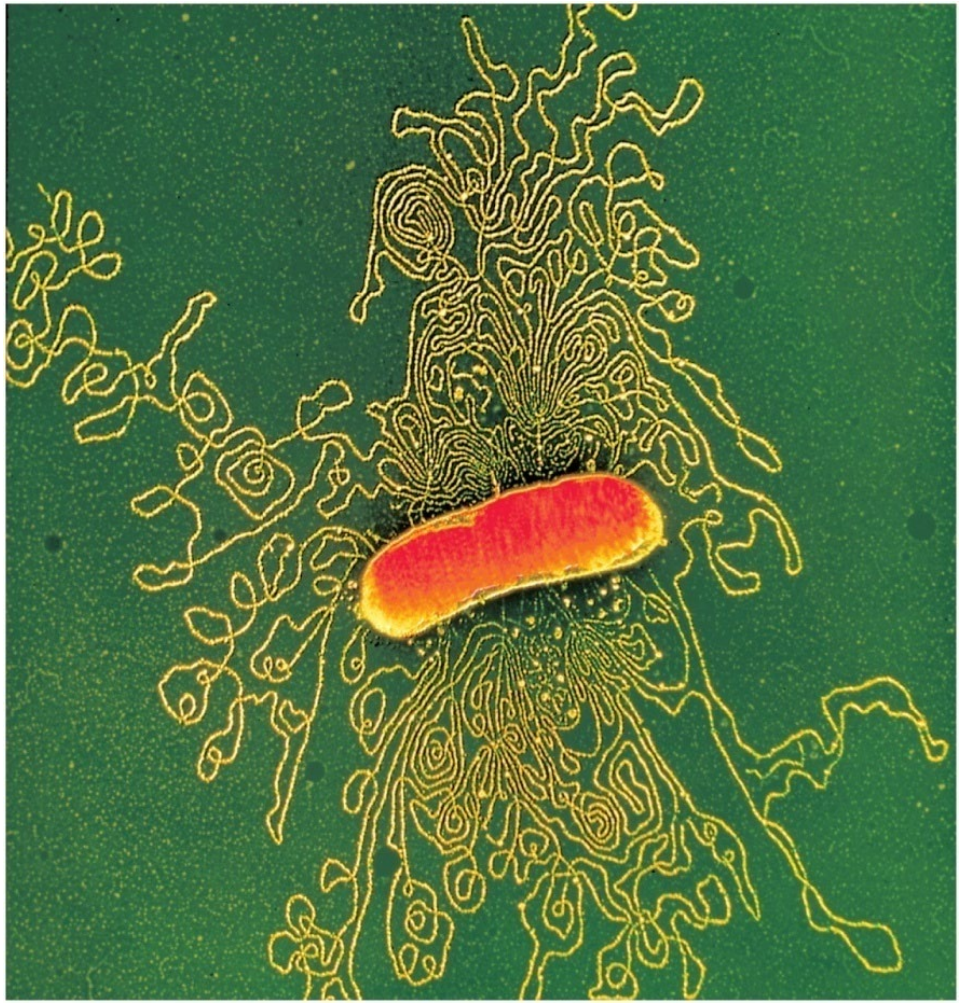
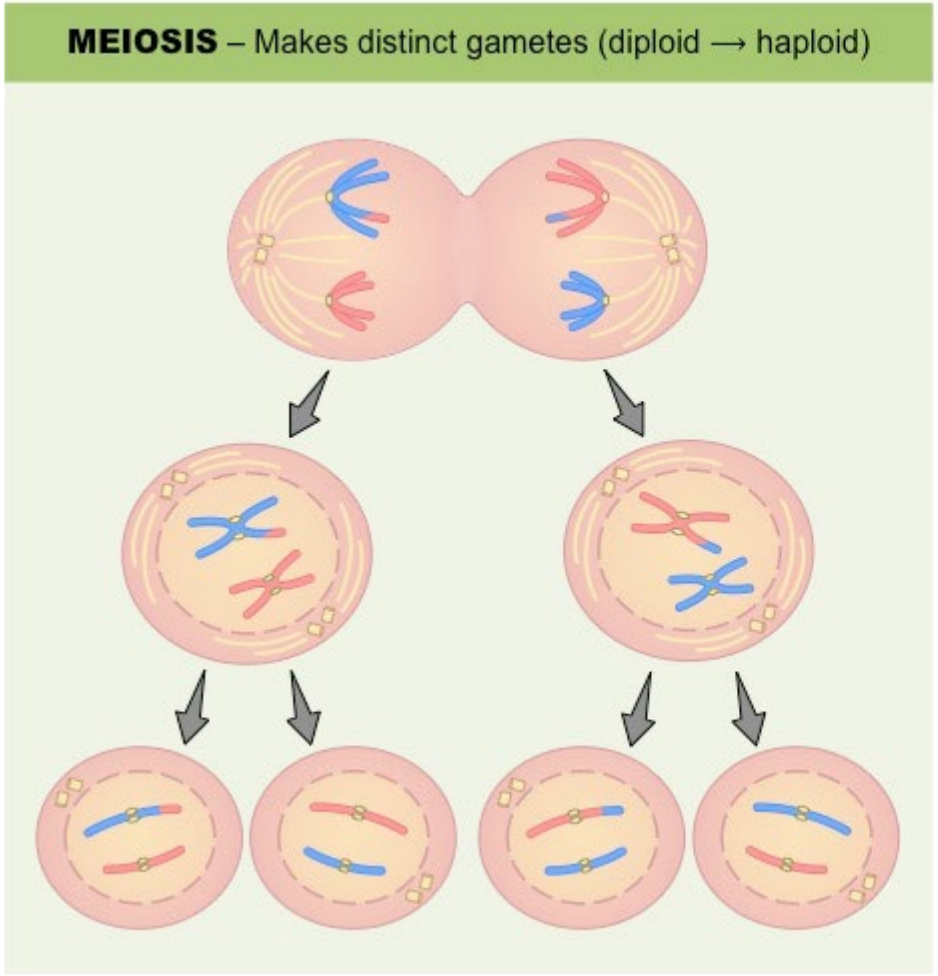
Chapter 4.1

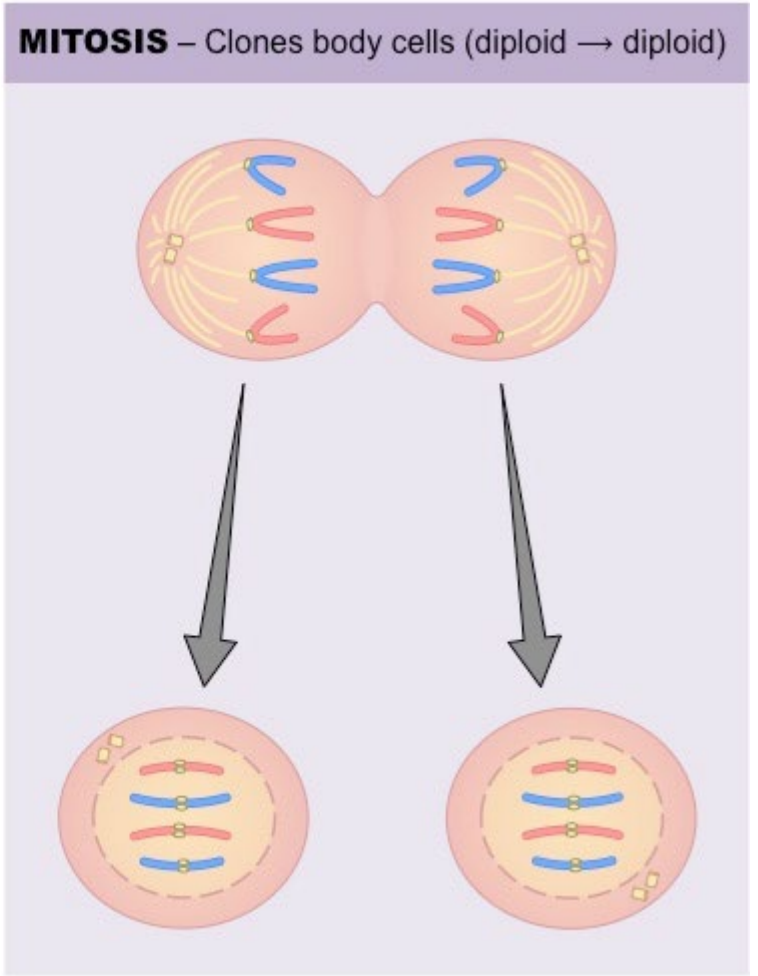
Cell Division – The Cell Cycle - DNA Replication



Two types of cell division occur in humans



46 chromosomes to 23 chromosomes



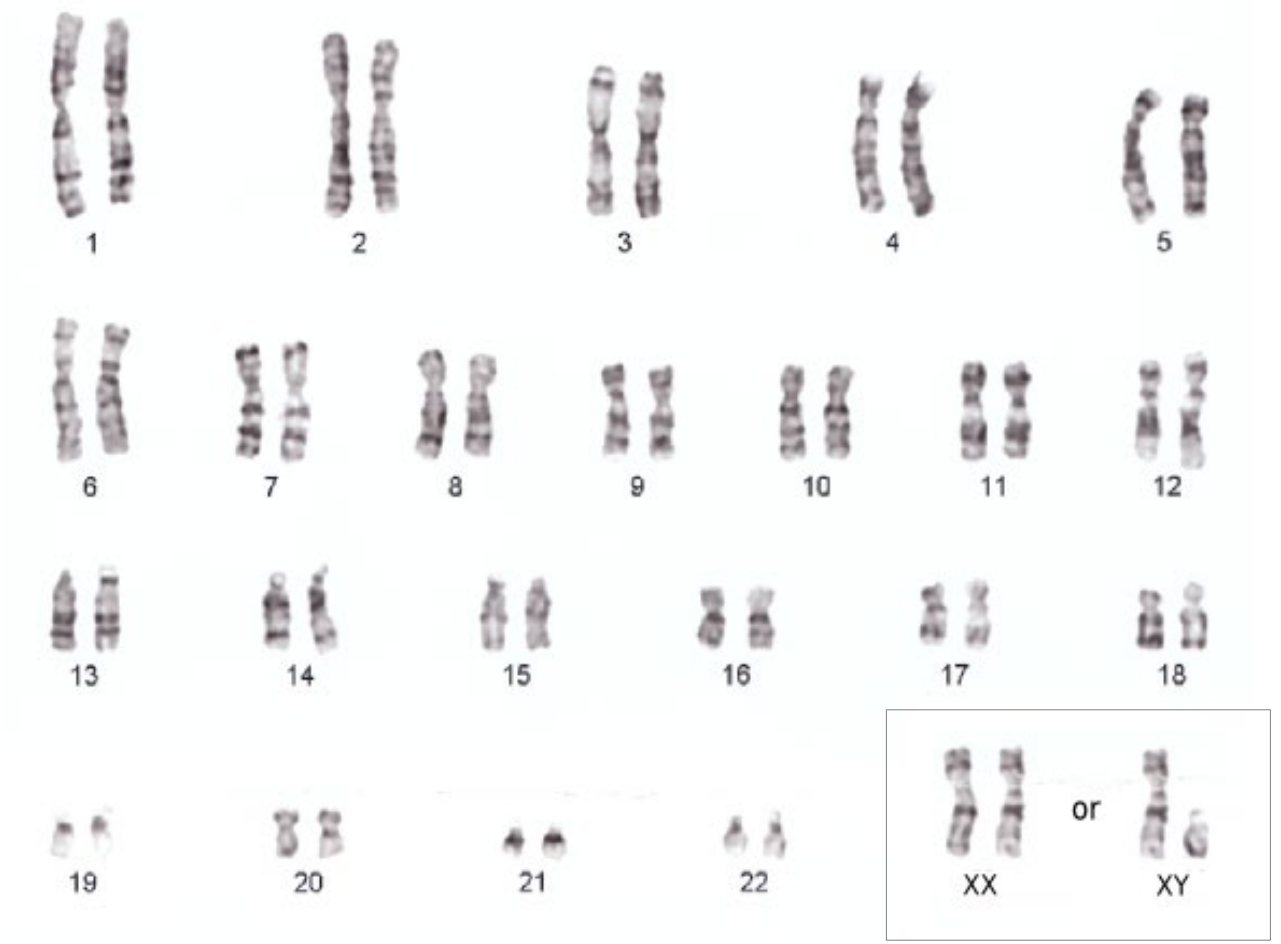
46 chromosomes to 46 chromosomes

Human Karyotype

Humans Have
46 Chromosomes

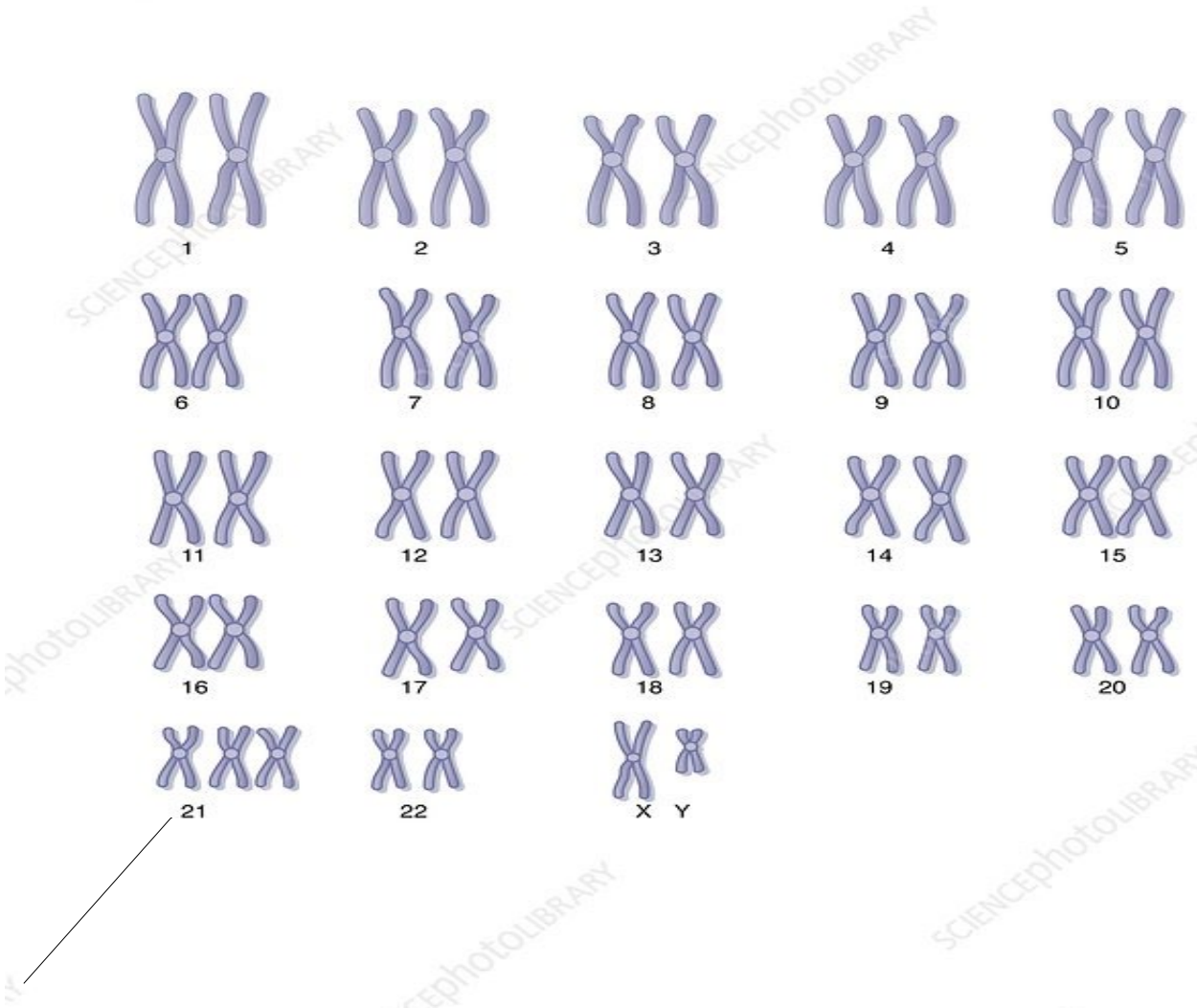
23 Pairs

One From
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 Mitosis

Mitosis: conserves chromosome number (humans = 46)

Mitosis takes place inside the nucleus

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

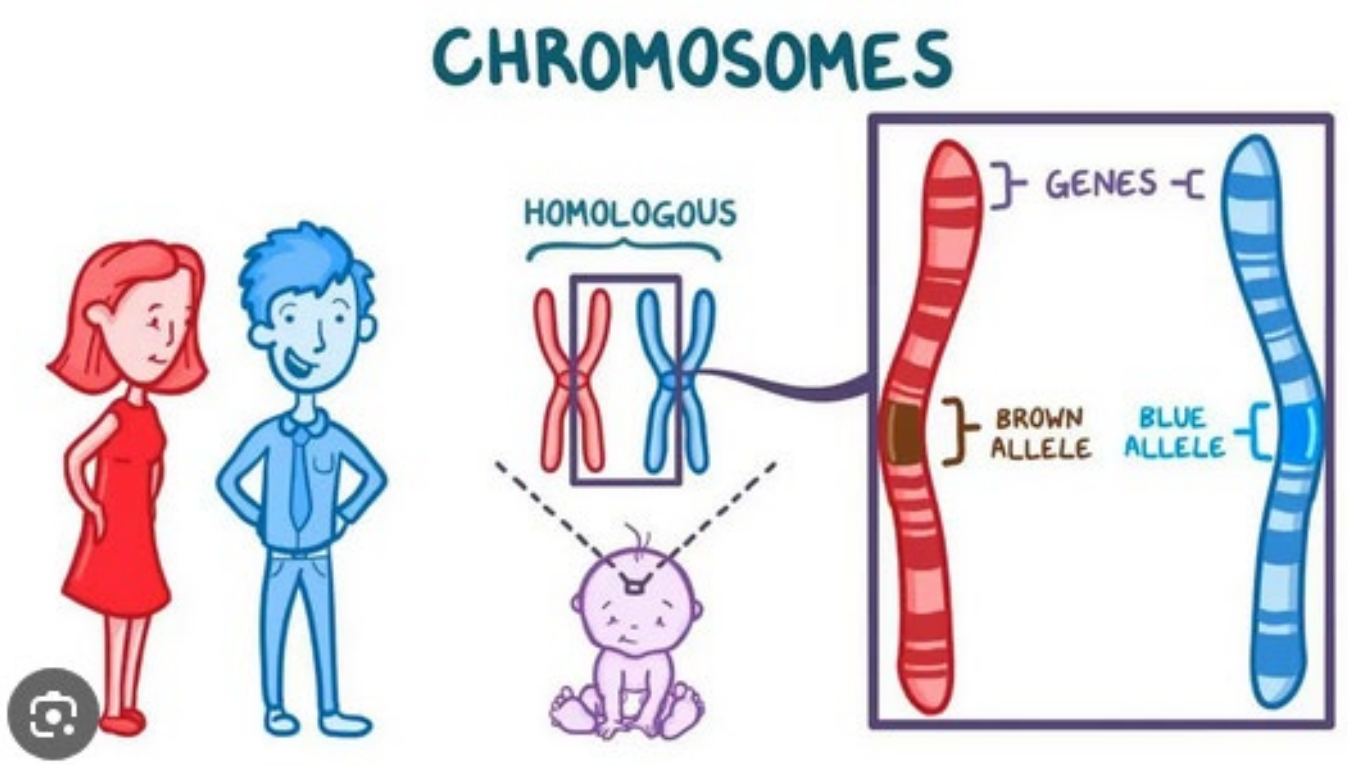
Somatic cells are called "diploid cells" /// 46 chromosomes

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

Each "chromosome pair" will have similar genes at same location

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

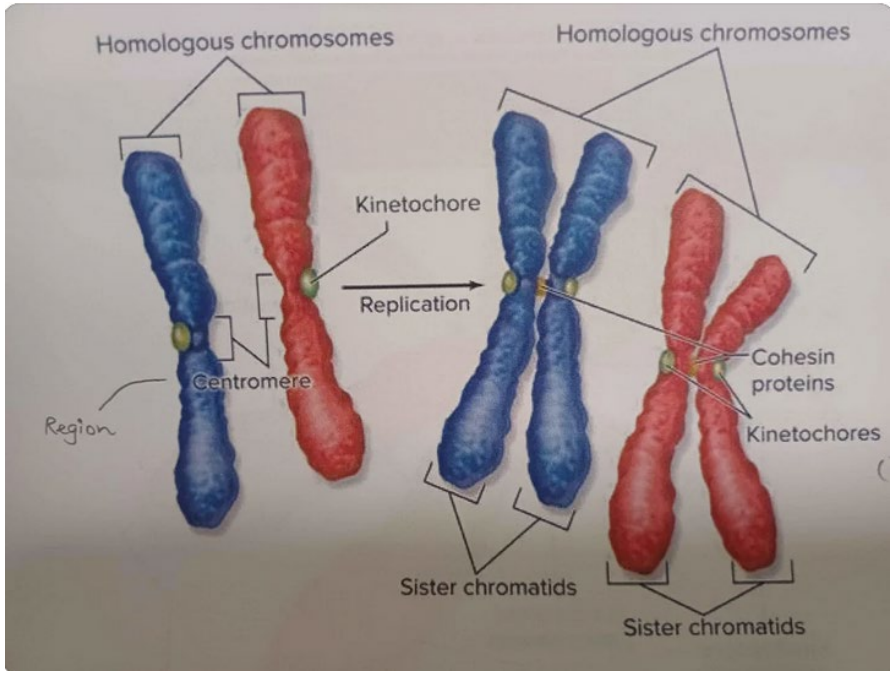
"Allele" is **the word that we use to describe the alternative form or versions of a gene**. People inherit one allele for each autosomal gene from each parent, and we tend to lump the alleles into categories.. Humans are diploid, meaning they have two alleles for each gene at a given genetic locus (one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

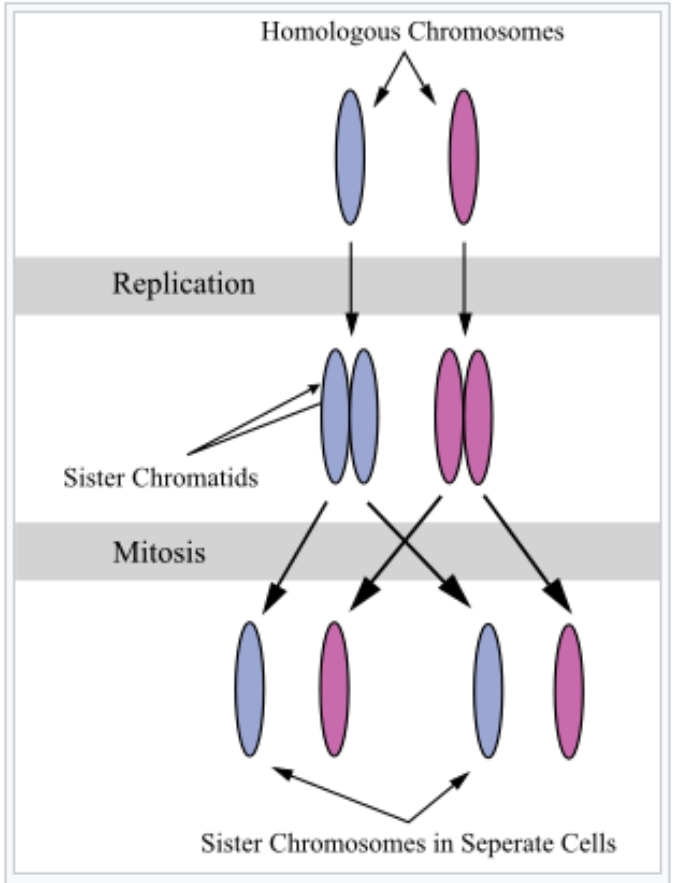
A chromosome is the entire structure containing genetic material, while a chromatid is one of the two identical copies of a replicated chromosome that are joined together at a centromere before cell division.

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.



Replicate 46 chromosomes to make 92 sister chromatids then divide them by half to make two new cells with each cell with 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.



About Meiosis

Meiosis: cell division that reduces chromosome number by ½

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

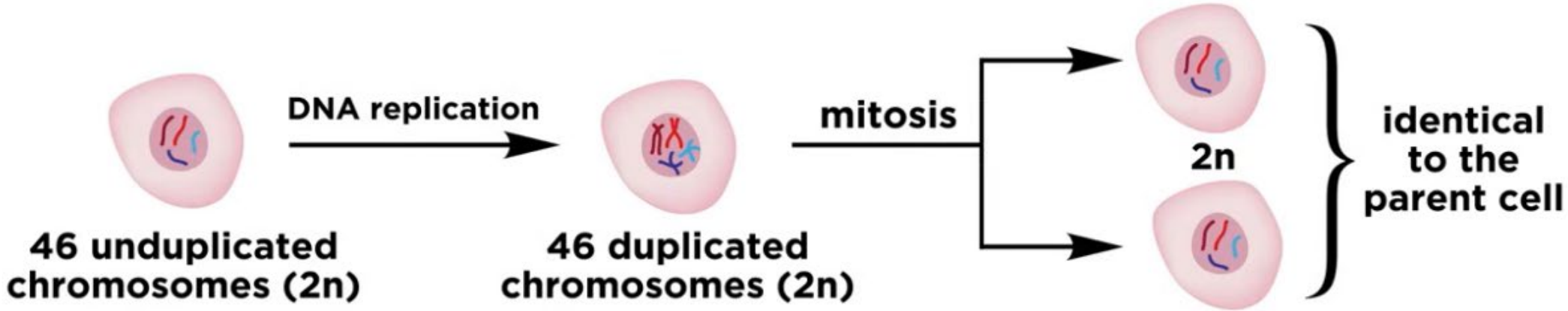
The gametes are "haploid cells" (somatic cells are diploid)

Haploid cells have 23 chromosomes

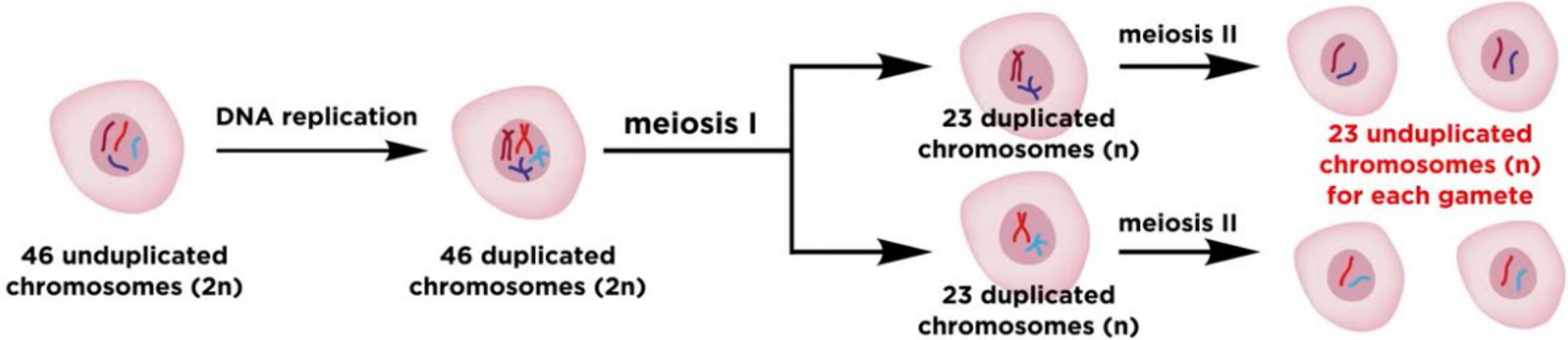
An egg and a sperm combine their chromosomes to create a new diploid cell called the zygote

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

Mitosis Produces Diploid Cells (2n)

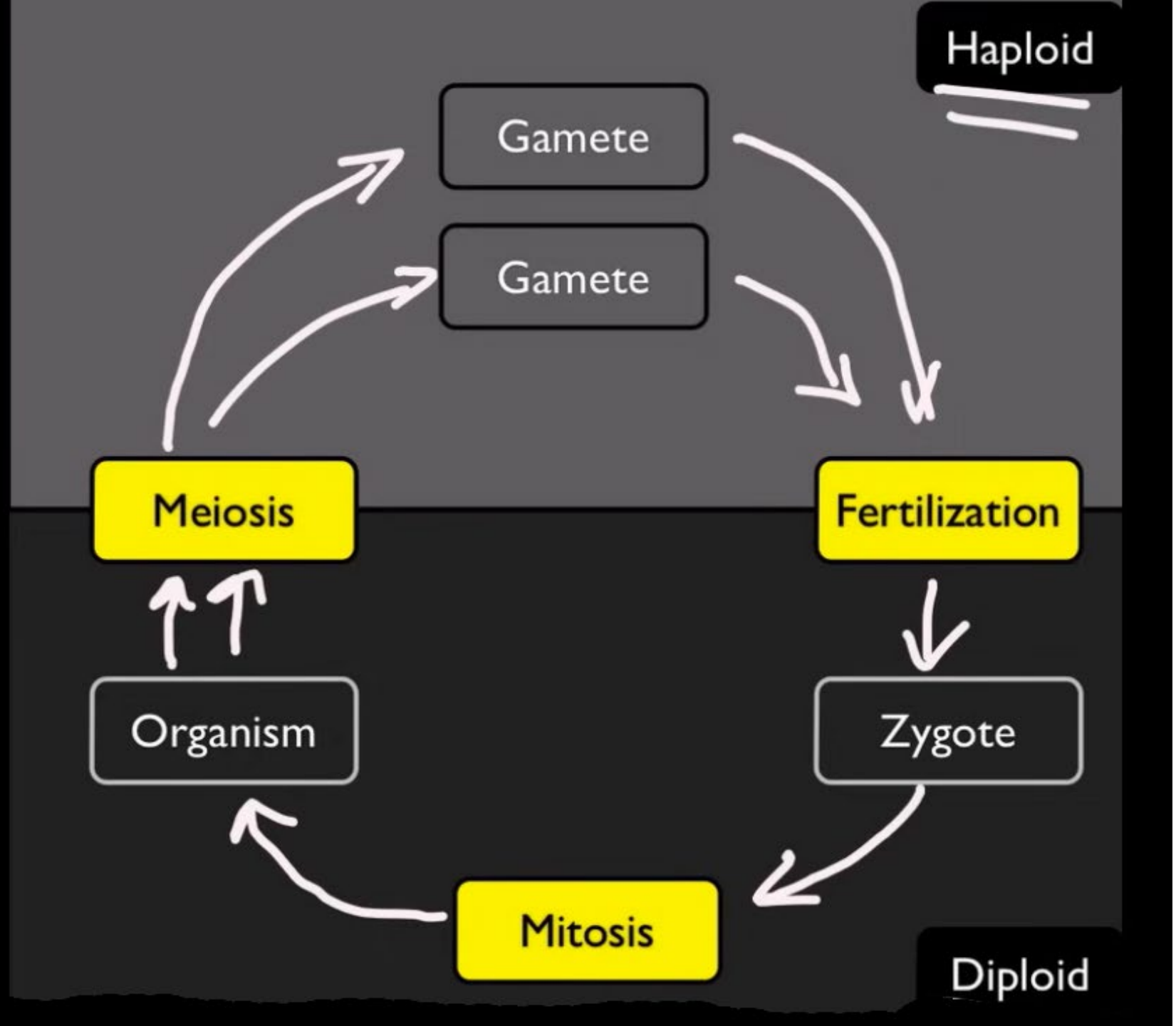


Meiosis Produces Haploid Cells (n)



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



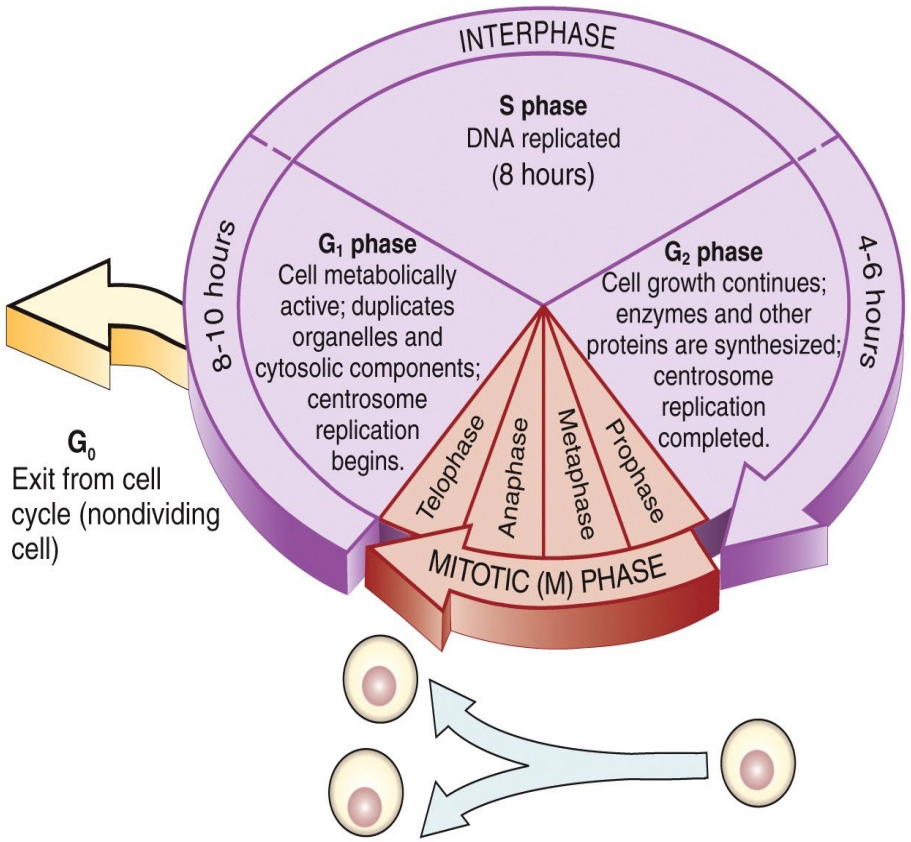
Cell Cycle

In a mitosis cell cycle a cell will pass through two phases before it produce two identical cells

The two phases
–mitotic phase
–Interphase

–phases are divided into sub-phases

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



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

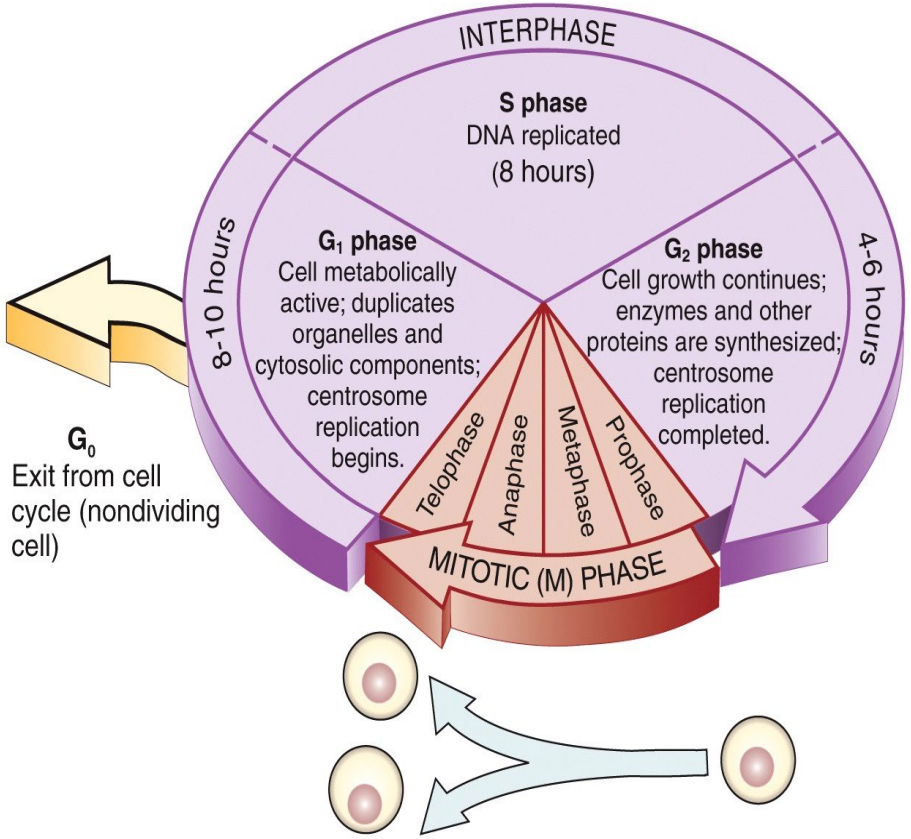
Cell Cycle

During embryonic development, genes are turned on or 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.



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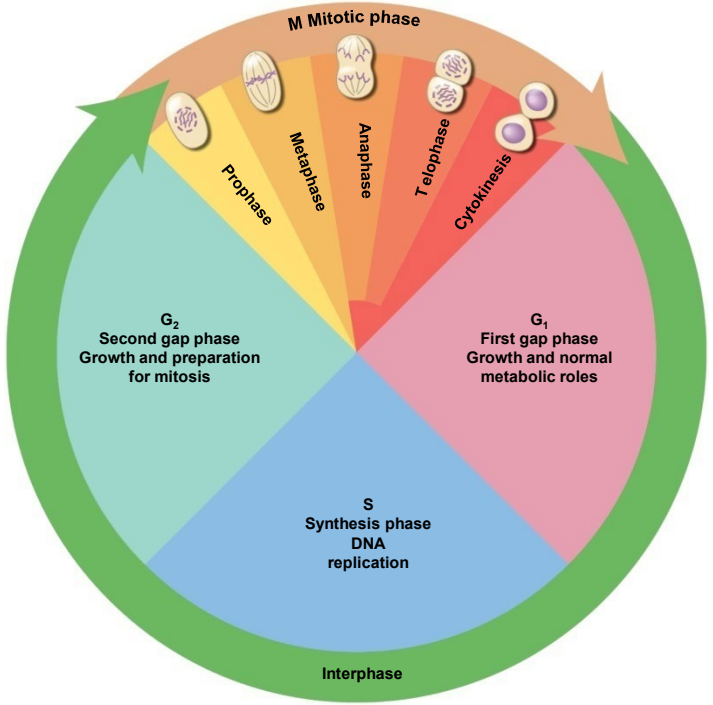
Cell Cycle

Interphase has three phases /// interphase is when the cell is "doing its work" and it is during interphase that the cell doubles its DNA (there is also an optional fourth phase called G zero)

G_1 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

G_2 phase, second gap phase
–interval between DNA replication and cell division
–finishes centriole duplication
–synthesizes enzymes that control cell division
–repairs DNA replication errors



G_0 (G zero) phase

Cells that leave the cell cycle to "rest" / temporary pause

Skeletal muscle and almost all nerve cells are examples of cells in G zero

Cell Cycle

M phase = Mitotic Phase

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

–cell must double DNA so each daughter cell will receive same amount of DNA as parent cell

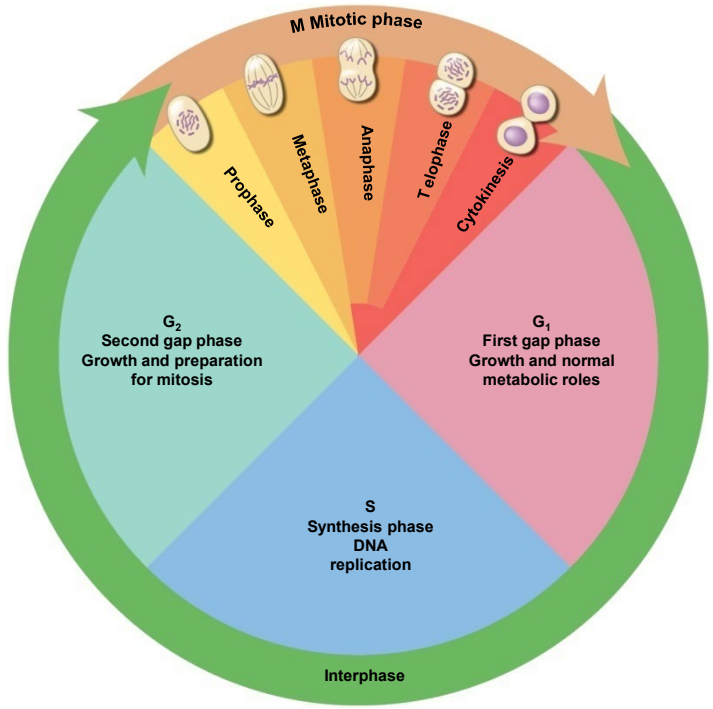
–after DNA is duplicated the cell pinches in two to form two new daughter cells

Interphase

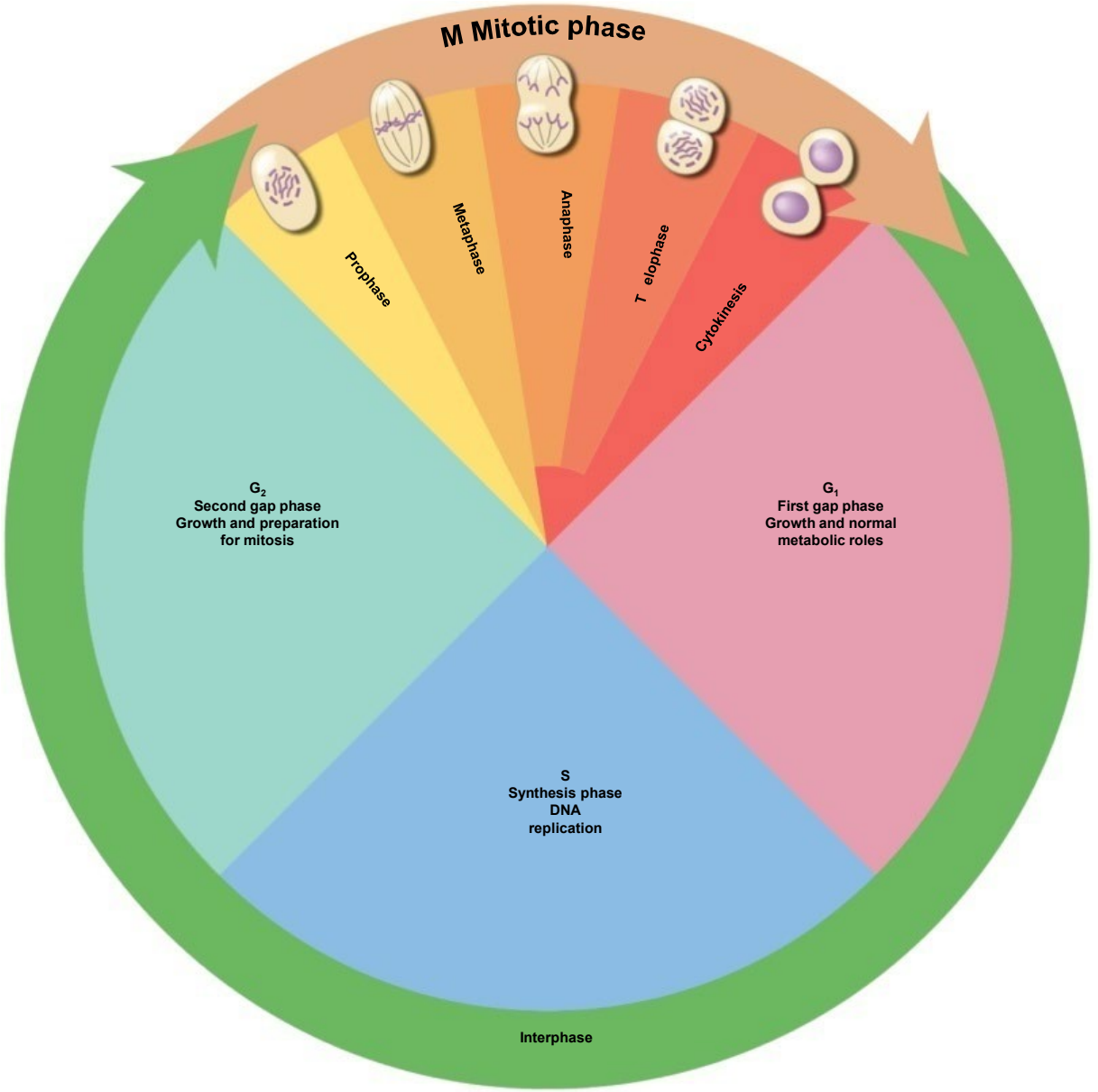
–G1, S, and G2 phases

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

Cell cycle duration varies between cell types



Cell Cycle

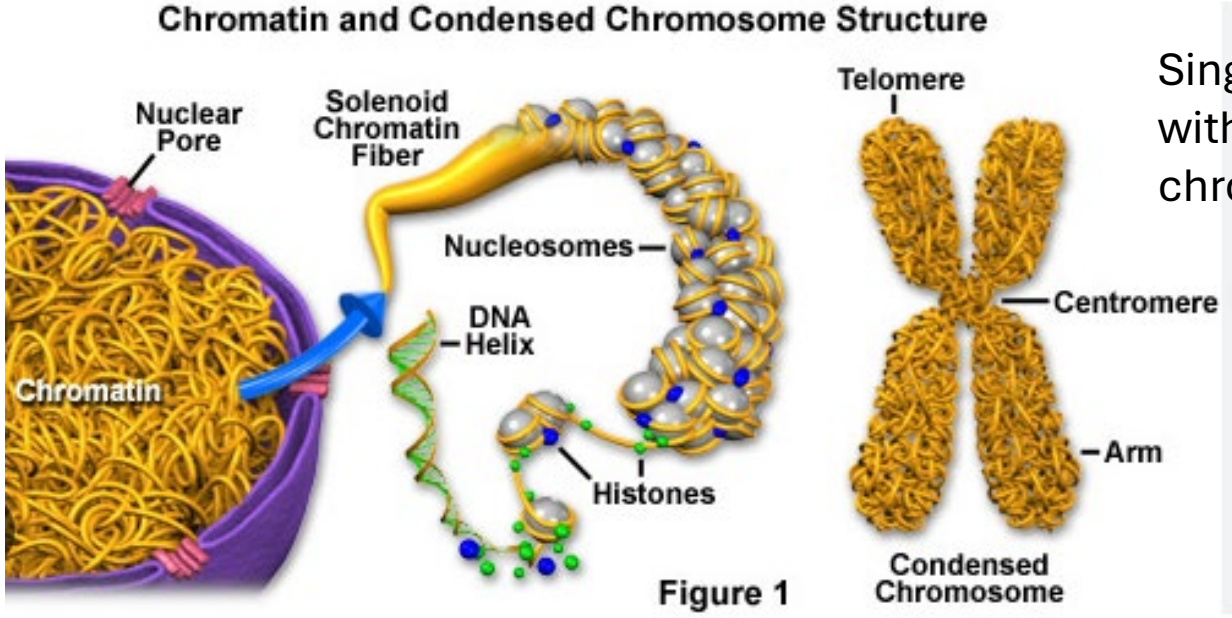

M Mitotic phase
Prophase
Metaphase
Anaphase
Telophase
Cytokinesis
G2
Second gap phase
Growth and preparation
for mitosis
G1
First gap phase
Growth and normal
metabolic roles
S
Synthesis phase
DNA
replication
Interphase

DNA Replication

Before a cells 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.

When DNA nucleic acids are tightly coiled during the mitotic phase the nucleic acids are visible and are called chromosomes



Single chromosome with two sister chromatids

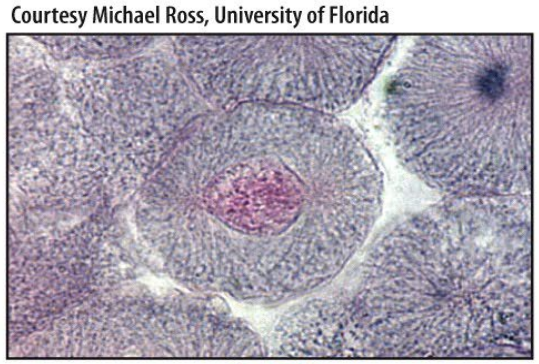
At end of interphase the parent cell (i.e. the original cell) has doubled its DNA /// now the parent cell can give each new cell (the daughter cell) a complete copy of DNA (46 chromosomes)

46 x 2 = 92 (or 46 identical chromosomal pairs)

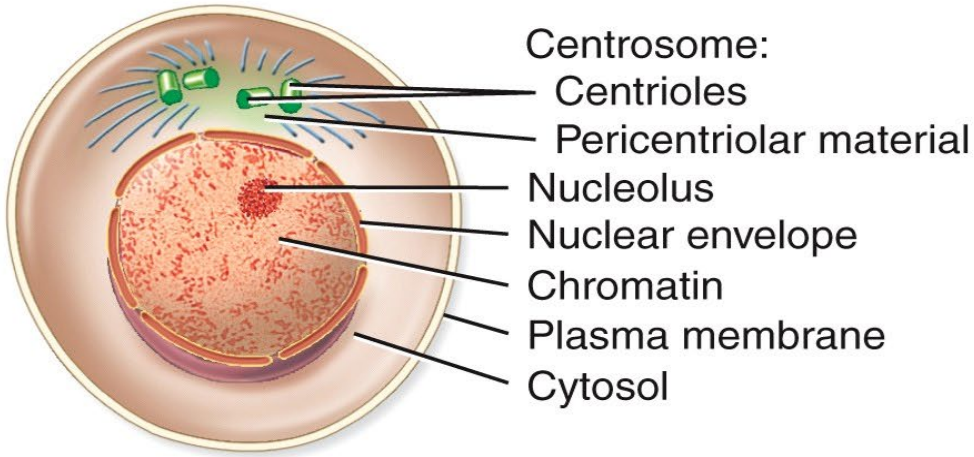
Since DNA controls all cellular function, this replication process must be very exact – no mistakes in duplication process /// a mistake = a mutation

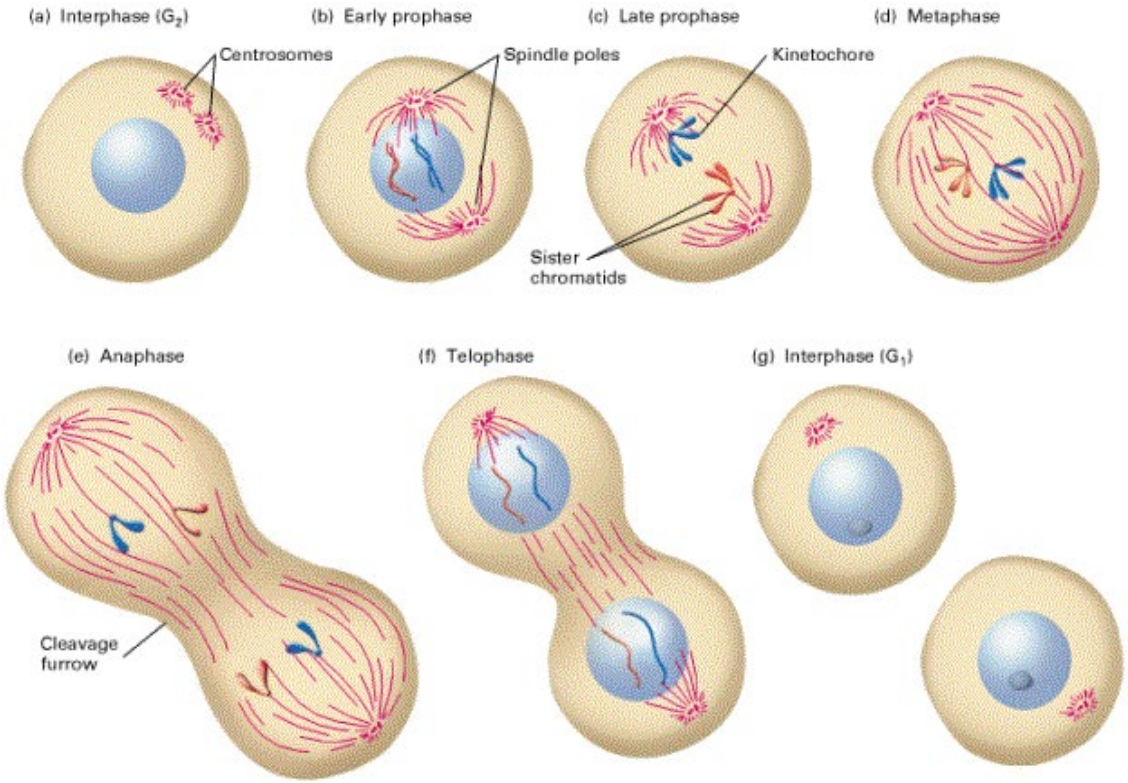
Chromosome genes are "recipes" for making protein. A gene is a segment on the DNA strand.

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



(a) INTERPHASE





Chromosomes form and are only visible in the mitotic phase.

During interphase, the DNA is diffused and called chromatin.

Two Laws Allow for Accurate DNA Replication

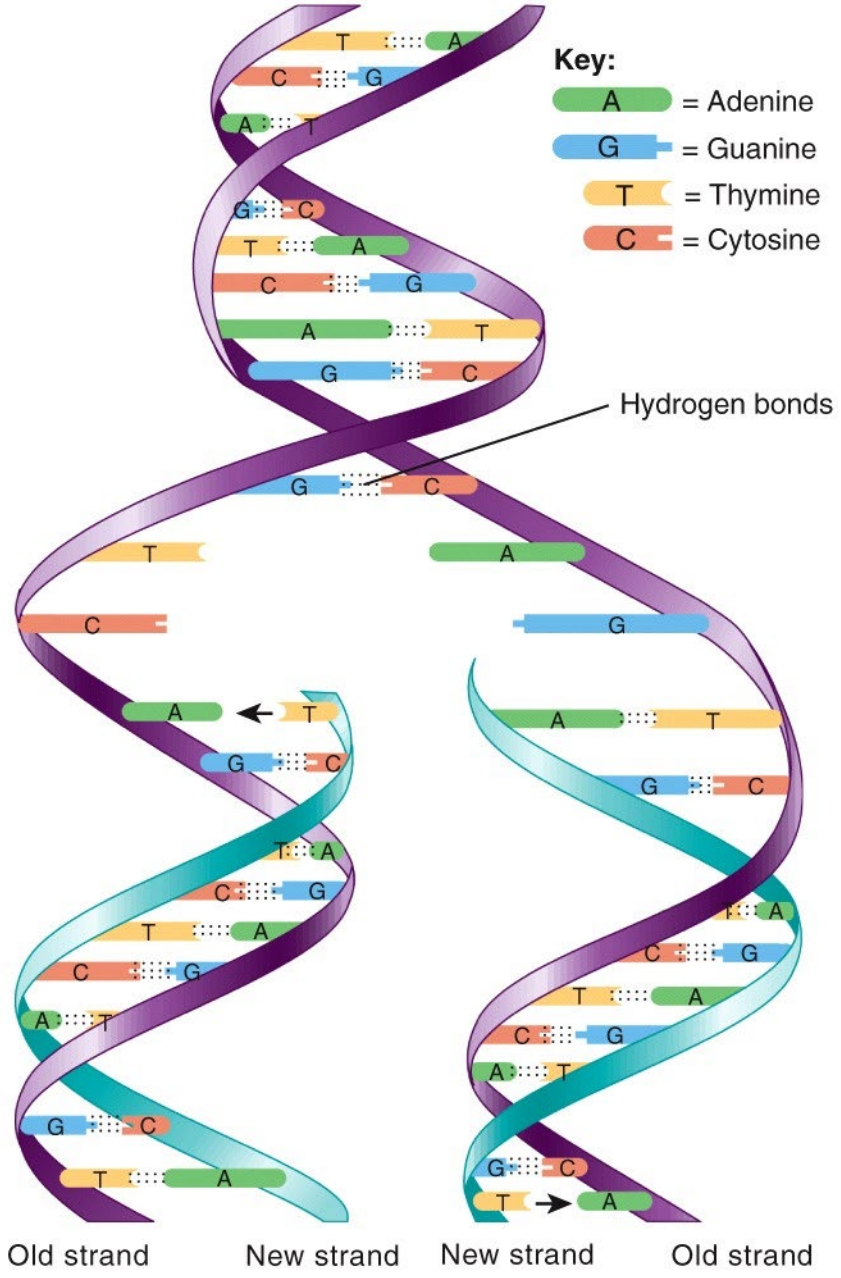
Law of Complementary Base Pairing

–we can predict the base sequence of one DNA strand if we know the sequence of the other

–enables a cell to reproduce one strand based on the information in another

Law of Semi-Conservative Replication

–A newly formed cell will contain a DNA molecule with one side made from new nucleotides and the other side of the DNA molecule will have the original DNA molecule



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

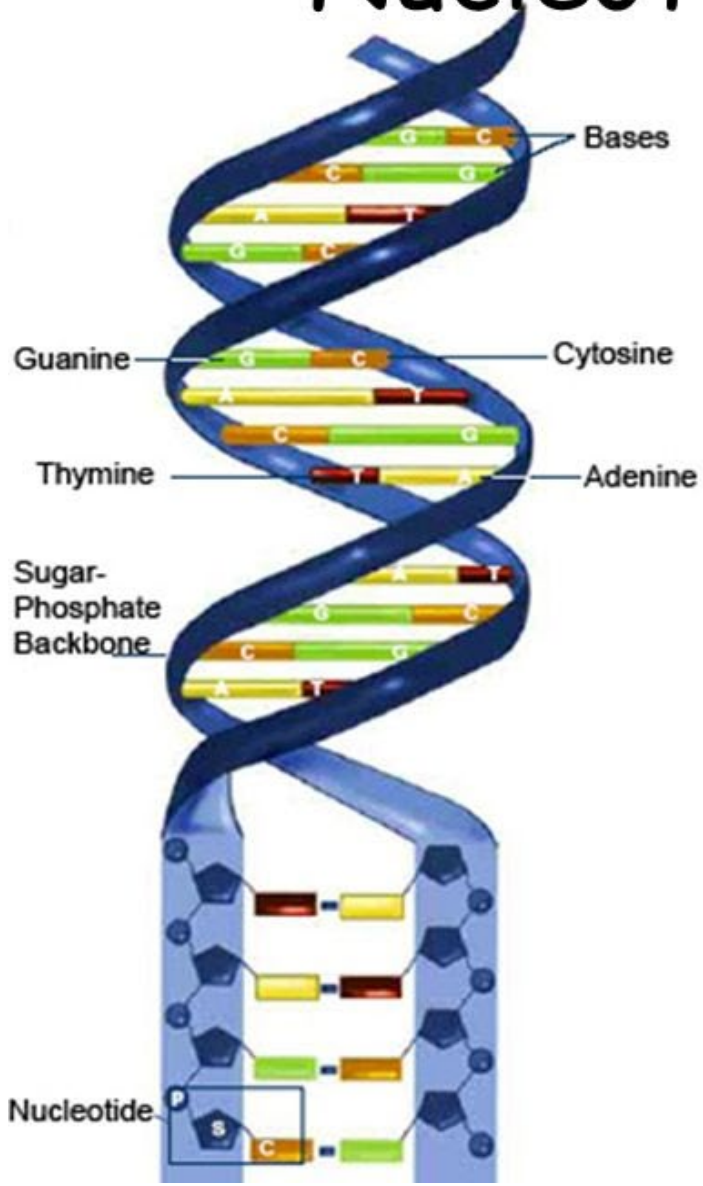
These four nucleotide molecules are used to make a strand of nucleic acid (DNA).

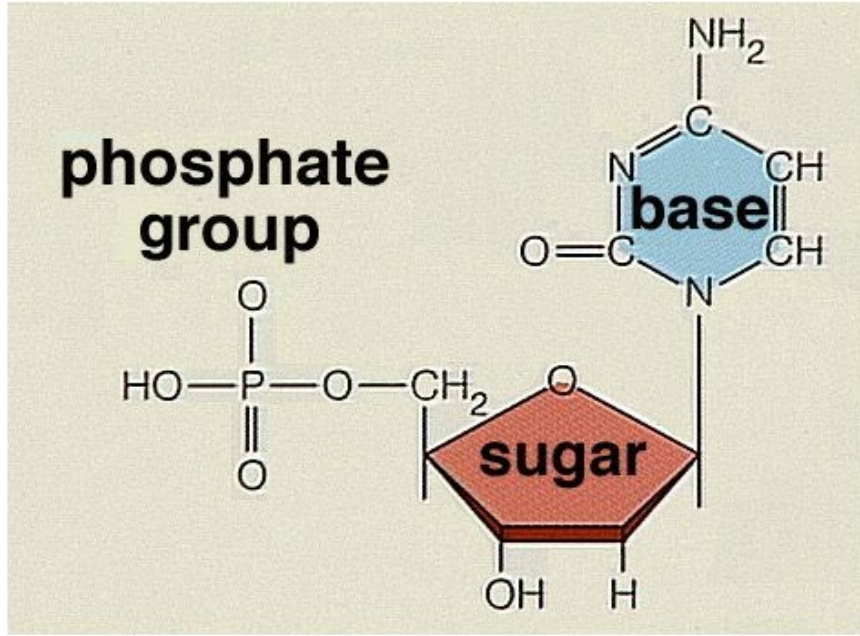
Adenine forms hydrogen bonds only with thymine. (A-T)

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.

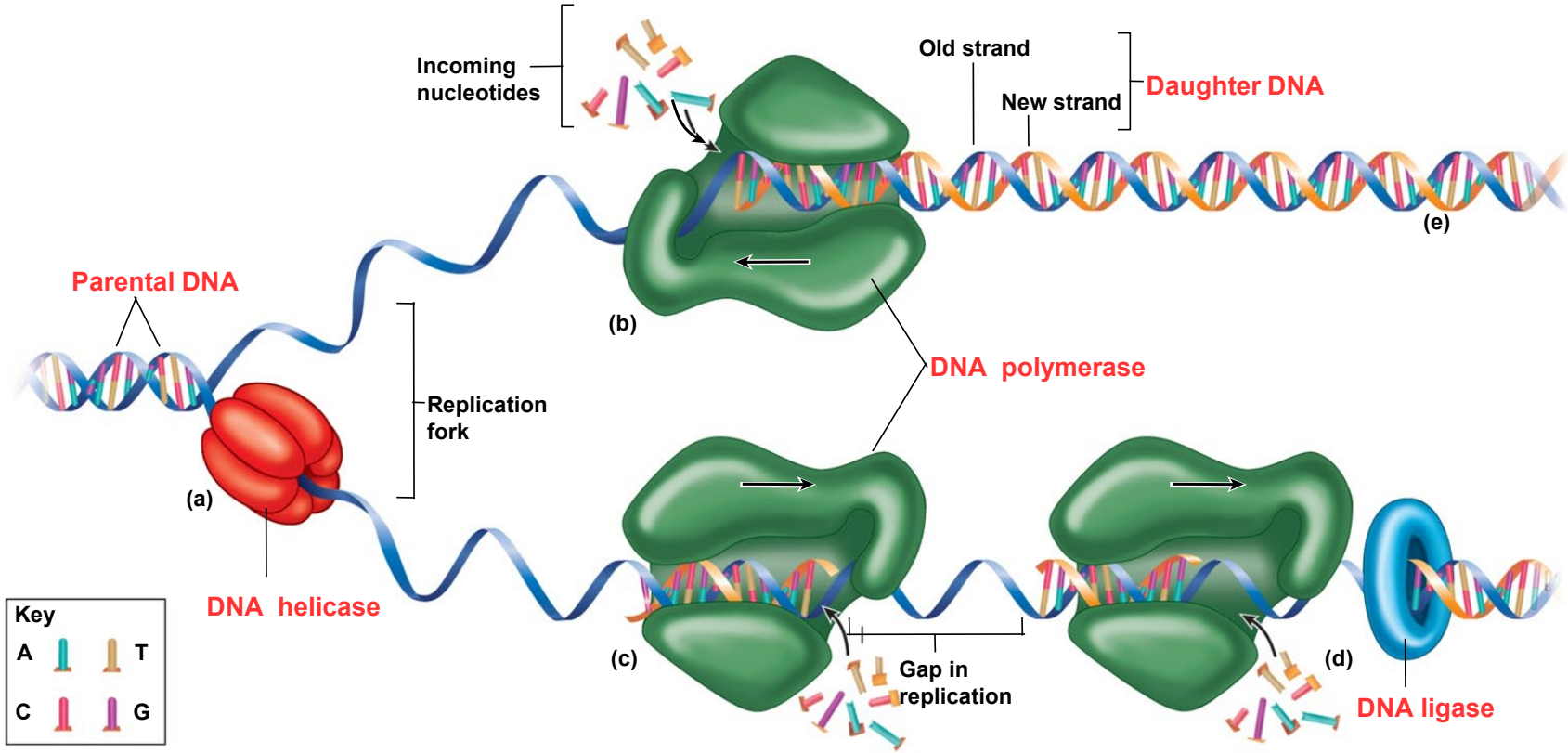
Nucleotides Form DNA





Nucleotide Structure

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

Functions of mitosis

–growth of tissues and organs after birth

–replacement of cells that die

–conserve chromosome number (diploid cell division.

Four mitotic phases

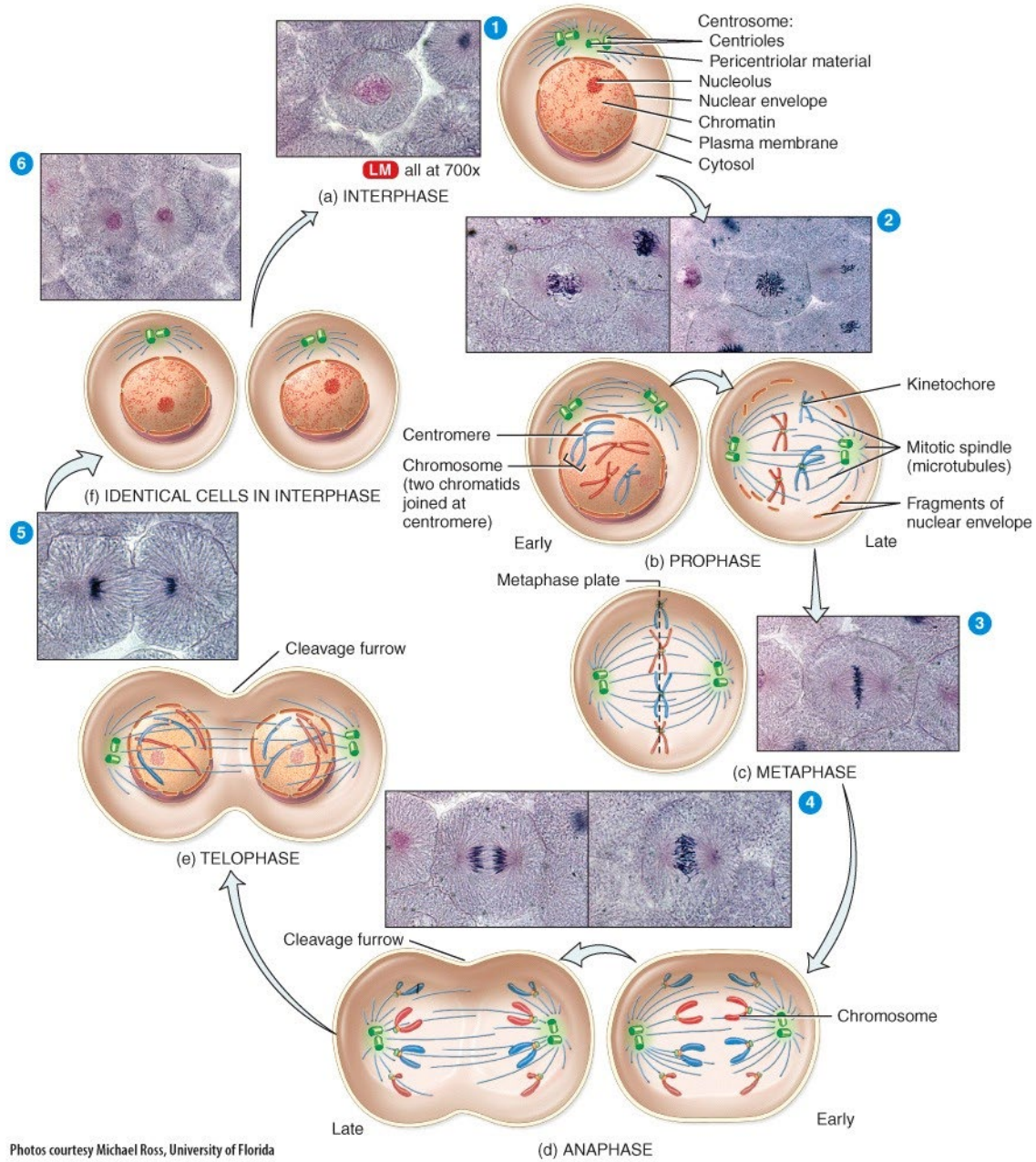
–Prophase

–Metaphase

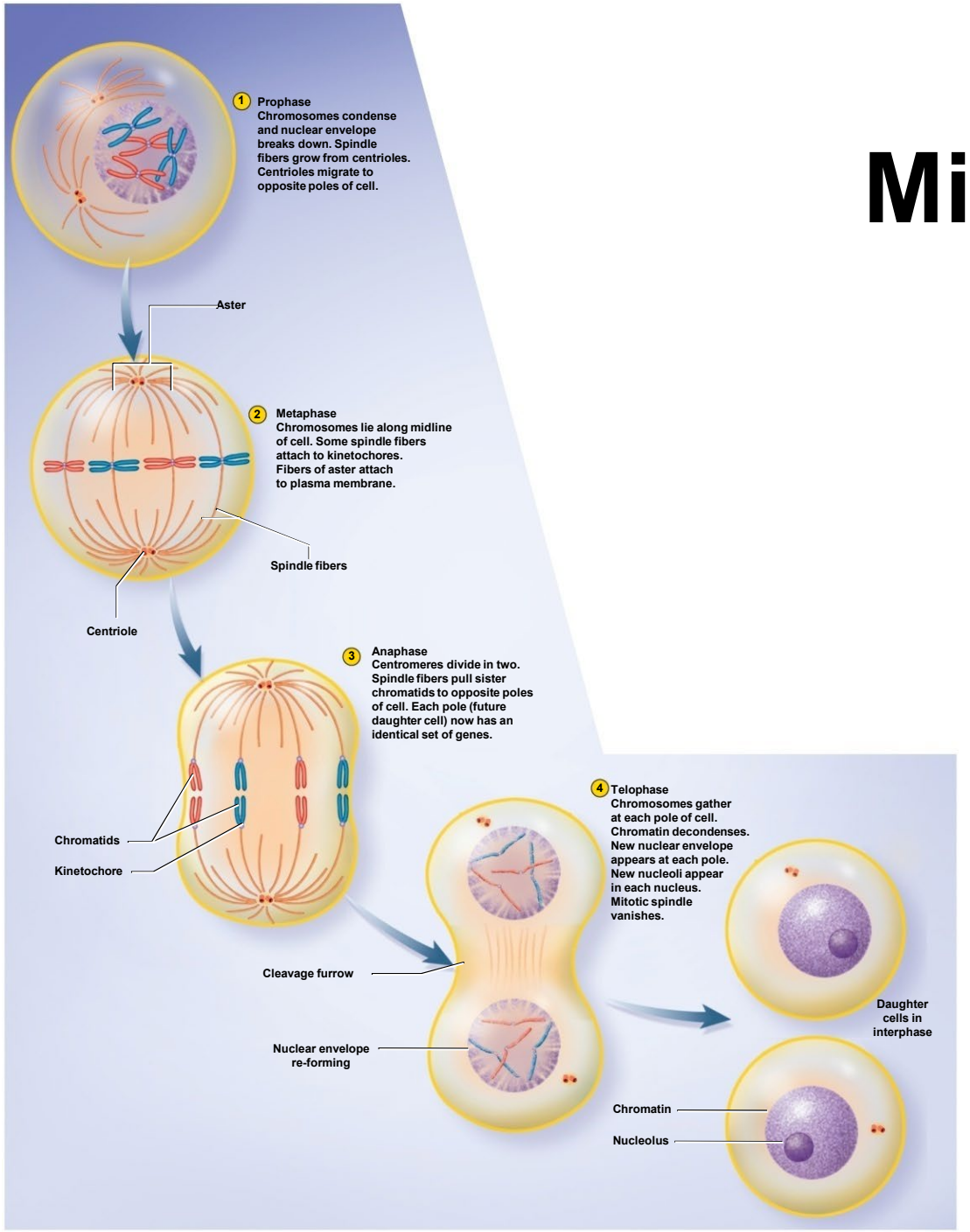
–Anaphase

–Telophase

–(Note: during telophase cytokinesis occurs)


1
Centrosome:
Centrioles
Pericentriolar material
Nucleolus
Nuclear envelope
Chromatin
Plasma membrane
Cytosol
LM all at 700x
(a) INTERPHASE
2
Kinetochore
Centromere
Chromosome (two chromatids joined at centromere)
Mitotic spindle (microtubules)
Fragments of nuclear envelope
Early
Late
(b) PROPHASE
3
Metaphase plate
(c) METAPHASE
4
Cleavage furrow
Chromosome
Late
Early
(d) ANAPHASE
Cleavage furrow
(e) TELOPHASE
5
(f) IDENTICAL CELLS IN INTERPHASE
6
Photos courtesy Michael Ross, University of Florida

Mitosis


1 Prophase
Chromosomes condense and nuclear envelope breaks down. Spindle fibers grow from centrioles. Centrioles migrate to opposite poles of cell.
Aster
2 Metaphase
Chromosomes lie along midline of cell. Some spindle fibers attach to kinetochores. Fibers of aster attach to plasma membrane.
Spindle fibers
Centriole
3 Anaphase
Centromeres divide in two. Spindle fibers pull sister chromatids to opposite poles of cell. Each pole (future daughter cell) now has an identical set of genes.
Chromatids
Kinetochore
4 Telophase
Chromosomes gather at each pole of cell. Chromatin decondenses. New nuclear envelope appears at each pole. New nucleoli appear in each nucleus. Mitotic spindle vanishes.
Cleavage furrow
Nuclear envelope re-forming
Daughter cells in interphase
Chromatin
Nucleolus

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

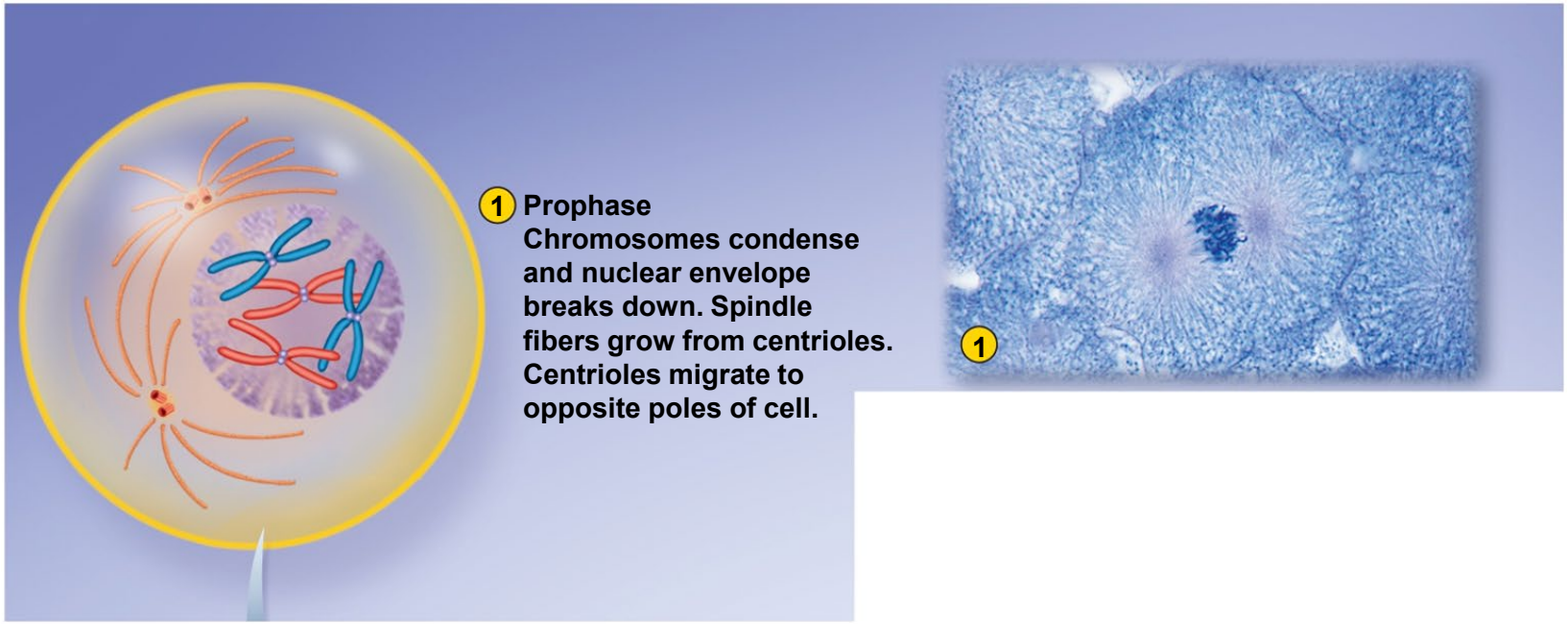
–pair of centrioles migrate to opposite poles of the nucleus

–after centrioles reach opposite sides /// spindle fibers grow toward chromosomes and attach to the kinetochore on each side of the centromere

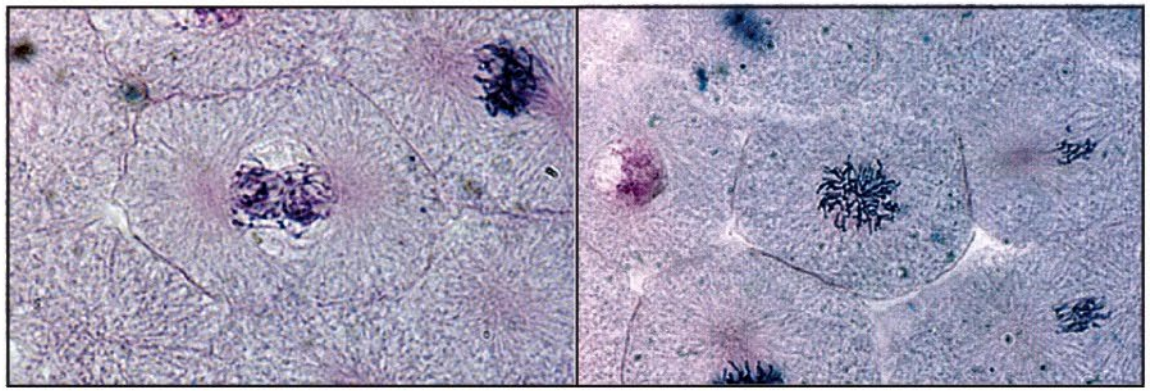
–Note: Kinetochore = point where chromatids attach to each other

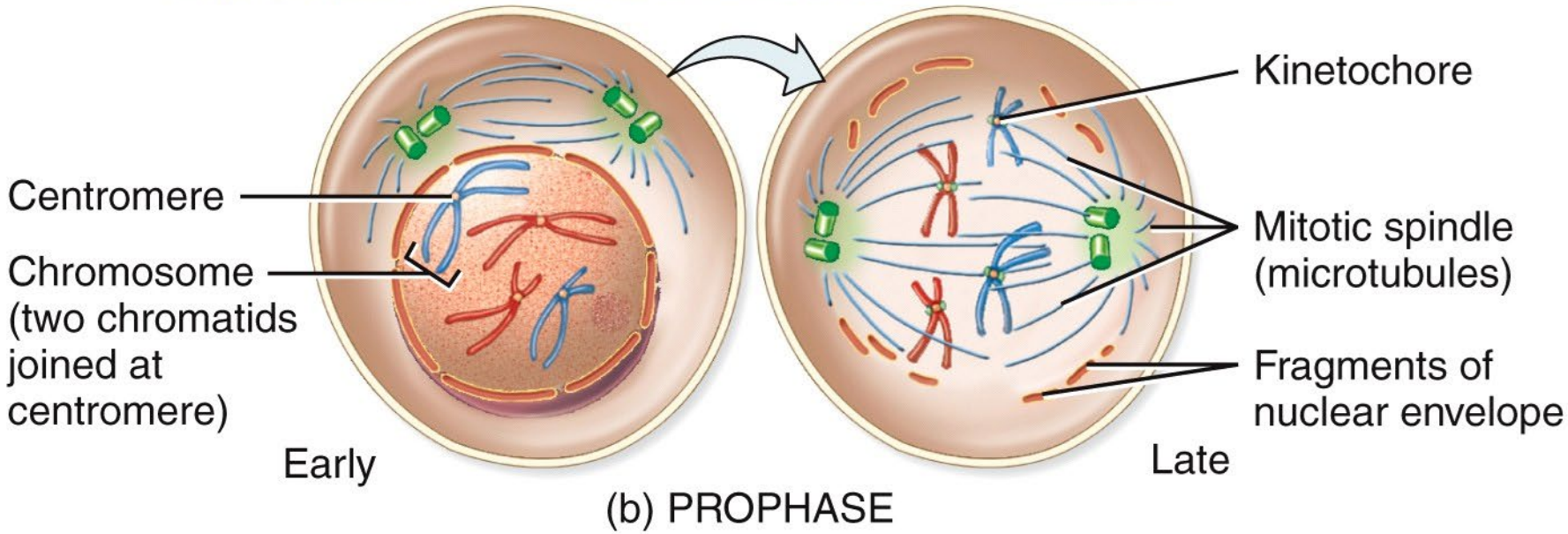
–spindle fibers then tug the chromosomes back and forth until they line up along the midline of the cell

Prophase



Courtesy Michael Ross, University of Florida





Metaphase

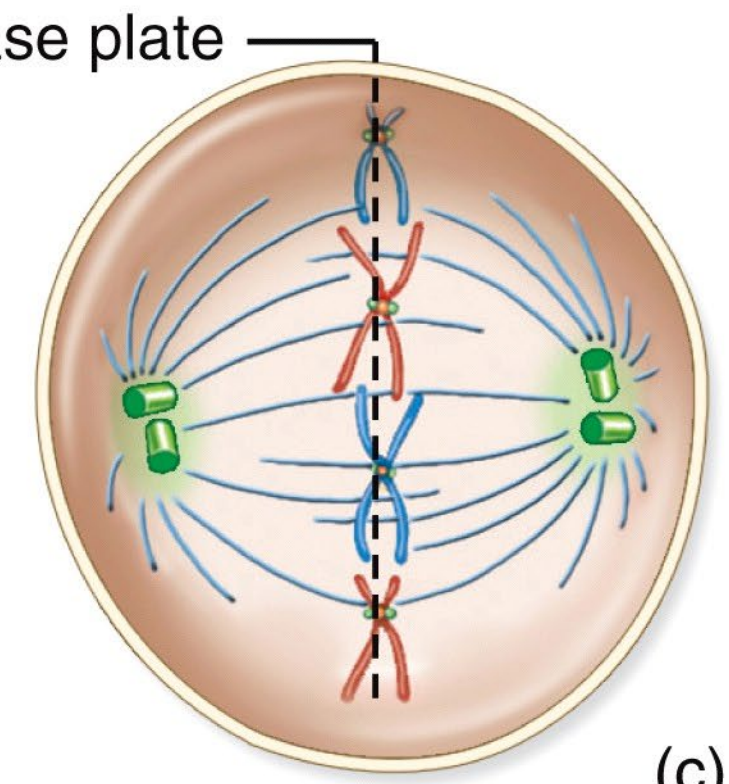
•Now chromosomes are aligned on cell equator

–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



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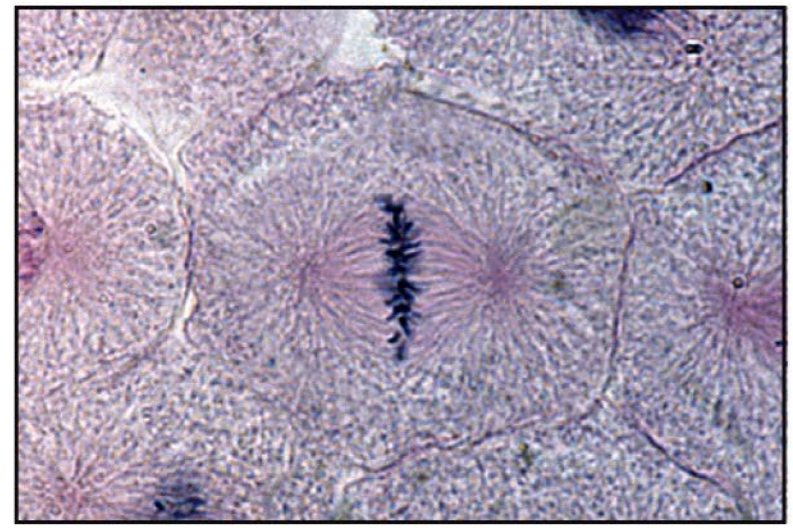


(c) METAPHASE

Anaphase

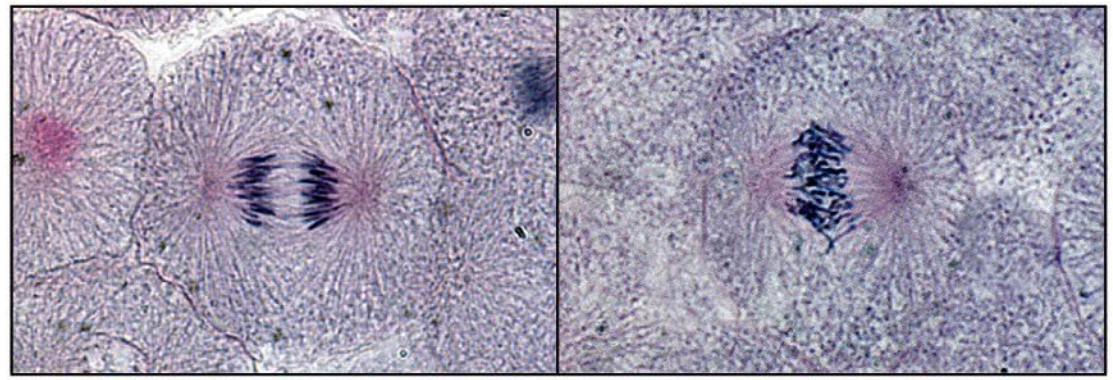
- Begins with activation of an enzyme that cleaves two sister chromatids /// separates the two chromatids at centromere (centromere = point where two chromatids are attachment)

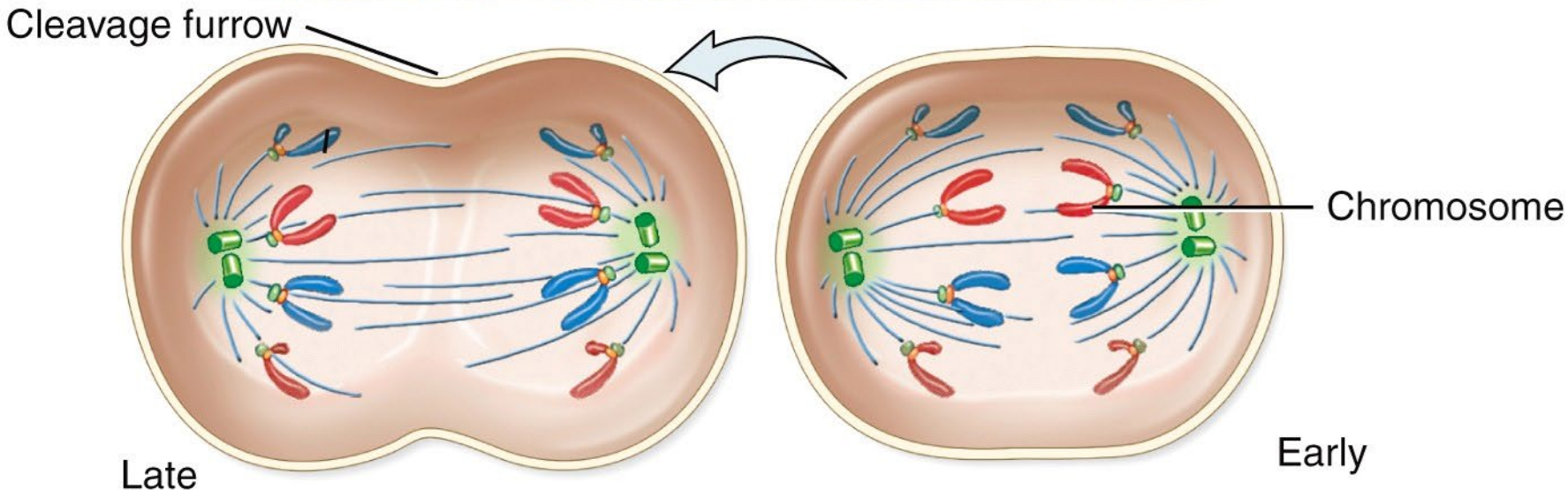
- Each chromatid now becomes a daughter chromosome which migrate towards opposite poles of the cell with centromere leading the way

–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





(d) ANAPHASE

Telophase

- chromatids (the daughter chromosome) cluster on each side of the cell

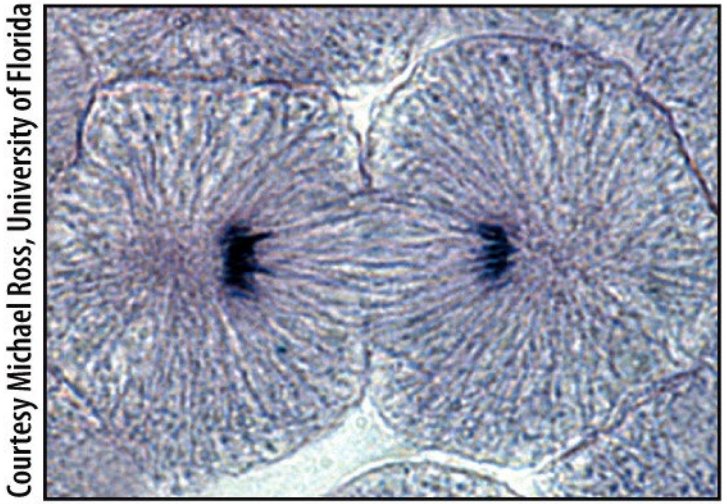
- rough ER produces new nuclear envelope around each cluster

- chromatids begin to uncoil and form the chromatin

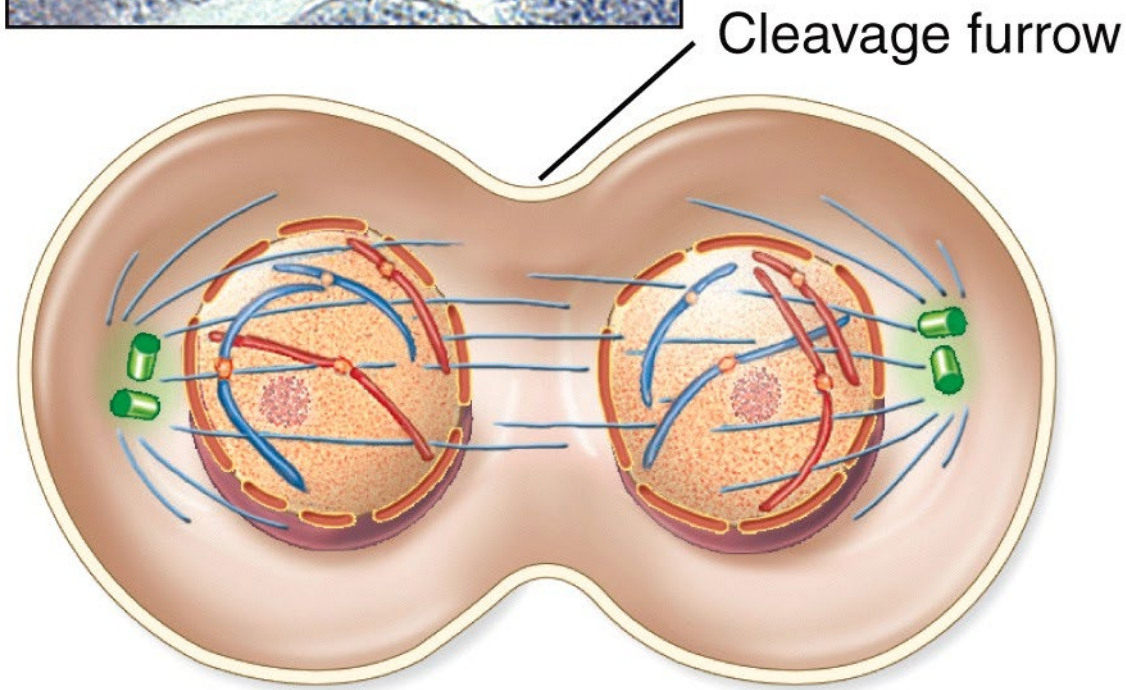
- remaining mitotic spindle breaks up and vanishes

- each nucleus forms nucleoli

–this indicates that cell has already begun making RNA and preparing for protein synthesis



Courtesy Michael Ross, University of Florida



(e) TELOPHASE

Cytokinesis

•Cytokinesis divides the cytoplasm between the two new cells

–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

•creates the cleavage furrow around the equator of cell

•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.

Timing of Cell Division

What will inhibit mitosis?

- When nutrients or growth factors are withdrawn

- If existing cells are too closely packed with neighboring cells / no room for new cells

- **Contact inhibition** – the cessation of cell division in response to contact with other cells

More About Meiosis

Meiosis: cell division that reduces chromosome number by ½

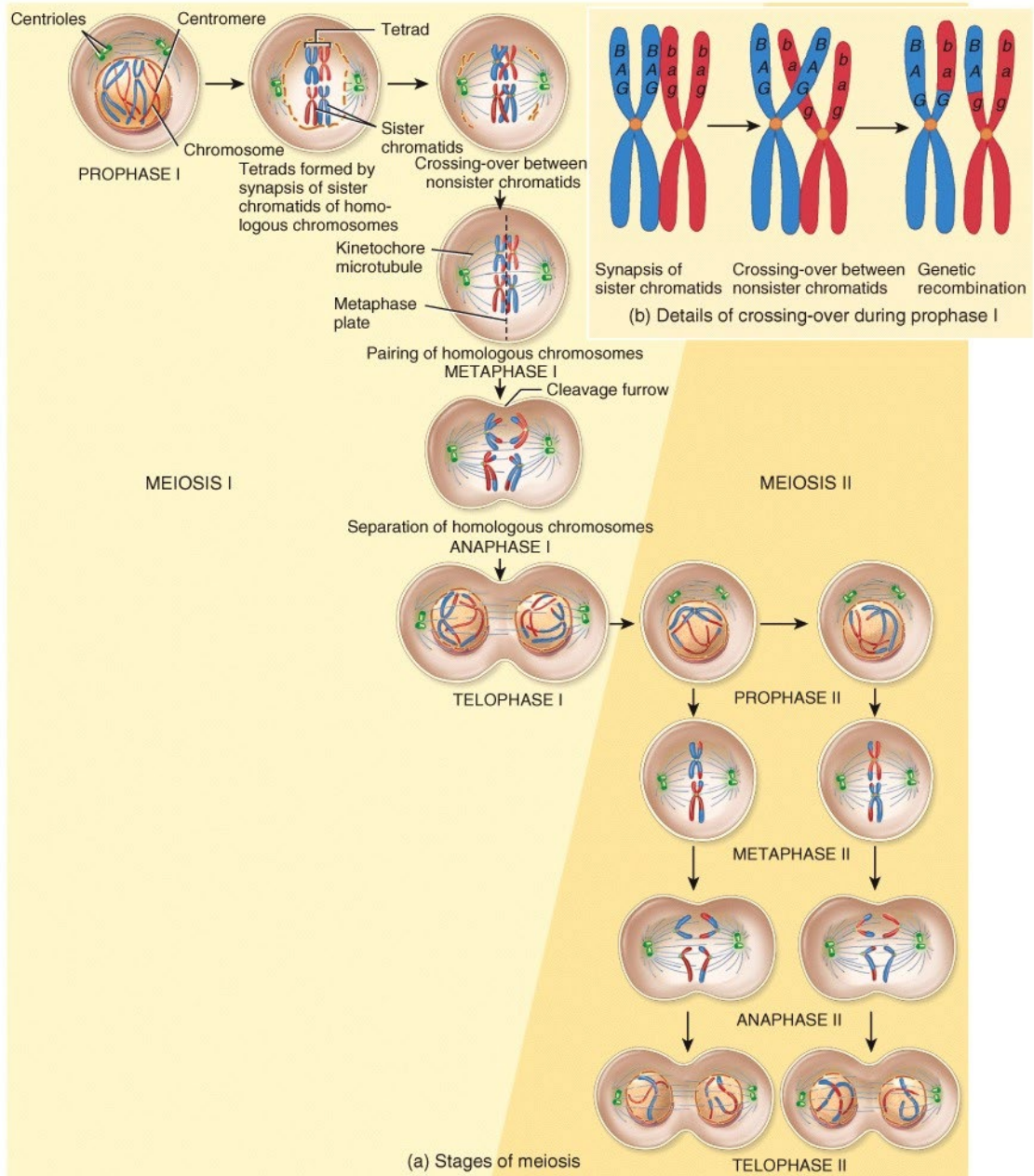
Human gonadal tissue produce gametes by meiosis (testes produce sperm and ovaries produce eggs)

The gametes are "haploid cells" (somatic cells are diploid)

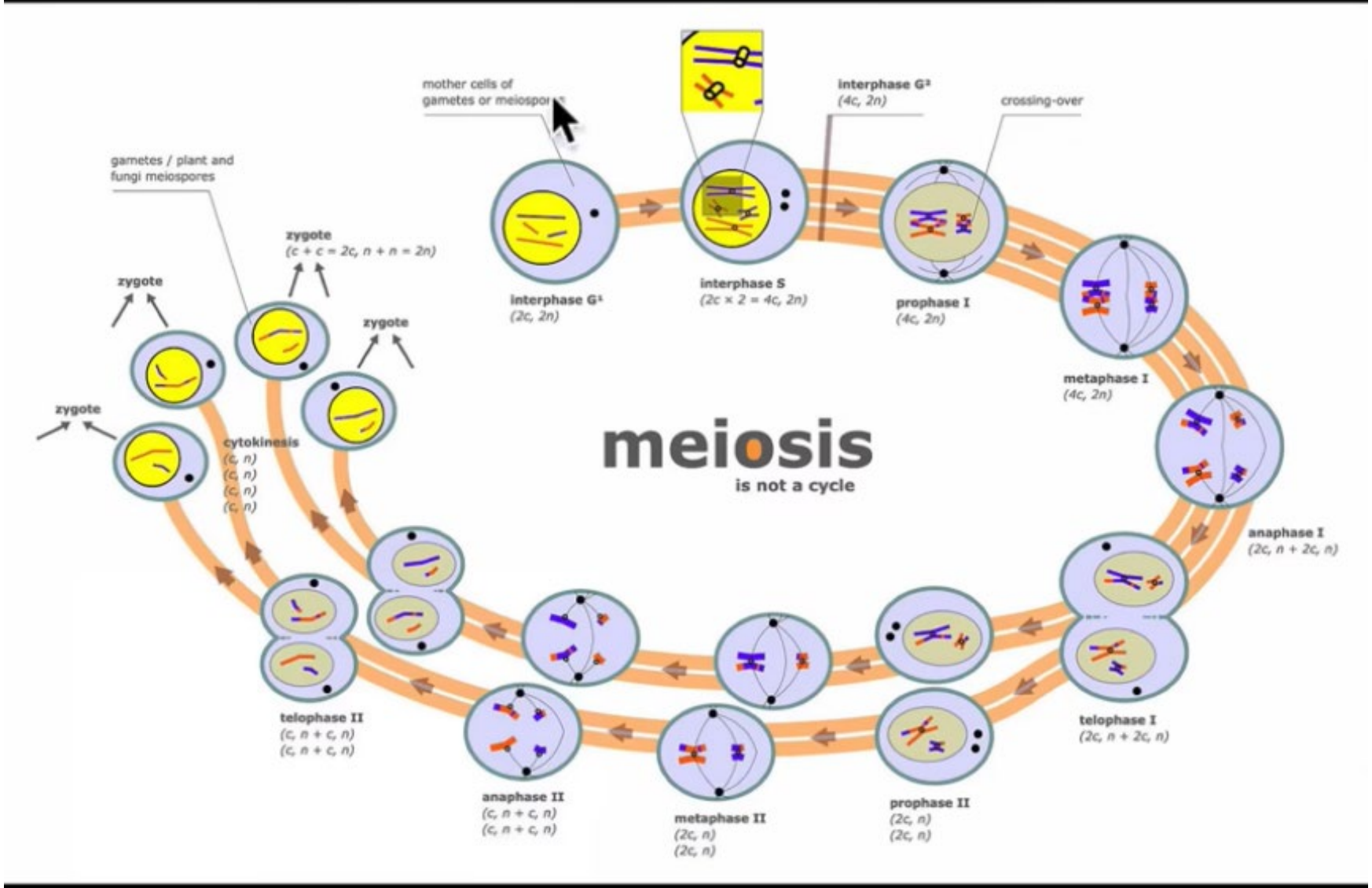
Haploid cells have 23 chromosomes

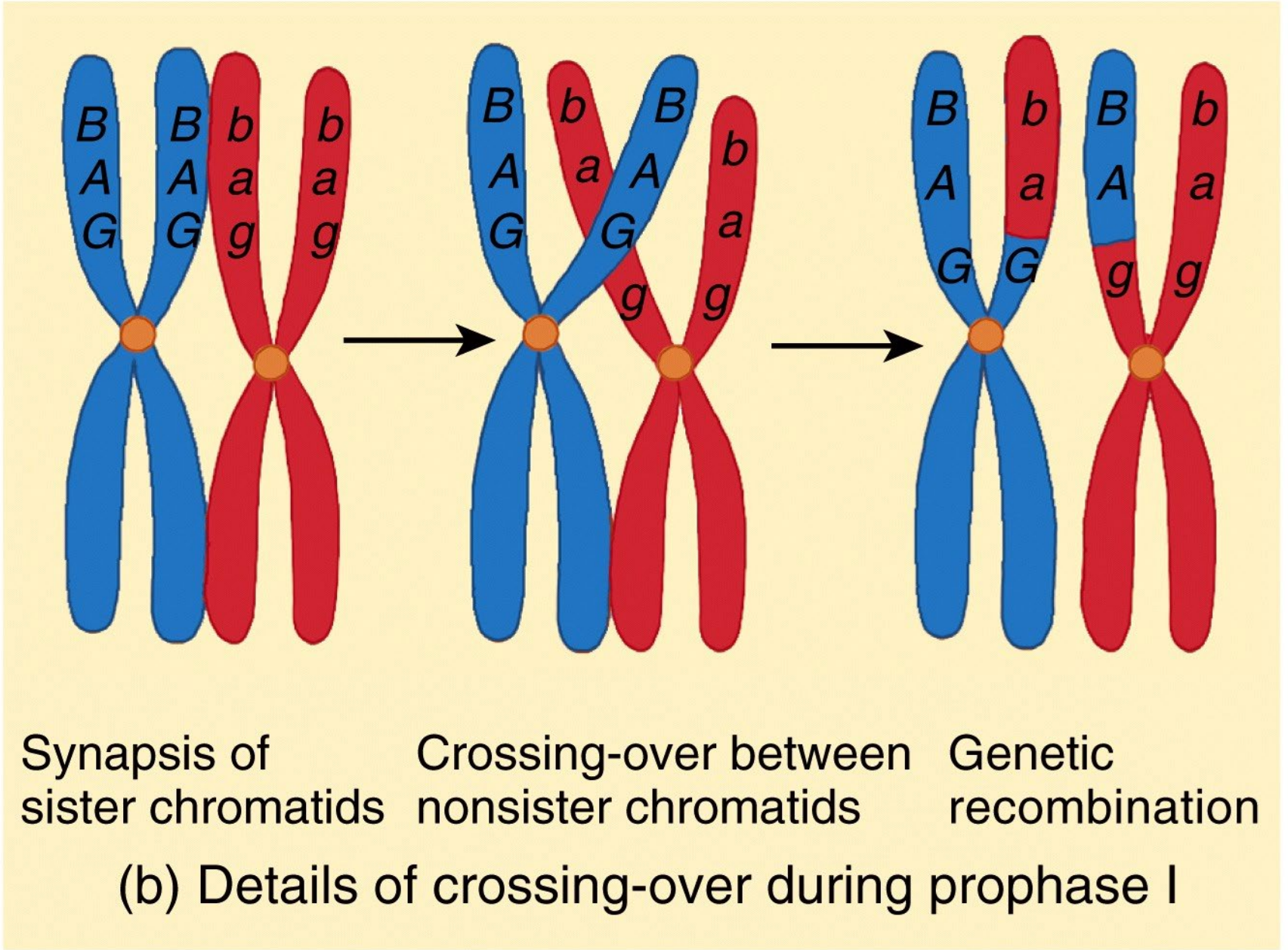
An egg and a sperm combine their chromosomes to create a new diploid cell called the zygote

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


Centrioles
Centromere
Tetrad
Chromosome
Sister chromatids
PROPHASE I
Tetrads formed by synapsis of sister chromatids of homologous chromosomes
Crossing-over between nonsister chromatids
Kinetochore microtubule
Metaphase plate
Pairing of homologous chromosomes
METAPHASE I
Cleavage furrow
MEIOSIS I
MEIOSIS II
Separation of homologous chromosomes
ANAPHASE I
TELOPHASE I
PROPHASE II
METAPHASE II
ANAPHASE II
TELOPHASE II
(a) Stages of meiosis
Synapsis of sister chromatids
Crossing-over between nonsister chromatids
Genetic recombination
(b) Details of crossing-over during prophase I

Phases of Meiosis



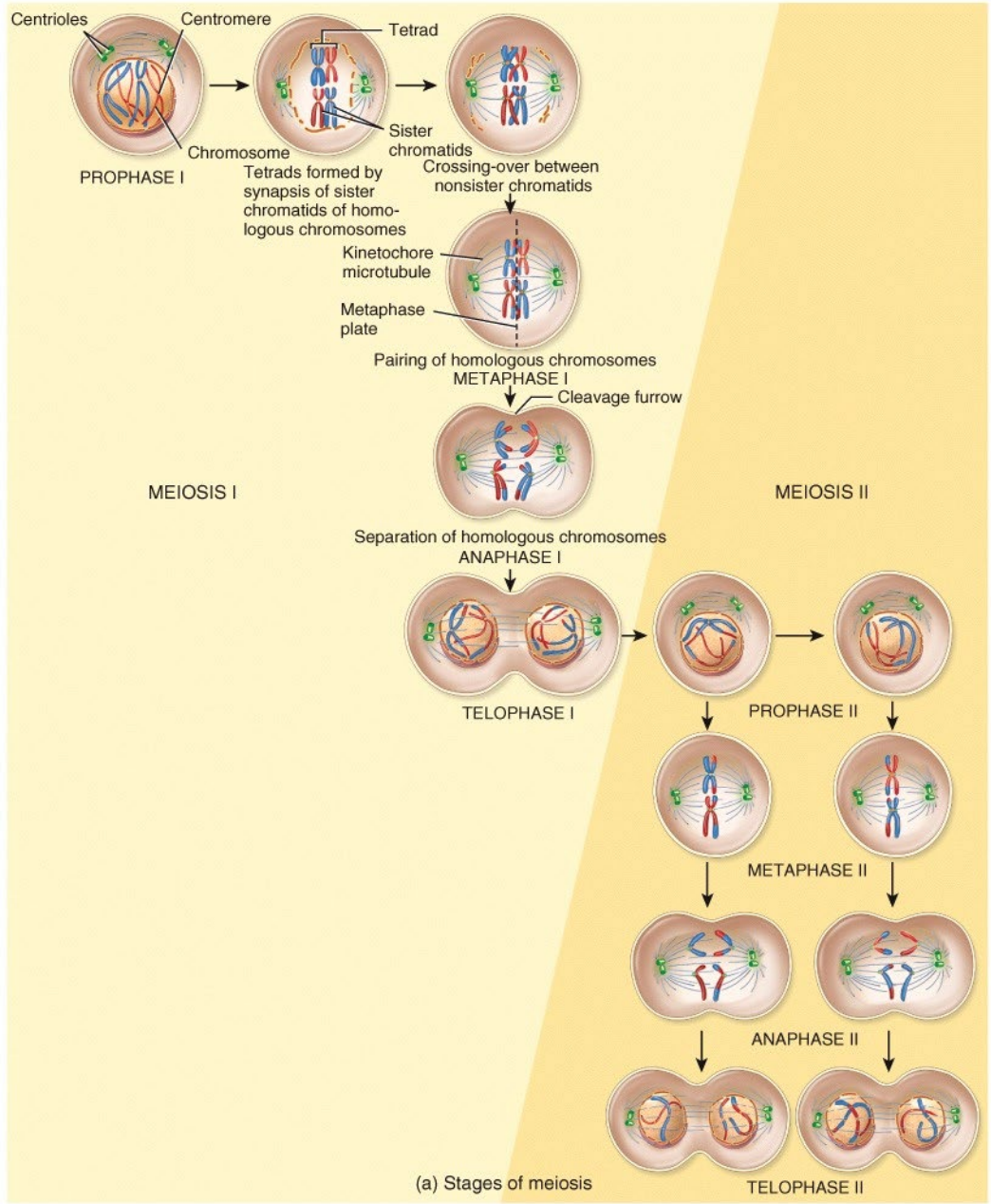


Synapsis of sister chromatids

Crossing-over between nonsister chromatids

Genetic recombination

(b) Details of crossing-over during prophase I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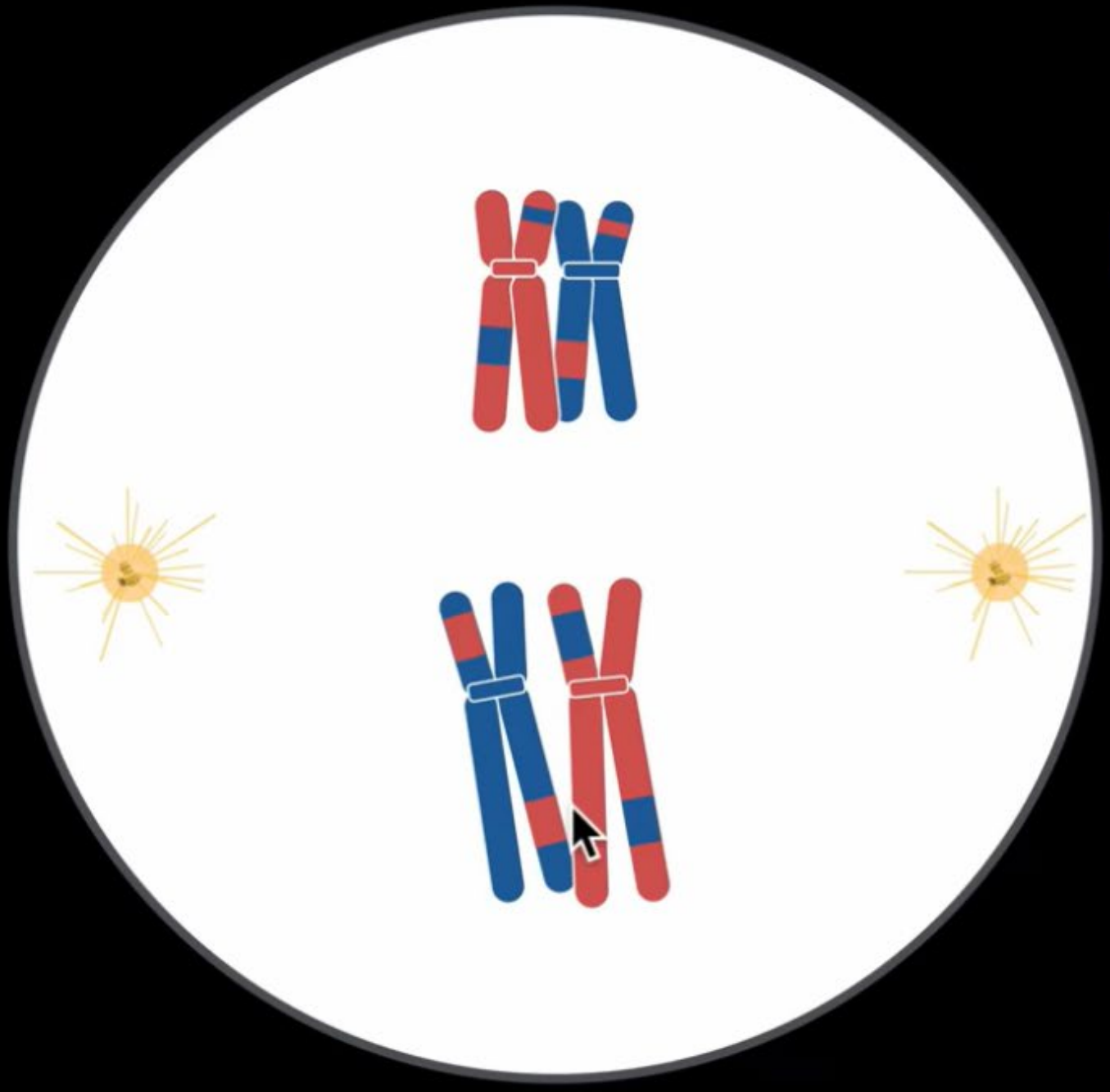
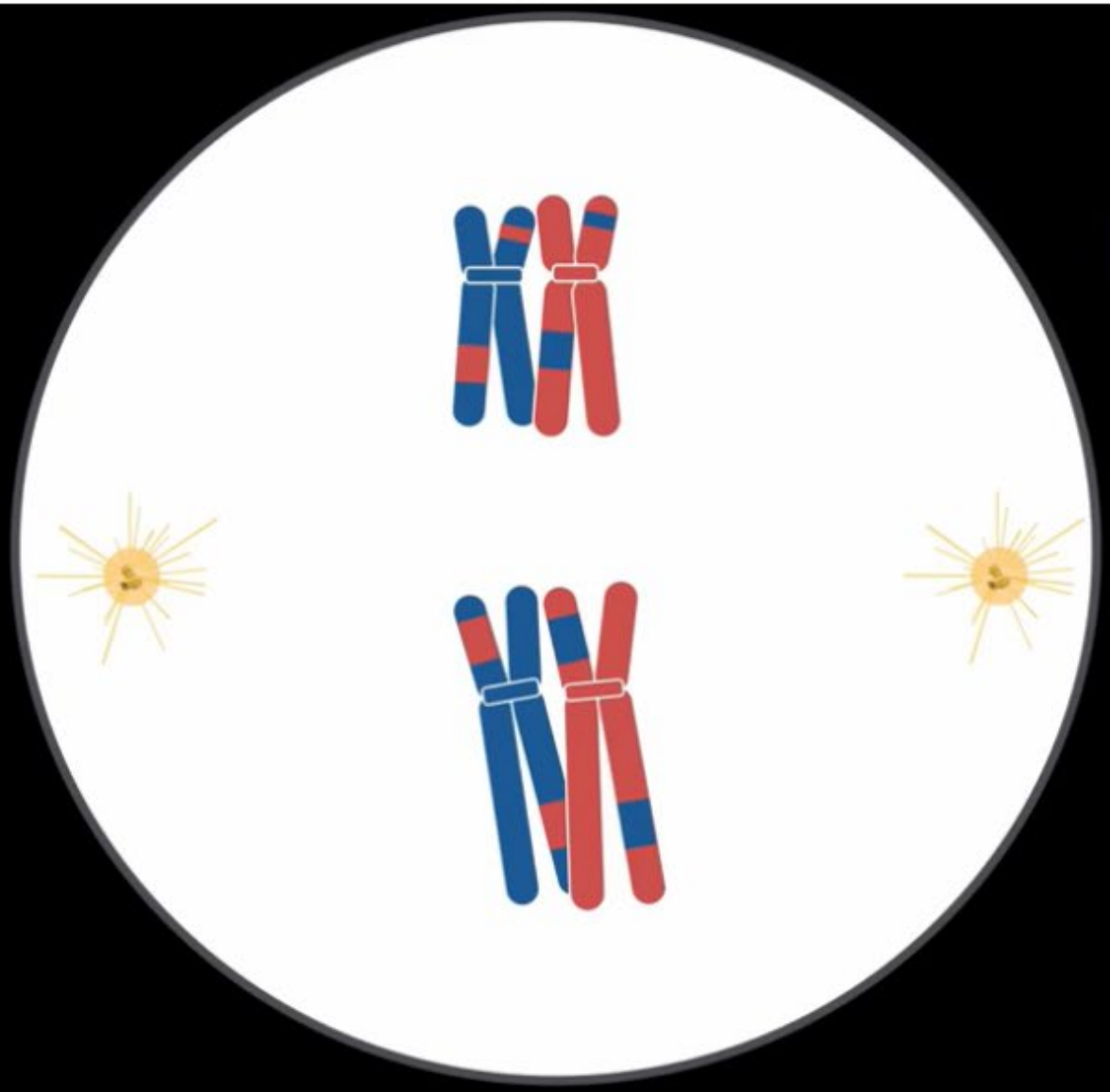
(a) Stages of meiosis



Metaphase I

Independent orientation

1



Metaphase I

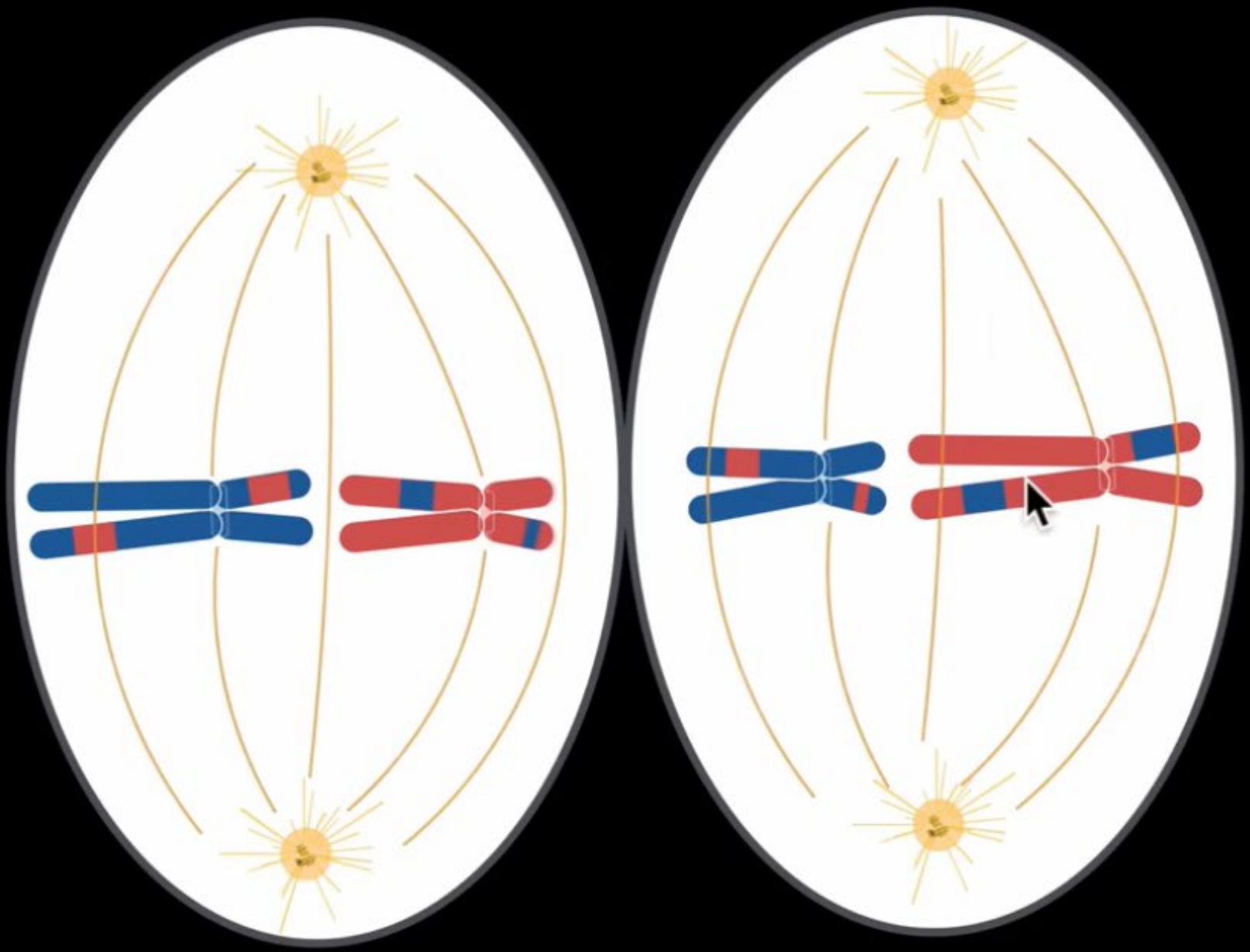
Independent orientation

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 predated our understanding of molecular biology and the discovery of DNA's role as the informational molecule responsible for heredity by almost 80 years.

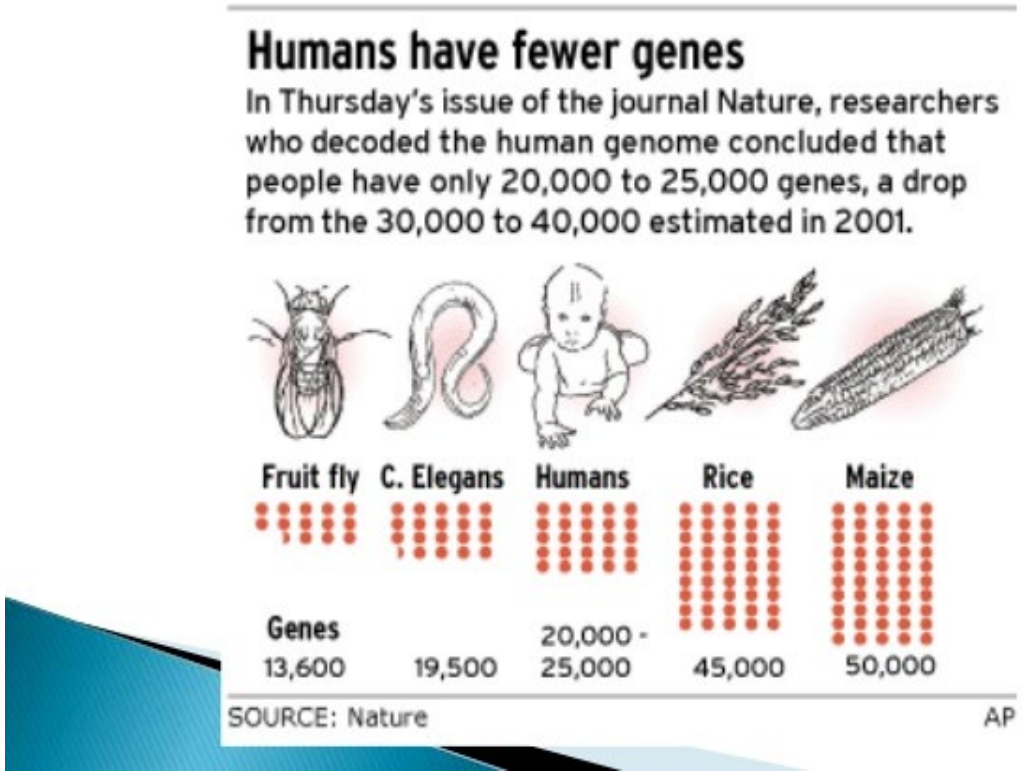
- Charles Darwin wrote On the Origin of Species in 1859. He explained how Evolution and Natural Selection create new species.

- 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.



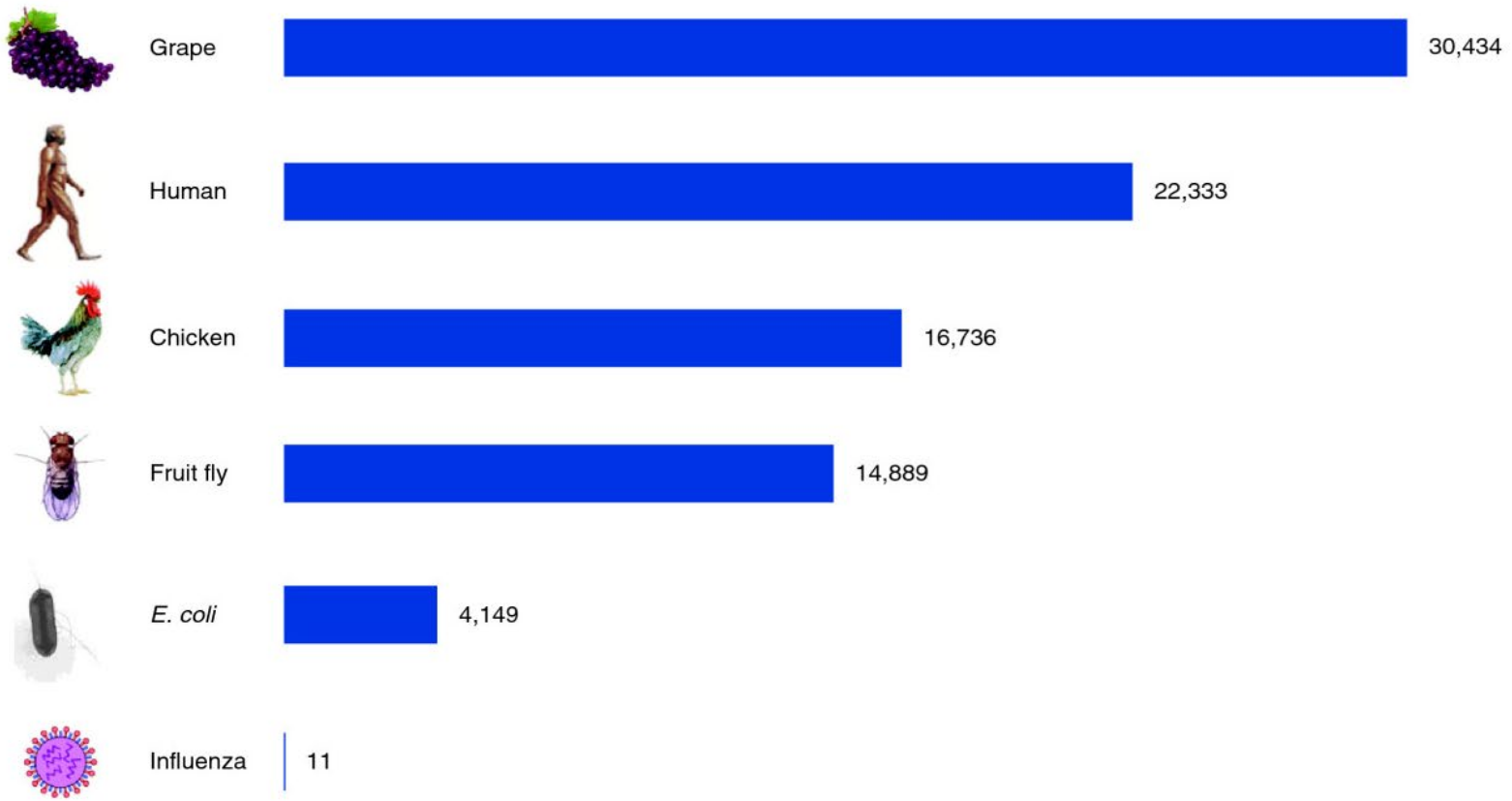
Genus species are defined by the number of chromosomes. The number of genes is just an index of how many different proteins the species is able to make.

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.

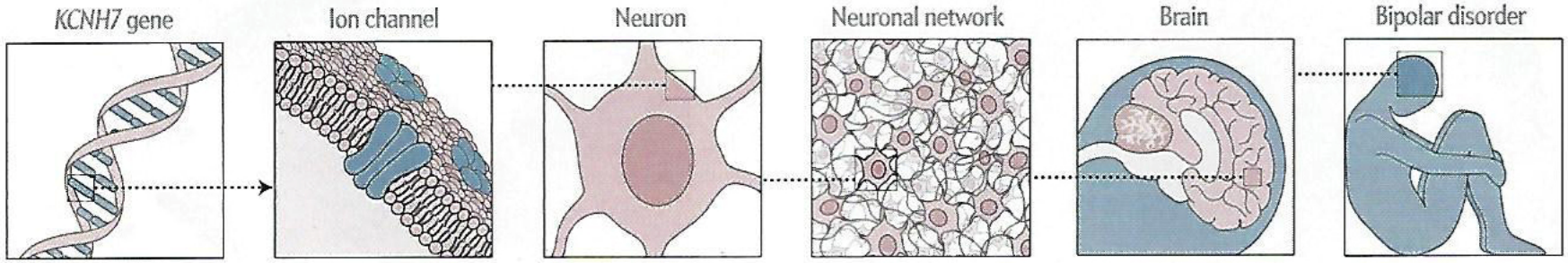
Number of Genes



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 mutations' 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 misspelled protein to perturbed brain function—could lead to fresh ideas for interrupting the chain of events underlying the disorder.