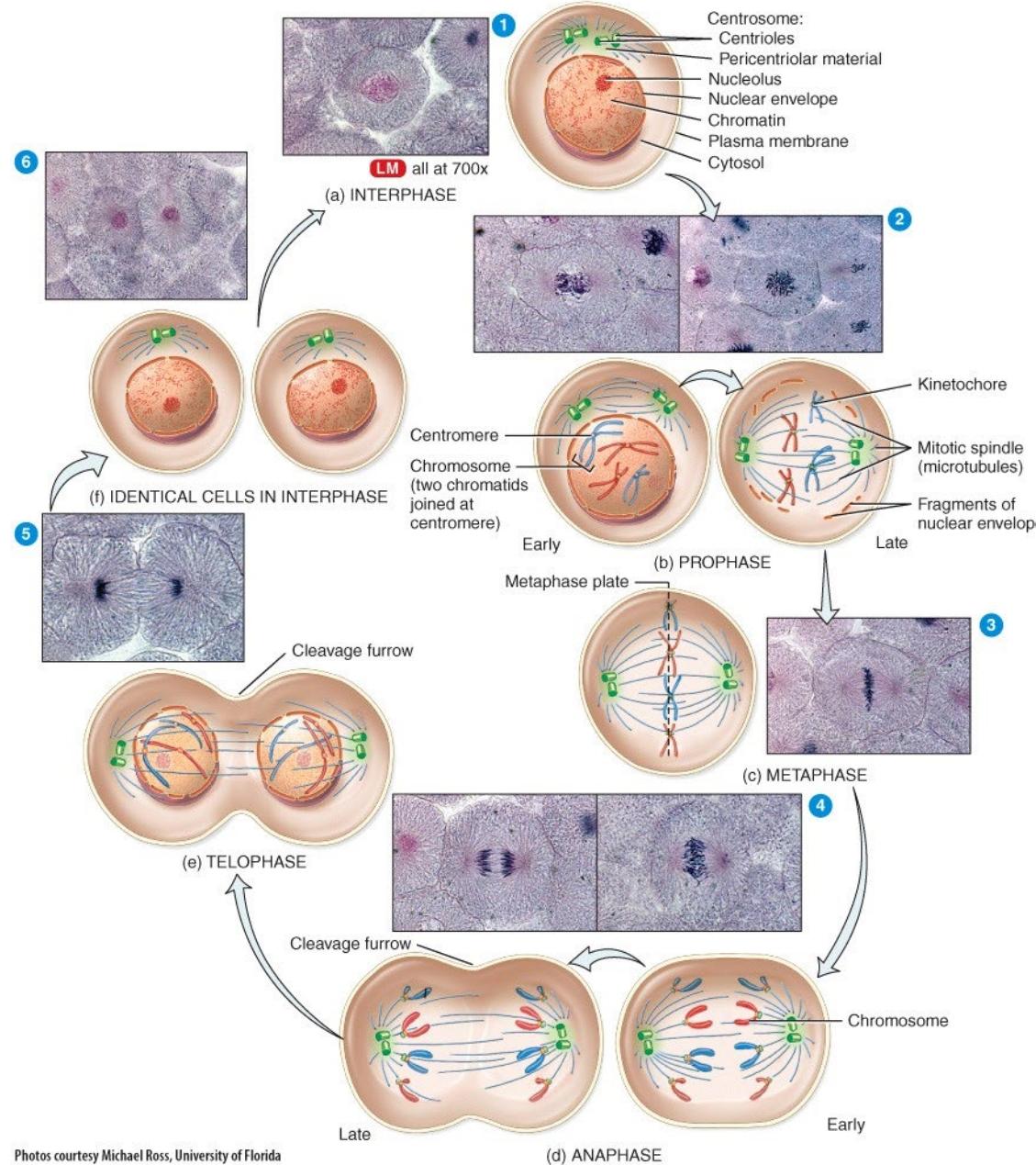
changes in DNA structure due to replication errors or environmental factors (radiation, viruses, chemicals)

some mutations cause no ill effects. others kill the cell, turn it cancerous or cause genetic defects in future generations.

More About Mitosis and Meiosis

The Following Details Are Not Included On the Unit Exam





Prophase

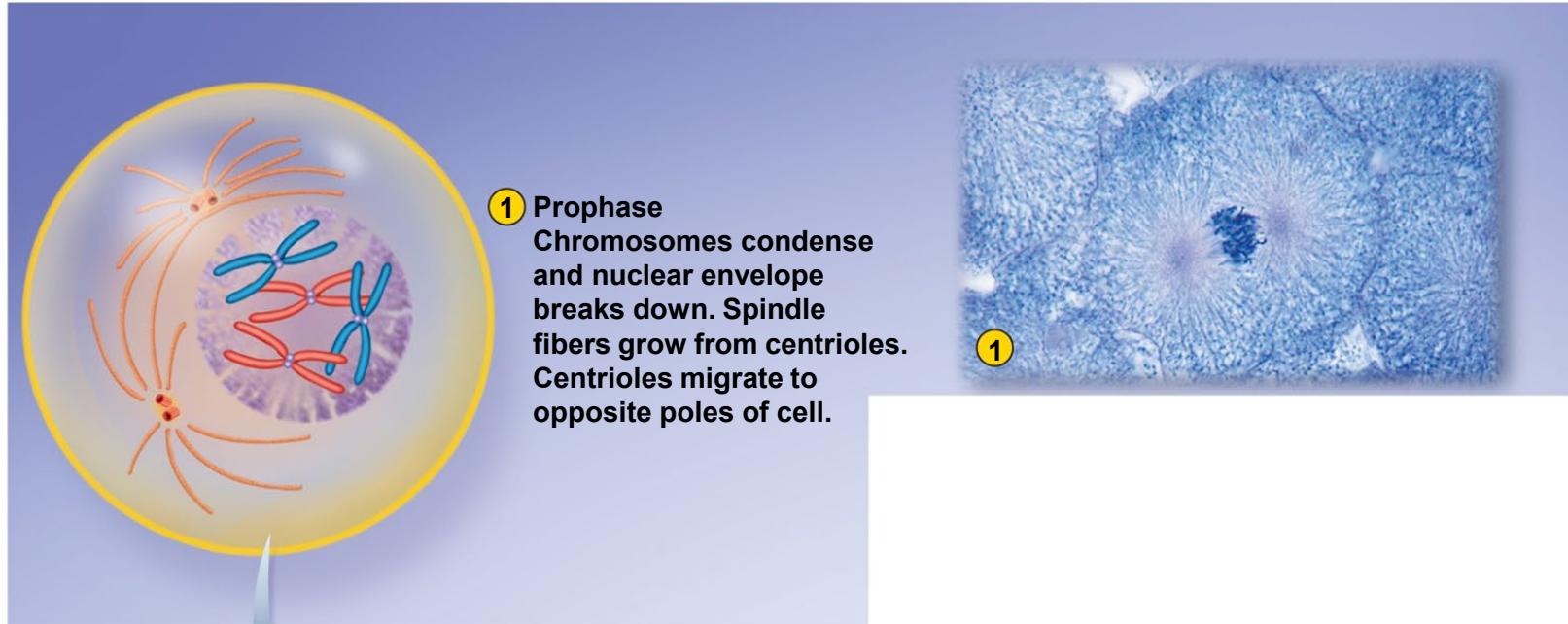
- Note: DNA is a polymer of nucleic acids /// the polymer can exist in different forms – either as diffused **chromatin** or condensed **chromosomes**
- DNA during S phase appears as chromatin /// chromatin shortens and thickens then coiling into compact rods called chromosomes during prophase --- Makes it easier to distribute to daughter cells than when in form of **chromatin**
- Homo sapiens have 46 chromosomes
- At end of S phase /// individual chromosomes are copied but held together /// each pair are now called **sister chromatids** = similar chromosome // this now doubled total amount of DNA (now equal to 92 chromosomes)
- In prophase nuclear envelope disintegrates and releases sister chromatids into the cytosol

Prophase (cont.)

- centrioles sprout elongated microtubules – called the spindle fibers
- push centrioles apart as they grow
- pair of centrioles migrate to opposite poles of the nucleus
- after centrioles reach opposite sides /// spindle fibers grow toward chromosomes and attach to the kinetochore on each side of the centromere
- Note: Kinetochore = point where chromatids attach to each other
- spindle fibers then tug the chromosomes back and forth until they line up along the midline of the cell

Prophase

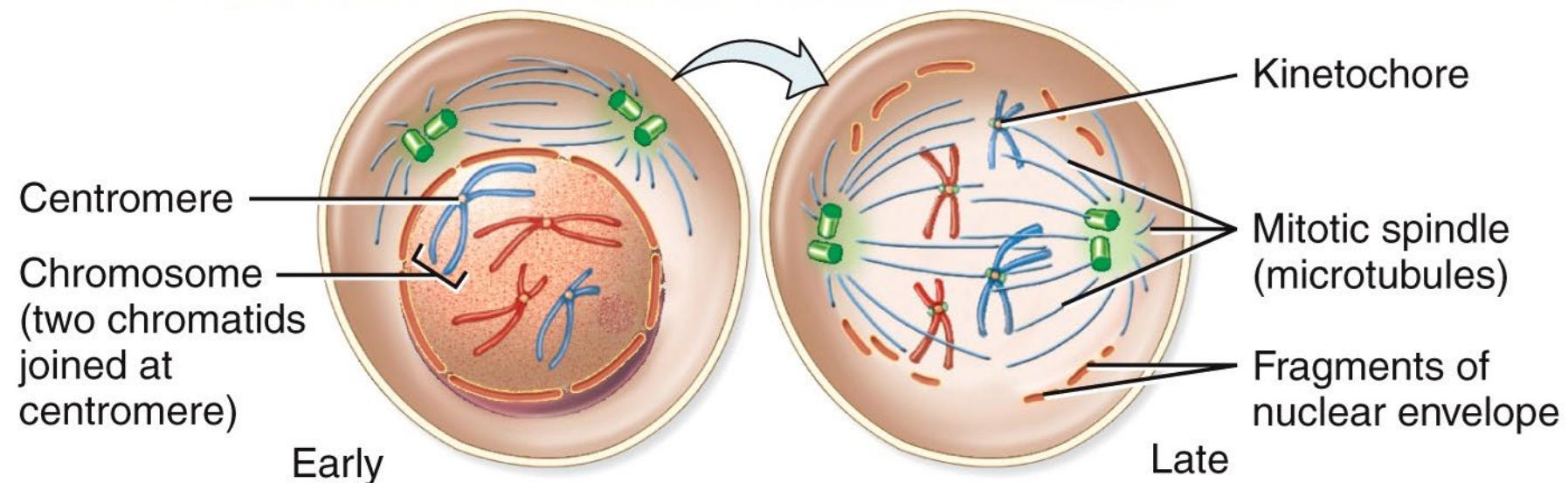
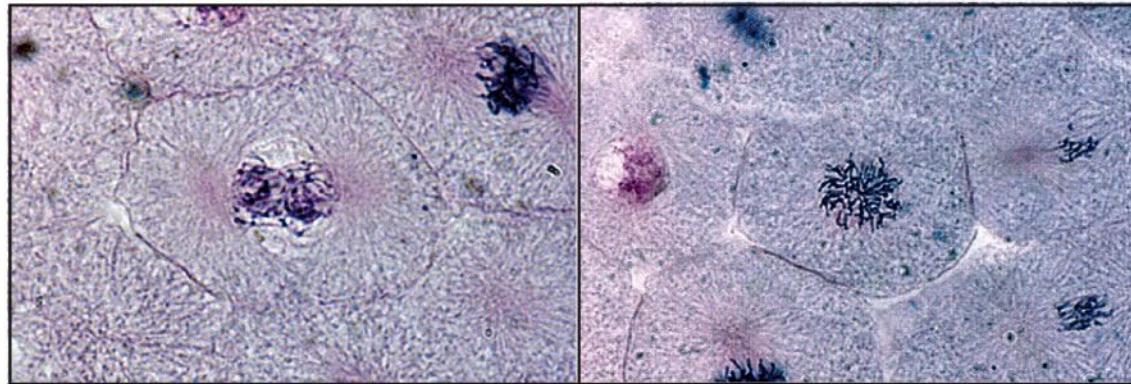
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The image is a composite of two panels. The left panel is a schematic diagram of a cell in prophase. It features a yellow circular boundary representing the cell membrane. Inside, several pairs of chromosomes are shown as blue and red X-shaped structures. From the center, four orange spindle fibers extend towards the opposite poles. The right panel is a light micrograph of a cell in prophase, stained with blue染色剂. The chromosomes are visible as dark blue dots, and the spindle fibers appear as a network of blue-stained fibers radiating from the centrosomes. A yellow circle labeled '1' points to the center of the cell, indicating the stage.

1 Prophase
Chromosomes condense and nuclear envelope breaks down. Spindle fibers grow from centrioles. Centrioles migrate to opposite poles of cell.

Courtesy Michael Ross, University of Florida

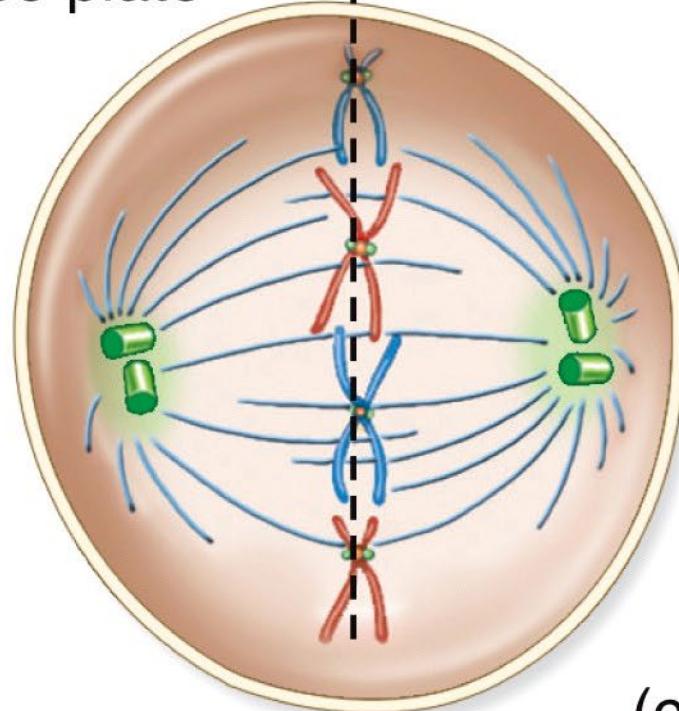


(b) PROPHASE

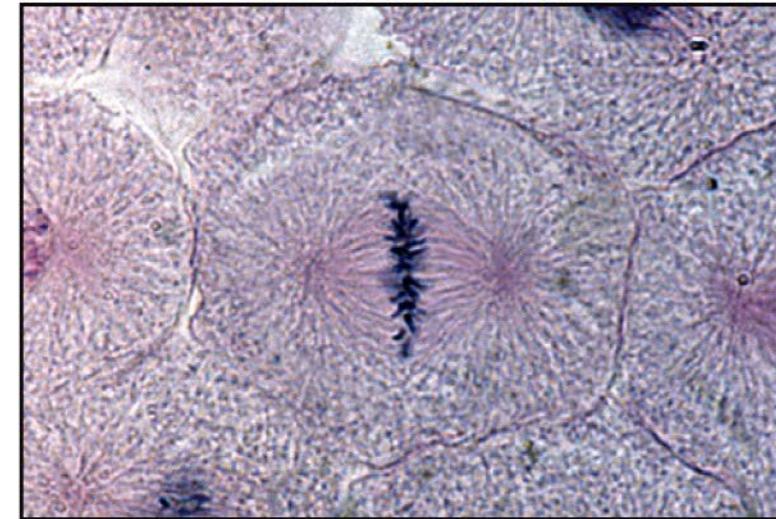
Metaphase

- Now chromosomes are **aligned on cell equator**
 - oscillating slightly and awaiting signal that stimulates each of them to split
- **Mitotic spindle** – lemon-shaped array of spindle fibers
 - long spindle fibers (microtubules) attach to chromosomes at kinetochore
 - shorter microtubules (**aster fibers**) anchor centrioles to plasma membrane at each end of cell

Metaphase plate —



Courtesy Michael Ross, University of Florida

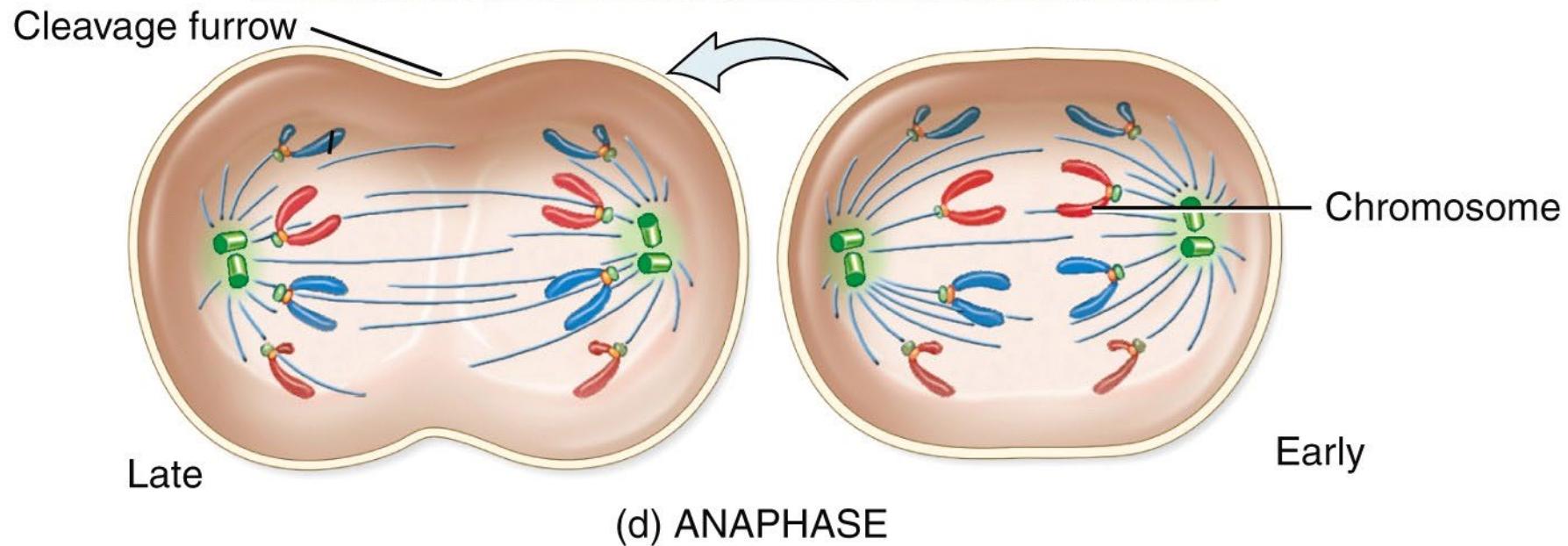
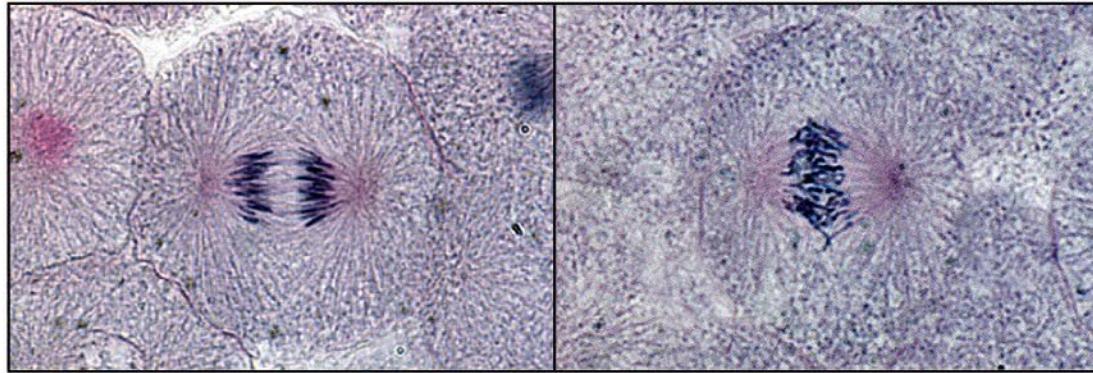


(c) METAPHASE

Anaphase

- Begins with activation of an enzyme that cleaves two sister chromatids // **separates the two chromatids at centromere**
(centromere = point where two chromatids are attachment)
- Each chromatid now becomes a daughter chromosome which migrate towards opposite poles of the cell with centromere leading the way
 - motor proteins in **kinetochore crawling along the spindle fiber** as the fiber itself is ‘chewed up’ and disassembled at the chromosomal end
 - Each daughter cell following mitosis are genetically identical

Courtesy Michael Ross, University of Florida



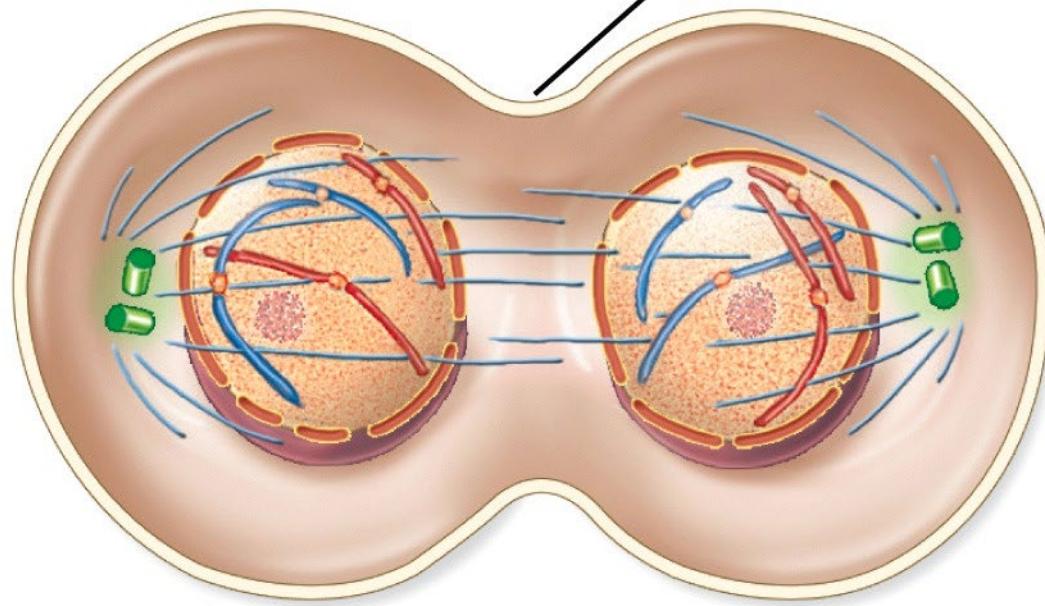
Telophase

- chromatids (the daughter chromosome) cluster on each side of the cell
- rough ER produces new nuclear envelope around each cluster
- chromatids begin to uncoil and form the chromatin
- remaining mitotic spindle breaks up and vanishes
- each nucleus forms nucleoli
 - this indicates that cell has already begun making RNA and preparing for protein synthesis

Courtesy Michael Ross, University of Florida



Cleavage furrow



(e) TELOPHASE

Cytokinesis

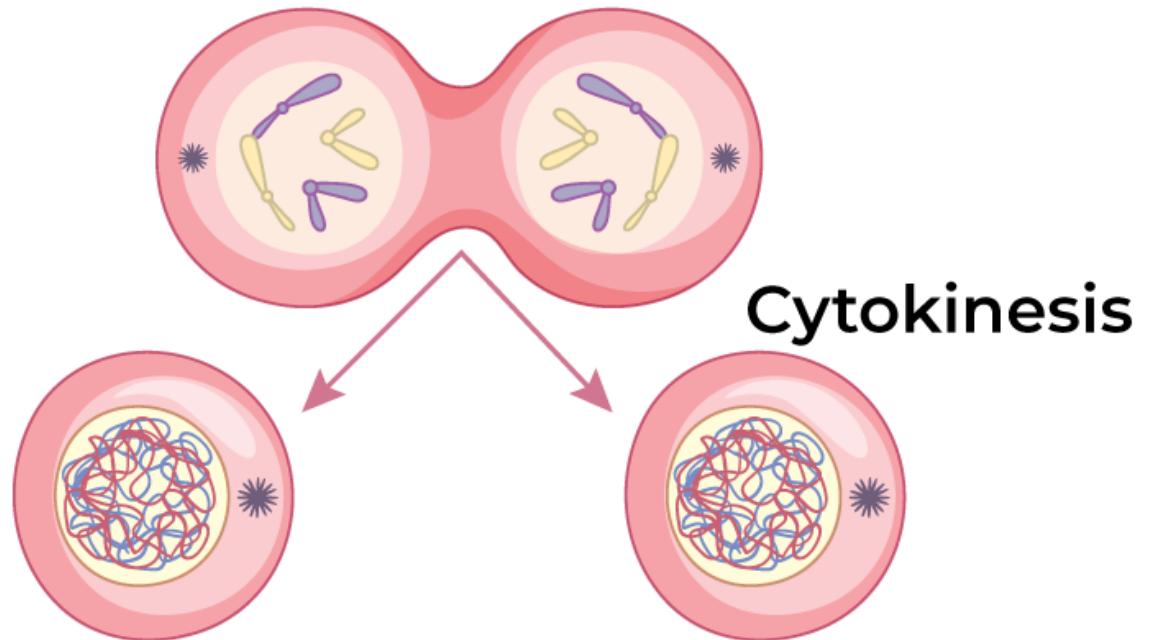
Cytokinesis divides the cytoplasm between the two new cells at the end of the mitotic phase

Creates the **cleavage furrow** around the equator of cell

Telophase is the end of mitosis but overlaps with cytokinesis

Early traces of cytokinesis visible in anaphase

Achieved by motor protein (myosin) pulling on microfilaments of actin in the



Timing of Cell Division

When may cells divide by mitosis?

If they have enough cytoplasm for two daughter cells

If they have doubled their DNA (made complete copy of all chromosomes).

If they have adequate supply of nutrients

If they are stimulated by growth factor

Chemical signals secreted by blood platelets, kidney cells, and other sources

If neighboring cells die. This opens up space in the tissue for new cells and prevents contact inhibition.

What will inhibit mitosis?

When nutrients are not available

Lack of growth factor secreted by cells in region.

Contact Inhibition

The cessation of cell division in response to contact with other cells

If existing cells are too closely packed with neighboring cell, then there is no room for new cells

More About Meiosis

Meiosis: cell division that reduces chromosome number by $\frac{1}{2}$

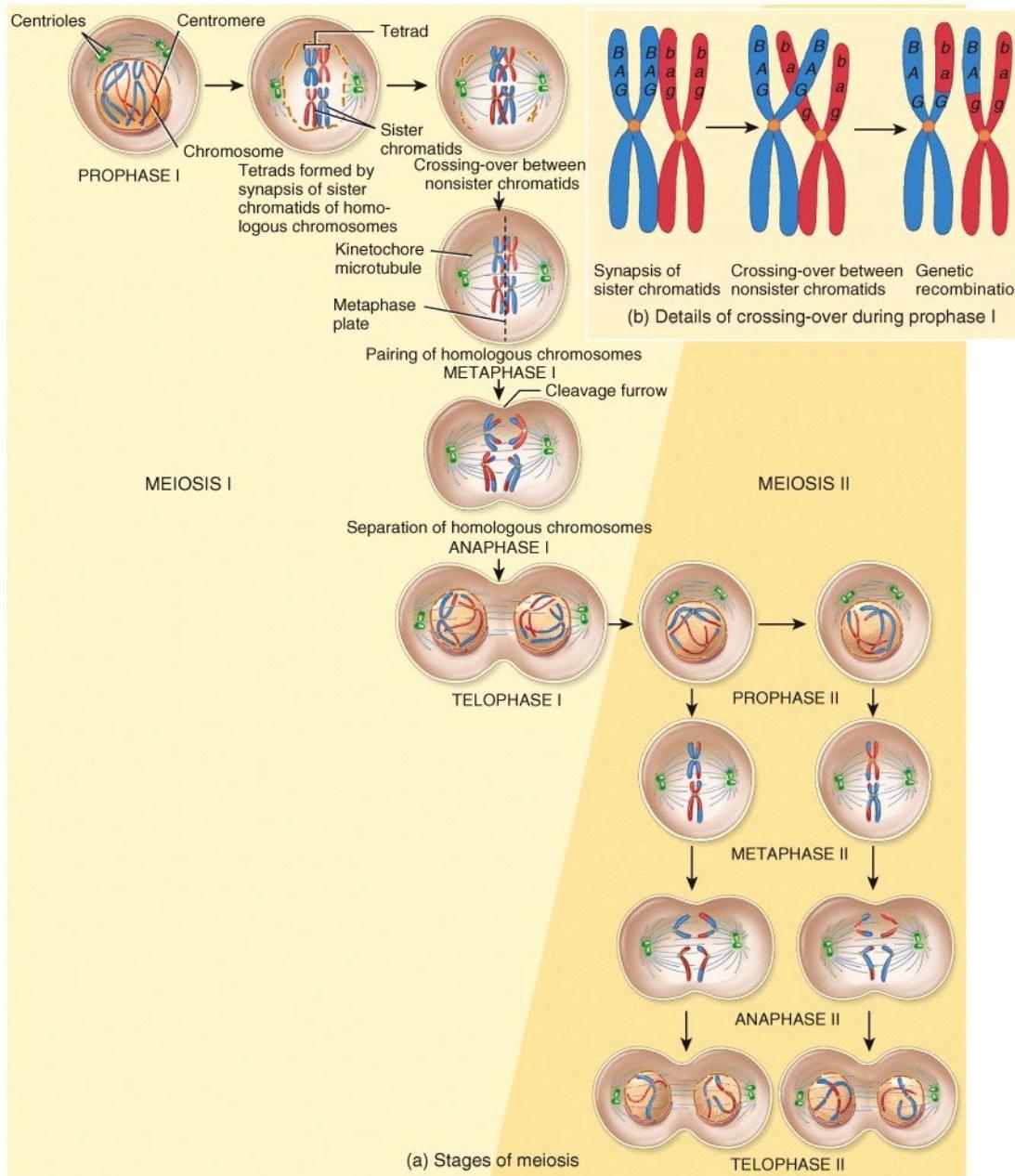
Human gonadal tissue produce gametes by meiosis (**testes produce sperm and ovaries produce eggs**)

The gametes are “**haploid cells**” (somatic cells are diploid)

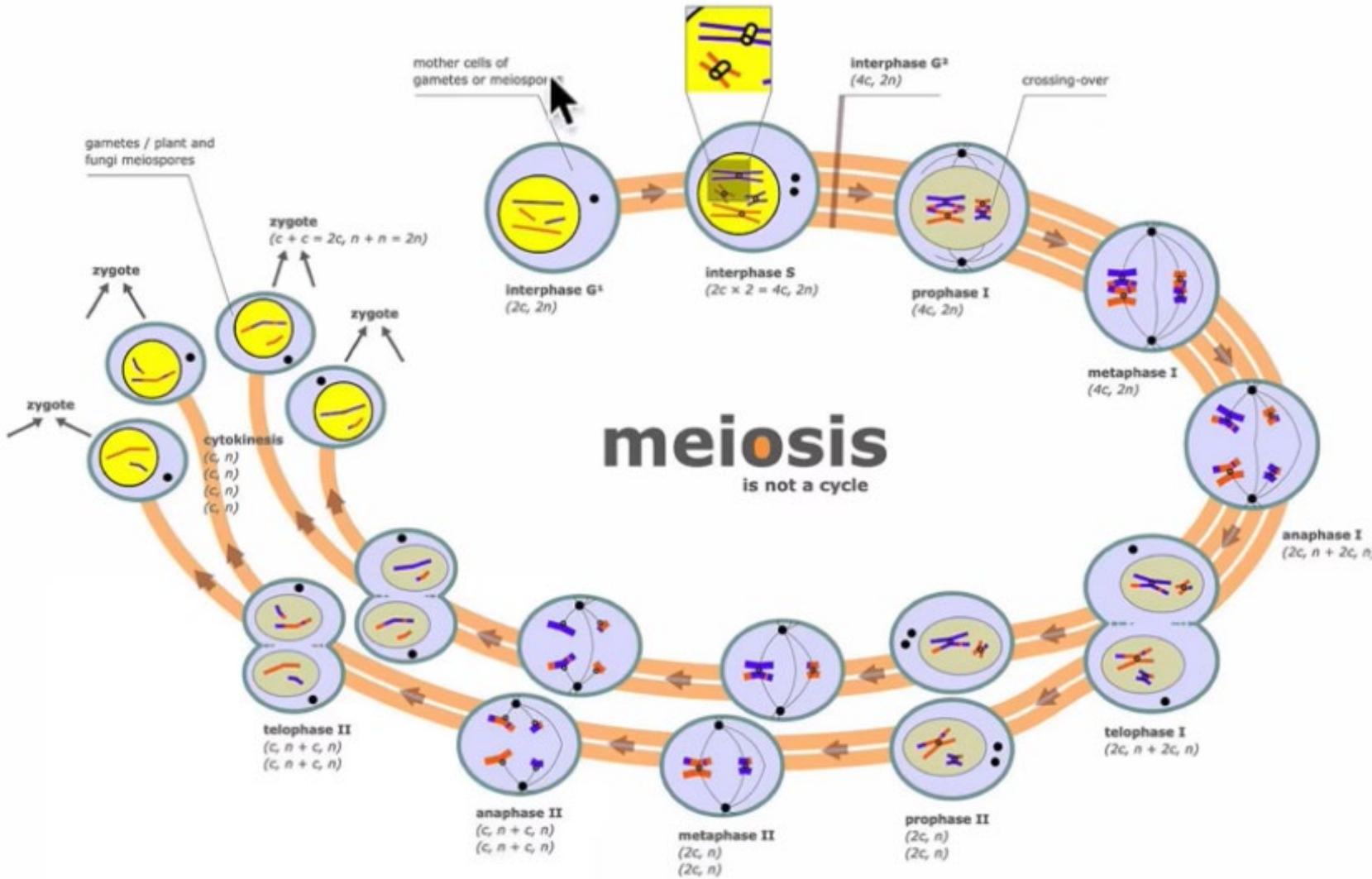
Haploid cells have 23 chromosomes

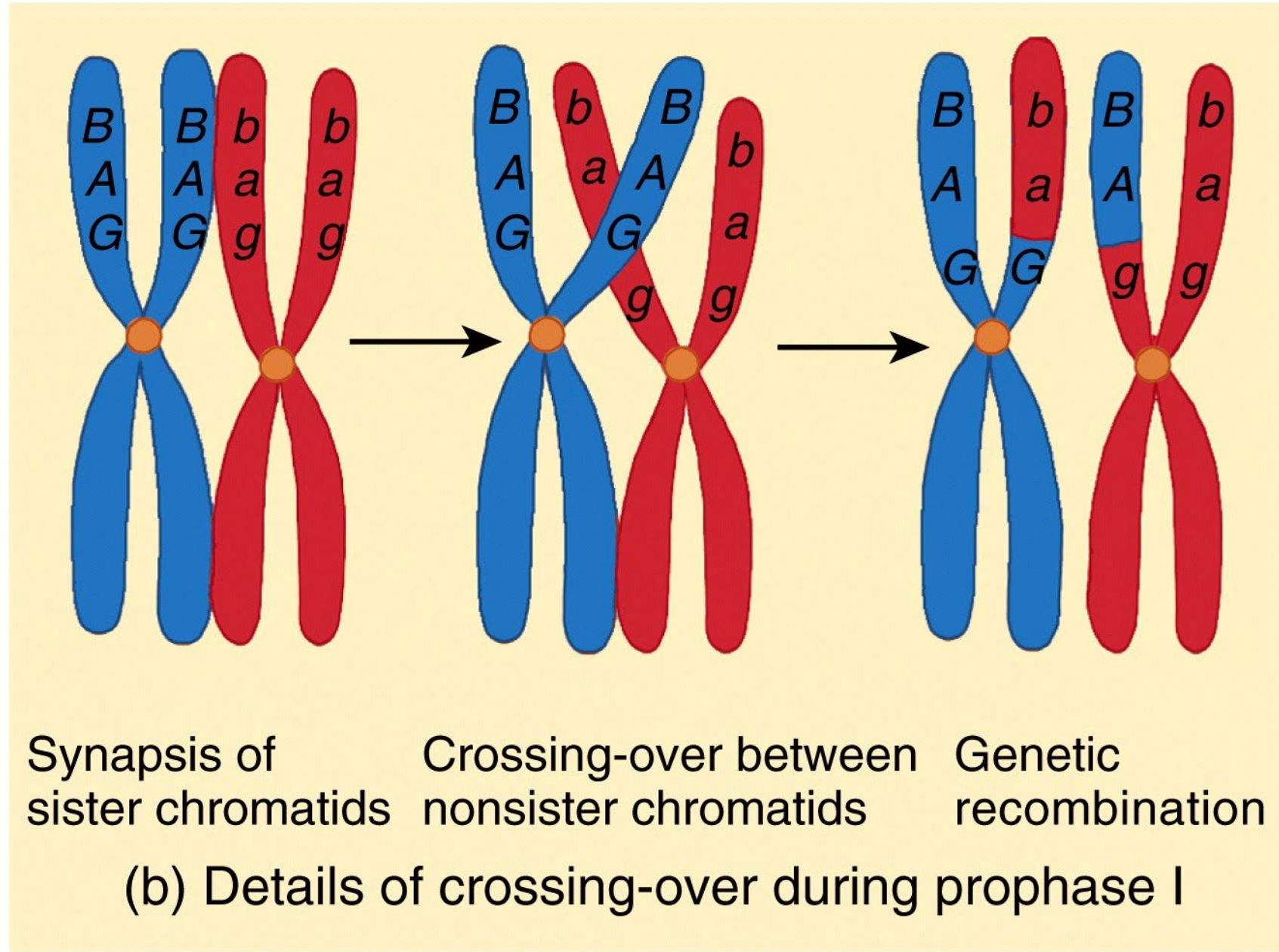
An egg and a sperm combine their chromosomes to create a new diploid cell called the zygote

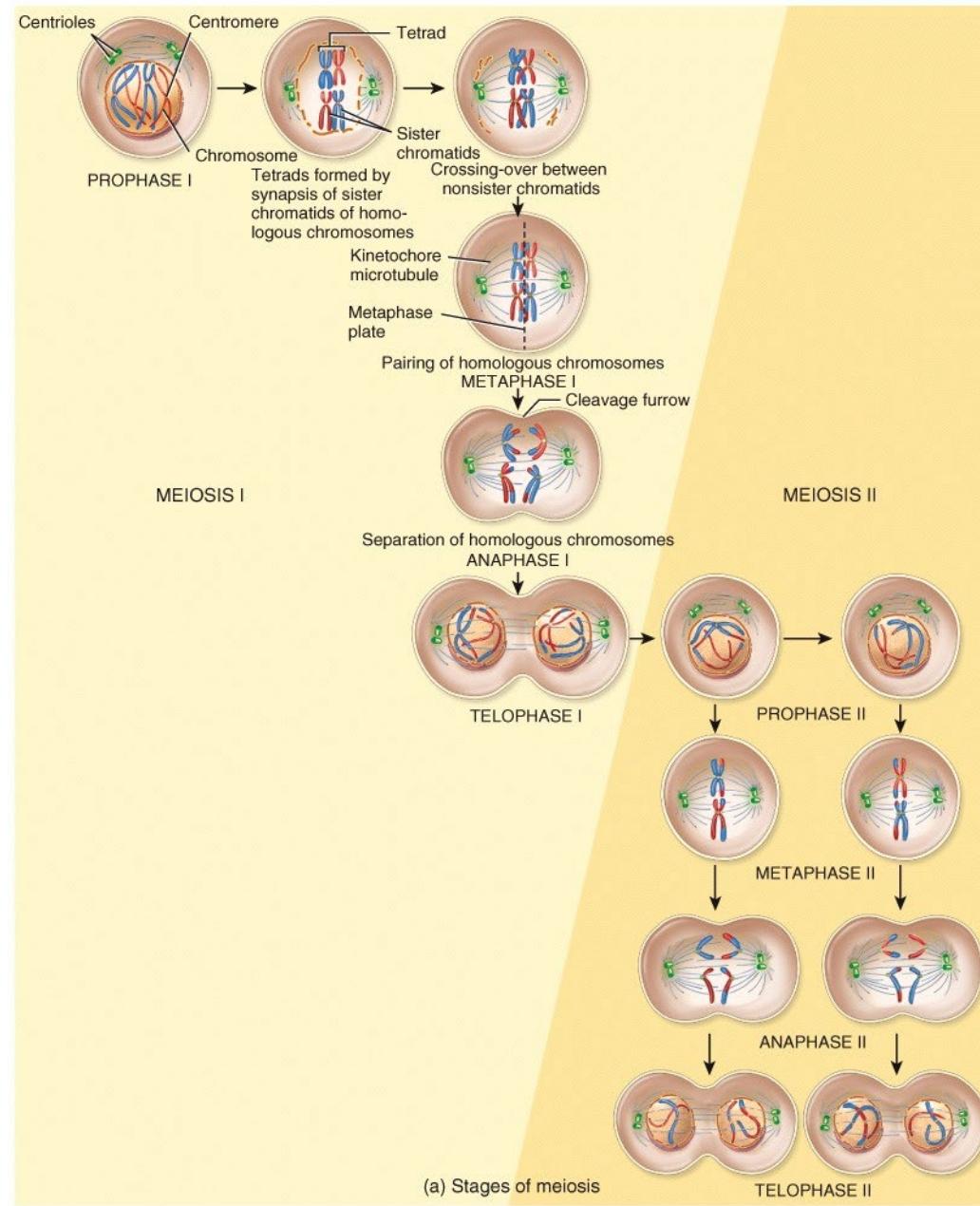
Everybody start life as a **zygote (a single diploid cell)**



Phases of Meiosis



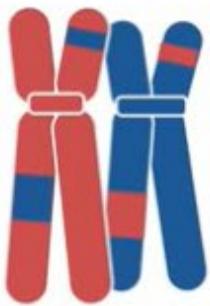




Metaphase I

Independent orientation

1



Metaphase I

Independent orientation

1

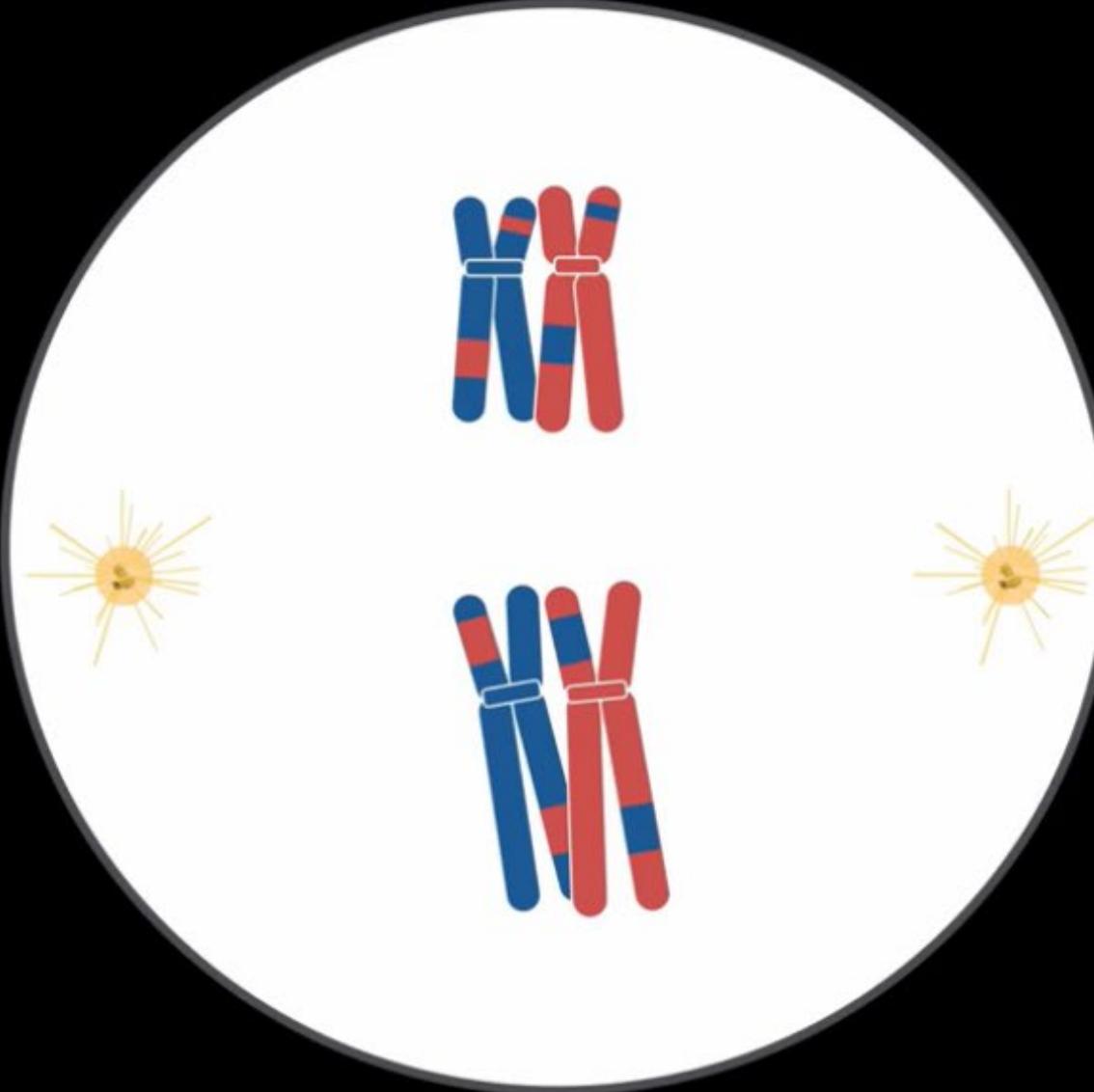
2

3

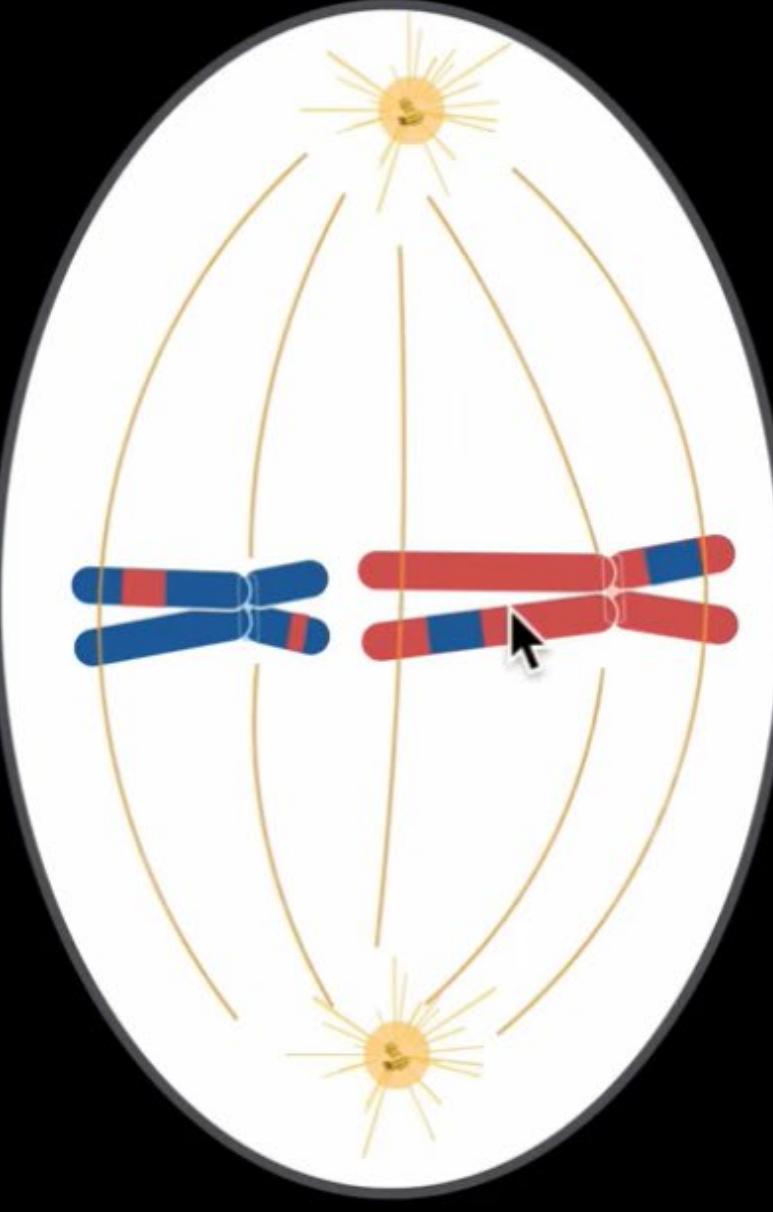
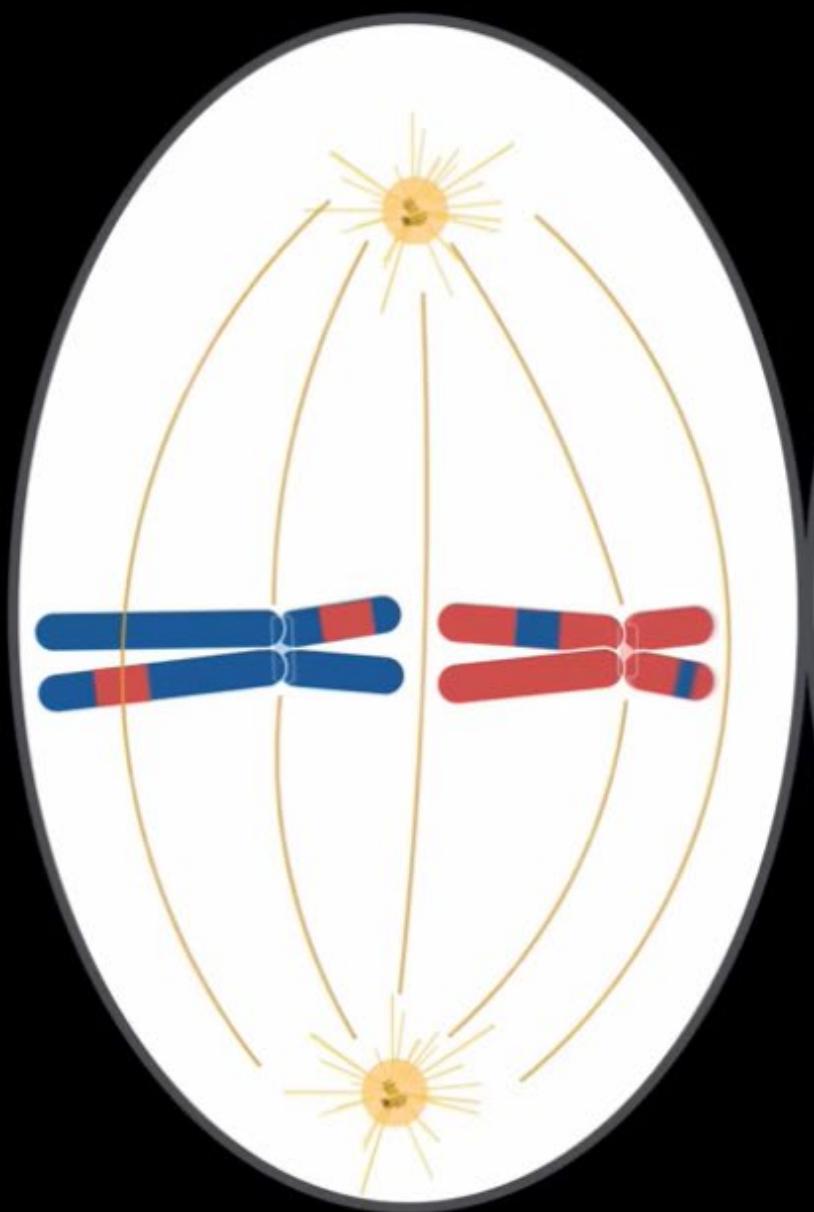
4

$$2^2 = 4$$

$$2^{23} = 8,388,608$$



Metaphase II





Classical Genetics VS Modern Genetics VS Epigenetics

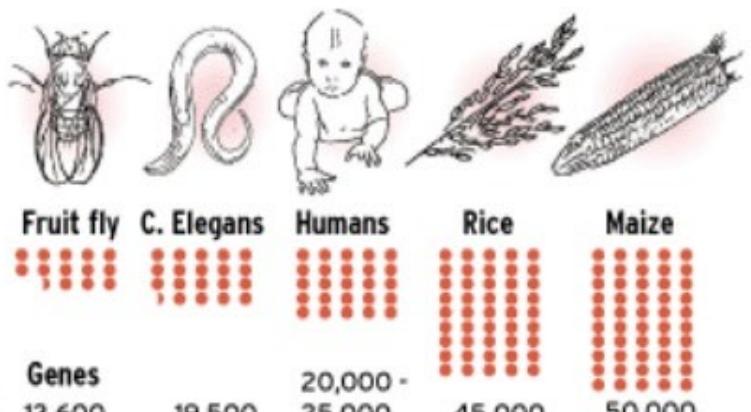
- Gregor Mendel is considered the **father of Classical Genetics**. He worked with pea plant's in the mid 1850s to demonstrate patterns of heredity. He coined the terms dominant and recessive traits. Mendel's early work predicated our understanding of molecular biology and the discovery of DNA's role as the informational molecule responsible for heredity by almost 80 years.
- Charles Darwin wrote On the Origin of Species in 1859. He explained how Evolution and Natural Selection create new species.
- Darwin and Mendel work is known as **Classical Genetics**. Our understanding of genetics was updated and renamed **Modern Genetics** in the 1940's to incorporate the role of DNA .
- A consensus definition of the concept of an **epigenetic** trait is a “stably heritable phenotype resulting from changes in a chromosome without alterations in the DNA sequence”. This was formulated at a Cold Spring Harbor meeting in 2008

Human Genom Project

- ▶ The human genome project was completed in 2003.
- ▶ It was established that human genome contains about 20,000 to 25,000 genes.

Humans have fewer genes

In Thursday's issue of the journal *Nature*, researchers who decoded the human genome concluded that people have only 20,000 to 25,000 genes, a drop from the 30,000 to 40,000 estimated in 2001.



SOURCE: *Nature*

AP

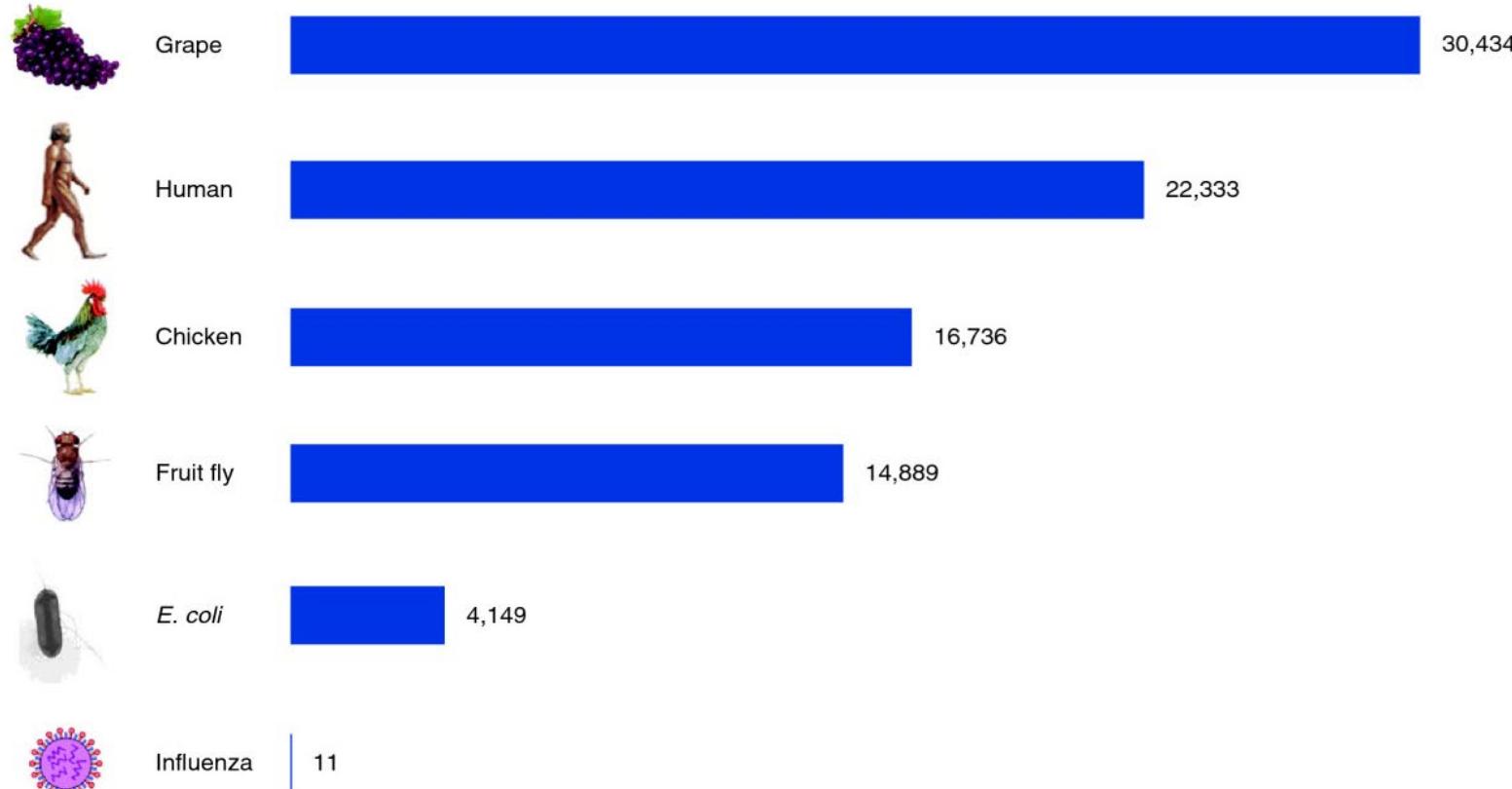
Genus species are defined by the number of chromosomes. The number of genes is just an index of how many different proteins the species is able to make.

Humans have 46 chromosomes.

In fact, each species of plants and animals has a set number of chromosomes. A fruit fly has 8 chromosomes, while a **rice plant has 12** and a dog, 39. Gorilla 48, monkey 54, strawberry 56, carp 100, black mulberry 308.

A gene has the information necessary to make a protein.

Number of Genes

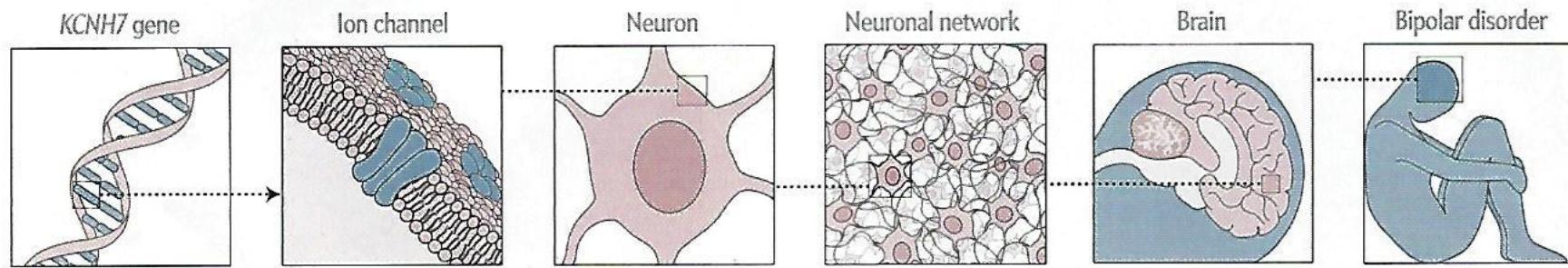


What molecule is made by the information contained in our genes?

How Genetic Mutations Lead to Disease

Gene mutations can disrupt biology at multiple levels (molecules, cells, tissues and organs) to cause disease. Certain mutations are particularly prevalent in Amish and Mennonite populations. For each patient the clinic sees, it applies advanced technologies to identify the individual's genetic variants, understand their causal links to disease, and devise ways to alleviate or prevent the muta-

tions' harmful effects. In related work, the clinic and its collaborators recently identified a gene mutation linked to bipolar disorder among the Amish, and they are now constructing a picture of how it might impair emotional regulation (below). This knowledge could lead to a deeper understanding of bipolar disorder in the general population and to new strategies for prevention and treatment.



Gene

A gene consists of a sequence of DNA "letters" that spell out the amino acids needed to make a protein. Proteins are the main workhorses of cells. A mutation in a gene can alter the functioning of the encoded protein. The bipolar study pinpointed a mutation in a gene called *KCNH7*.

Protein

To function properly, proteins must have the right structure, location and abundance in each cell. *KCNH7* encodes a protein that spans the cell membrane, forming a channel that regulates the flow of potassium ions. The mutant is altered at just a single amino acid, but this subtle change affects potassium movement across the membrane.

Cell

All cells contain the same genes, but many genes are expressed (that is, give rise to proteins) only in select cell types. The ion channel encoded by *KCNH7* is used by neurons throughout the brain. Potassium currents critically shape each neuron's electrical behavior, and the mutant alters the cells' firing patterns.

Tissue

Tissues can contain a mixture of cell types. Brain tissue, for instance, includes neurons and supporting cells called glia. The mutant *KCNH7* gene would be expected to disrupt the operation, not only of individual nerve cells, but of whole neuronal circuits, such as those regulating emotions and behavior.

Organ

Nerve cells throughout the brain make the ion channel encoded by the *KCNH7* gene, but the channel is most abundant in brain regions underlying emotions and cognition. Consistent with that finding, mutation of the gene has been tied to mania observed in laboratory animals.

Behavior

Bipolar disorder is marked by a spectrum of behaviors that can include depression, mania and psychosis. New insight into how the *KCNH7* mutation affects each level of biology—from mis-spelled protein to perturbed brain function—could lead to fresh ideas for interrupting the chain of events underlying the disorder.