Note: if the handout links don't work, find the handouts in the handout list.

UN2005/UN2401 '17 Lecture 21

21A = Meiosis/Mitosis 21B = Chromosome squashes, karyotypes & chromosome structure 21C (Nondisjunction & 'super cycle'), and Handout 21D (individual life cycles).

I. Problems/issues of (Eukaryotic) Cell Division

A. So we know how prokaryotes divide. How do eukaryotes do it? First let's consider how individual cells (or unicellular eukaryotes) → 2 cells and then how one multicellular organism → multicellular offspring.

B. How do individual eukaryotic cells do it? Eukaryotic cell structure and implications

1. Structure/location of genome

a. Many chromosomes (multivolume encyclopedia as vs one vol.) = genetic material is divided into several pieces.

b. Chromosomes are linear and not attached to anything.

c. Much more DNA per cell and more per piece. 2-5 X 10^7 BP per euk. chromosome (or more); clearly > million; *E. coli* only 3 million BP total and all in one chromosome/piece. Also replication forks move more slowly (so replication takes longer even for same # nucleotides).

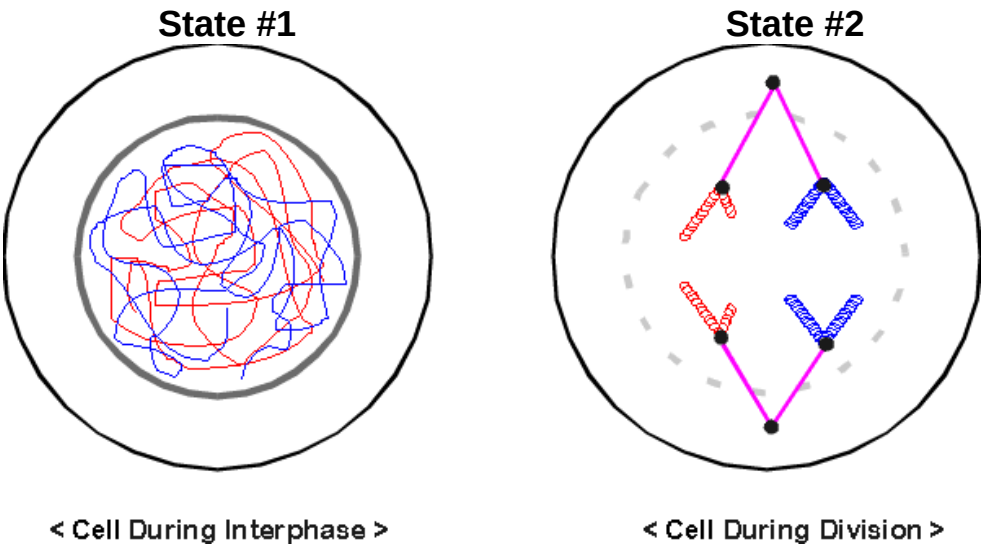
d. Chromosome and cell structure is more complex. Entire nuclear & chromosome structure as well as DNA must duplicate.

- Chromosomes are in a separate compartment = the nucleus. In prokaryote, entire cell is one compartment.
- More complex chromosome structure in eukaryotes; DNA is complexed with proteins called histones. Tune in next term for details.

Comparison of Organization of Genetic Information in Eukaryotes & Prokaryotes		
Property of Chromosomes	**Prokaryotes**	**Eukaryotes**
Number	**one**	**many**
Shape	**circular**	**linear**
Attached to something?	**yes**	**no**
Size of chromosome(s)	**3 X 10^6 base pairs for *E. coli***	**2-5 X 10^7 base pairs/ av. chromosome**
In separate compartment?	**no (no nucleus)**	**yes (in nucleus)**
DNA associated with histones?	**no**	**yes**

2. Resulting Problems -- how will cell get DNA (& histones) doubled in time and distributed properly?

II. Basic Eukaryotic 'two state' solution -- Have 2 different states of nucleus & DNA (see diagram below or Sadava fig. 11.7 (11.8). Also have separate times for synthesis of DNA and for distribution of DNA. Always have DNA in double helix and super coiled with proteins. The difference between the two states is the extent of super-super coiling. (Details next term.)



A. State one -- between divisions (during interphase) -- DNA accessible to polymerases

1. Chromatin. DNA + associated proteins (mostly histones) form tangled mass called chromatin.

- Relatively loose coiling of most of the DNA.
- DNA accessible to polymerases for transcription and replication.
- DNA not ready to distribute.
- No distinct chromosomal structures visible in microscope.
- **Note:** some 'loose' chromatin sections are more loosely coiled than others, but all relatively loose sections look about the same in the light microscope whether they are being transcribed or not. (Any differences will be discussed next term.)

2. Nuclear membrane (and nuclear structure) intact -- nucleus organized for RNA and DNA synthesis, splicing of RNA (to remove introns from primary transcript), transport to cytoplasm, etc. = chromatin in separate compartment

3. No spindle -- DNA not attached to anything.

4. DNA can act as template -- All transcription and replication occurs in this stage.

B. State two -- for distribution during divisions

1. Chromosomes (visible in state 2 only).

- DNA (+ associated proteins) visible in microscope as individual structures called chromosomes.
- DNA tightly coiled, easy to distribute but not accessible to enzymes of replication and transcription.
- DNA is condensed > 10,000 X.

- State 2 vs state 1: Like individual balls of string (in state #2) vs unwound, tangled mess (in state #1, between divisions).
- Chromosomes can look like J's, V's, rods or X's, depending on how the parts are connected and what stage of division you are looking at; see below.

2. Nuclear membrane (compartmental separators) disassembled . Disassembly is temporary -- membrane components not lost, just taken apart into subunits. (Lego castle disassembled -- will be reassembled into two smaller castles after division).

3. Spindle -- have set of fibers attached to chromosomes (and to structures at poles). Assembly of spindle is temporary -- fiber components are not new, but were rearranged to form a new structure. (Building blocks or Legos rearranged -- take apart one structure and build another using the same pieces.)

4. DNA can not serve as template -- No transcription or replication in this stage.

C. Reminder: Eukaryotic DNA is in a double helix, super-coiled, AND associated with special proteins called histones at all times -- in both states 1 & 2. It's super-super-coiling and association with additional proteins that changes. The details of the structure of chromatin & chromosomes. will be covered next semester. For an advanced peek, see Becker Chap. 16 -- esp. fig. 16-18 (chap. 18 -- esp. fig.18-22) or Sadava Chap. 11 (esp. fig. 11.8 (11.9)).

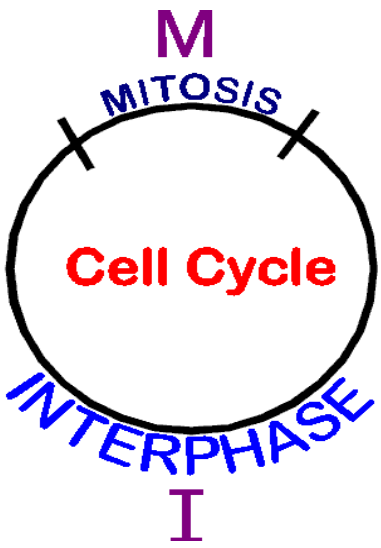
D. To review: Try filling in the following table:

	Cell State	Interphase	Division
1	DNA-histone complex -- relatively loose or tight?		
2	DNA can act as template for replication?		
3	DNA can act as template for transcription?		
4	Spindle present?		
5	Nuclear Membrane intact?		
6	Distinct chromosomes visible?		
7	DNA associated with histones?		

III. Cell Cycle

A. What is it? Look at what goes on during the various stages as a single cell goes from newborn (small; just made by cell division) to double-size = ready to divide again → division → start over. This called the cell cycle. See Becker fig. 17-1 (19-1) or Sadava fig. 11.3.

You can divide the cycle into 2 major stages described above: I (interphase) and M (mitosis or division). The picture below puts the element of time in -- cell goes around and around. The two stages of I and M corresponds to the two states of DNA described above.



B. When is DNA made? Can I (interphase) be subdivided?

1. DNA made in I, prior to M. (How we know is below.)

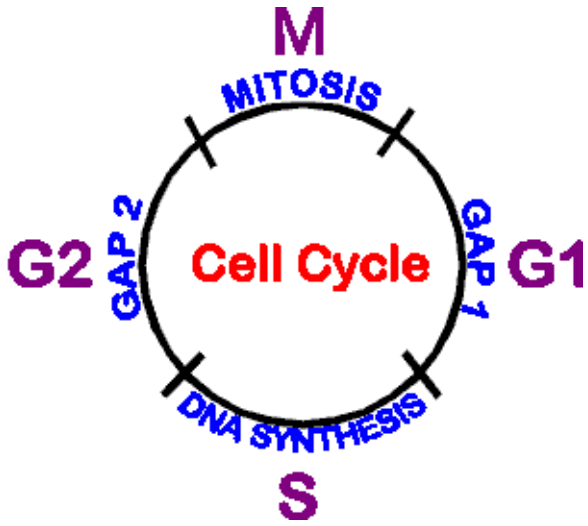
2. Stages -- Can I be subdivided? Does DNA replication take all of I?

a. G-1. There is a period in interphase, after division but before DNA made; this is called G-1 or gap 1.

b. G-2. There is a period after DNA is made but before division which is called G-2 or gap 2.

c. S. DNA is made in the middle of interphase -- the period when DNA is made is called S, for Synthesis (of DNA)

Therefore interphase can be divided into G-1, S (period of DNA synthesis) and G-2 as follows:



3. How were stages of cell cycle discovered?

If you supply radioactive T (T*) when cell isn't in S, the T* doesn't get into DNA. In other words, cells don't make radioactive macromolecules (from T*) when they are in G-1, G-2 or M.

Q: If you supply labeled/radioactive U, will this precursor be made into macromolecules throughout interphase? During M? What if you add radioactive amino acids during I or M. Will these precursors be polymerized into macromolecules?

4. Lengths of stages. FYI only -- Typical lengths of stages for mammalian cells:

S about 8 hrs; M = 1, G2 = 3 and G1 = 3 to 12 (in culture); >12 in adult tissues. G-1 varies most; more details next term.

5. Replication of Eukaryotic DNA -- The replication fork in eukaryotes moves more slowly than the fork in prokaryotes. Therefore getting the DNA replicated in time (since S is so short) is a complex process requiring multiple bidirectional origins of DNA replication and other details which we will skip for the time being. Next term we will discuss some of the complications and regulation of the stages of the cell cycle. For now we will assume DNA can be replicated properly and packaged into chromosomes (with histones) and we will concentrate on how the DNA is distributed to the daughter cells.

IV. Chromosomes, Chromatids and Centromeres.

See handout 21B bottom panel, and box on 21A.

Why are chromosomes sometimes drawn in a X shape or a V shape as on Handout 21A? Chromosomes at start of cell cycle (before S) must contain one double-stranded DNA molecule. Chromosomes after S must contain two double-stranded DNA molecules. How are these DNA molecules related and/or connected? (Remember you can't see the chromosomes during interphase.) This section is a summary of all the terminology.

- *Terminology:* By the end of the cell cycle, chromosomes are doubled -- each chromosome has two (identical) parts called **chromatids** (sister chromatids) which are connected (by proteins) at a section of the chromosome called a **centromere**. see Sadava 11.7 & 11.11 (11.8 & 11.12)

- *How much DNA per chromatid?* Each chromatid contains one double-stranded DNA molecule.

- *Sister/Sibling Chromatids*: The DNA molecules in sister chromatids are identical because they are the two products of a single semi-conservative DNA replication.

- *How many chromatids per chromosome?* Can be 1 or 2; depends on where cell is in the cell cycle.
  Before S, each chromosome has one chromatid (containing one double-stranded DNA molecule).
  After S, each chromosome has 2 chromatids (each containing one double-stranded DNA molecule).

- *Centromere position*. The centromere = the region where the two sister chromatids are connected. The connection forms at a specific region of the DNA (with a specific sequence). The connecting material itself is protein. See Sadava fig. 11.11 (11.12) The centromere can be at the end of the chromosome or anywhere in the middle, so a doubled chromosome containing two chromatids can look like a V or an X.

- *Note:* The term 'centromere' can refer to the region of the DNA where the connection forms (the centromeric DNA), or to the structure connecting the two chromatids. See the key to 8-2 in the Learner's Manual.

- *Double vs single chromosomes.* Whether a chromosome is said to be single or double refers to the number of chromatids per chromosome. Not to whether the DNA in the chromosome is double or single stranded. The DNA is always double stranded. A 'single' or 'undoubled' chromosome does NOT contain single stranded DNA. It contains double stranded DNA that has not replicated yet. See chromatids and chromosomes below and/or see box on 21A or bottom panel of 21B.

- *Double chromosomes may not look doubled:* When chromosomes are observed, in the beginning of M, the two chromatids of a double chromosome can stick together and look like a single structure.

To review the terminology, try problem 8-0, 8-1, parts A-B, and 8-2 Parts A-C. If you are feeling very confident, try 8-6.

V. Mitosis -- How DNA is distributed (see handout 21A) First let's go through stages as shown. See Sadava fig. 11.9 (11.10 or Becker fig. 24-2 & 24-3 (fig.19-20 & 21). When we get to meiosis we'll compare and contrast the two processes (mitosis & meiosis). For important features, see table at end of lecture notes (& see Sadava fig. 11.19 (11.20)). Important points to notice about each stage of mitosis.

- *Interphase:* All DNA is doubled (in S prior to division) **before** M.

- *Prophase:* this stage is reached when you can see chromosomes (as opposed to just chromatin) and nuclear membrane starts to break down. Chromosomes are doubled (2 chromatids/chromosome) but the two sister chromatids can stick together and appear as a single unit. So chromosomes may or may not *look* doubled (in microscope) even though they are. When they don't look doubled, the centromere is often visible as a constricted region of the chromosome.

- *Metaphase:* Chromosomes achieve the maximum degree of condensation; all the chromosomes are lined up in the same plane (metaphase plate) = slice through equator on handout. Idea of mitosis is to separate or segregate sister chromatids, so the chromatids line up in pairs. (In meiosis, chromosomes, not chromatids, will line up in pairs.)

- *Anaphase:* Sister chromatids separate; each chromatid now becomes a full fledged chromosome and is pulled to pole by an attachment to a structure at its centromere. Chromosomes can appear V or J or rod shaped, depending on position of centromere.

- *Telophase:* Start putting cells back to normal. Start reassembling nuclear membrane, decondensing chromosomes, and starting to divide cytoplasm. (See Sadava fig. 11.12 (11.13) or Becker fig. 24-8 & 24-9 (19-28 & 29) for how cytoplasm is divided.)

- *Daughter cell stage:* End product of mitosis = two cells with genetic information identical to that of original.

- *Mechanism:*
  Chromatids separate at anaphase because protein connecting chromatids comes apart.
  Pulling is done by spindle fibers; not shown on handout.
  For pictures see Sadava fig. 11.11 (11.12) or Becker fig. 24-4, 24-5, & 24-6 (fig. 19-22, 24 & 25).
  See Becker for details of spindle and mechanism of chromosome movement if you are interested.
  More details of mechanism will be discussed next term. For now, emphasis is on where the genetic material ends up.

To review mitosis and the cell cycle, do problem 8-13.

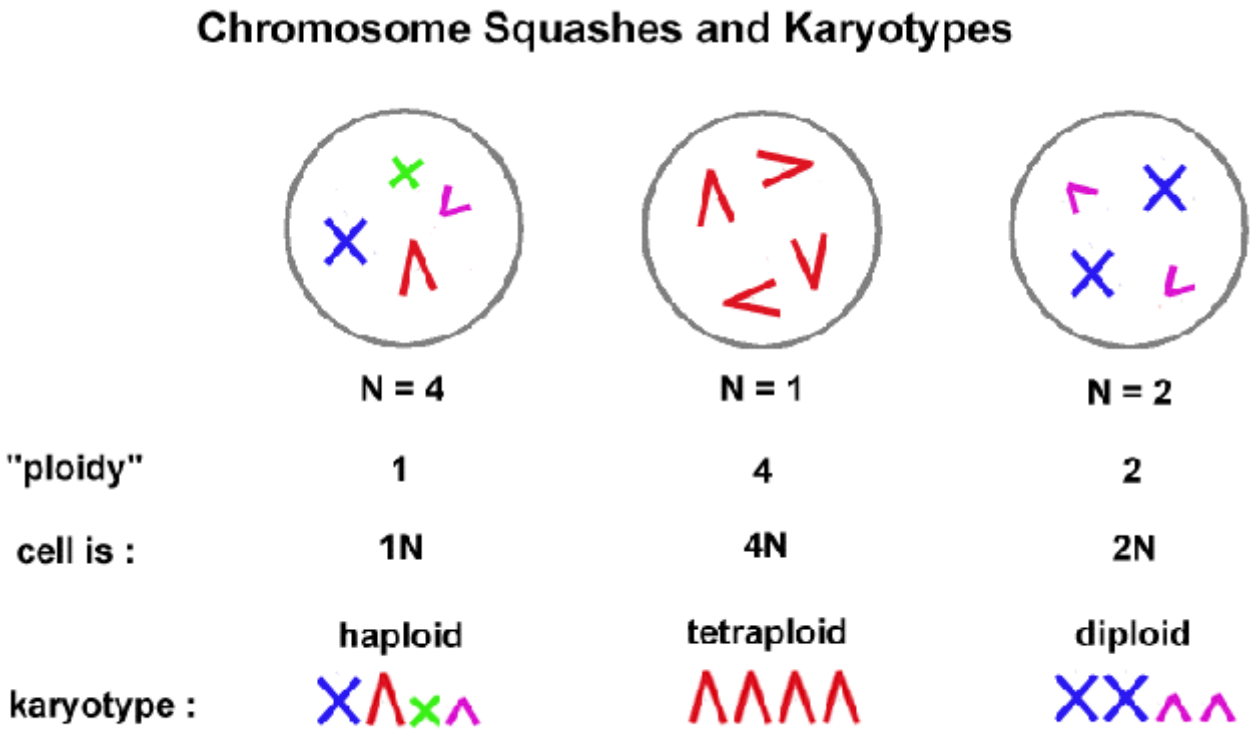
VI. Karyotypes

A. What are Karyotypes and how do you get them?

There are drugs that stop cells at metaphase (the drugs interfere with spindle fiber function). So what? This allows you to conveniently collect lots of cells at metaphase and look at the chromosomes.

1. Chromosome squash. Can squash cells in plane of metaphase plate and see all chromosomes spread out. Picture of this = chromosome squash. (See picture below or handout 21B or Sadava fig. 11.20 (11.21), left.)

2. Karyotype. If make squash, cut out each chromosome (or do the electronic equivalent) and line them up in order of size, this = karyotype. Gives standard pattern for each species. (Squash is harder to analyze, if there are a lot of chromosomes, since chromosomes are in random order.) See picture below or Becker fig. 16-22 or 16-A-2 (fig. 19-23) or Sadava fig. 11.20 (11.21).



B. What do you see in a normal squash or karyotype?

1. Each species has a standard karyotype with a fixed number of chromosomes.

a. Constancy: Karyotype is the same in all body (somatic) cells and in each generation.

b. Implications: You can use similarities and differences between karyotypes to evaluate relationships between species and to detect certain abnormalities, which we will discuss later.

2. Important general features of a (normal) karyotype

a. "N" -- Number of different types or kinds of chromosomes is called N.

- For humans, N = 23. See Sadava table 9.1 (8th ed). for typical values of N.
- For examples, see cases above. How do you know the value of N in each case?

b. Ploidy = number of chromosomes of each type. Cell can be

- haploid -- 1N -- have one of each type of chromosome (for humans, this occurs in gametes -- eggs and sperm)
- diploid -- 2N -- have two of each type of chromosome (for most multicellular organisms, this is the state in most body cells).
- triploid (3N) or tetraploid (4N) -- has 3 or 4 of each type of chromosome. (Higher multiples of N are possible too in plants.)
- For examples, see cases above.

c. Sex Chromosomes -- In some species a normal male karyotype is different from a normal female one. Usually only one chromosome pair differs. This will be covered next time.

3. How do you tell chromosomes apart?

a. Shape: What determines shape? Position of centromere.

b. Size: Different chromosomes can be different sizes. (In karyotypes, chromosomes are ordered from largest to smallest.)

c. Banding: What if different chromosomes are the same shape and size? You can identify each individual type of chromosome by banding pattern.

- Banding = procedure to stain chromosomes with standard dyes; different dyes give different patterns of dark and light regions.
- Each band = block of 100's of genes, not a single gene.

4. Homologs

a. Definition: Homologs = all the chromosomes of each type. Except for sex chromosomes, homologs = all chromosomes of same size, banding pattern, & position of centromere (shape). Sex chromosomes are explained below.

b. Number: There are 2 homologs = 2 of each type of chromosome in diploid cells. One from mom, one from dad.

c. Relationship of genes on homologs; alleles. Homologs (except for sex chromosomes) carry homologous DNA. They carry the same genes, in the same order, in corresponding places (loci), but they do not necessarily carry the same version (allele) of each gene. Examples:

(1). Gene for Blue vs Brown Eye Color. The "eye color gene" determines blue vs brown eye color (if everything else is held constant). This gene is in the same place (the eye color locus) on both homologs, but the eye color gene on a particular chromosome could be the blue-determining version (blue allele) or the brown-determining version (brown allele). Each homolog carries one allele of the eye color gene. Homologs carry the same genes, but not necessarily the same alleles.

(2). Gene for Beta Chain of Hemoglobin. The beta chain gene is always in the same position, the beta chain locus. However an individual chromosome could carry the Hb A or Hb S allele (version) at the beta chain locus.

d. Sister chromatids vs homologs:

- Sister chromatids = 2 halves of a doubled chromosome. Why are they identical? Because they contain the two products of a semi-conservative DNA replication. The two sisters **do not** come from different parents.
- Homologs **need not be** identical -- each came from a different source (a different parent).

Important: be sure you know the difference between homologs (homologous chromosomes) and sister chromatids.

To review mitosis and normal karyotypes, try problem 8-8 parts A-D, & G.

C. What can you see in an abnormal karyotype?

1. Only large changes are visible. Since you can do banding, you can tell all the chromosomes and chromosome regions apart. Therefore you can detect **large** abnormalities affecting whole chromosomes and/or large blocks of genes from looking at karyotypes. Many of these abnormalities are associated with known genetic conditions -- diseases and/or tendencies thereto. Reminder: a band = a block of genes, NOT a single gene.

a. Chromosomal mutations. Large changes that are visible in a karyotype are known as "chromosomal mutations." Only changes in large sections containing many genes (kilobases not bases) affect the banding pattern and are visible in karyotypes.

b. Gene mutations. Changes that are too small to be visible in a karyotype are usually called "gene mutations." Changes of a few bases or even a few genes **cannot** be detected in a karyotype. Remember that each band on a chromosome is a large block containing hundreds of genes; therefore 'gene mutations' do not change the banding pattern.

2. Rearrangements. You can pick up extra, missing and rearranged pieces. (If large enough, loss, additions, inversions, or translocations are visible.) Smaller changes must be detected using other methods.

3. Euploid vs Aneuploid. Since you can tell all the individual chromosomes apart, you can readily detect cases of missing or extra chromosomes.

a. Euploids. Cells are normally haploid (N), diploid (2N), or polyploid (3N, 4N, 6N, etc.) All of these are called 'euploid.' (All are multiples of 'N'.)

b. Aneuploids.

- Cells with extra or missing chromosomes (2N + 1, or N -1, etc.) are called aneuploid.
- Most aneuploid fetuses abort spontaneously but a few survive to birth. (See handout 21B for examples of aneuploids.)
- Origin of aneuploids will be discussed next time.
- In humans, aneuploidy is a major cause of miscarriages = spontaneous abortions.

D. Some Details of Aneuploidy (See 21B)

1. Terminology. The terms "monosomic" and "trisomic" apply to diploid cells as follows:

a. Monosomic or monosomy = one chromosome missing = one chromosome has no partner (no homolog), but all other chromosomes still occur in pairs.

b. Trisomic or trisomy = one chromosome has 3 copies (3 homologs) but all other chromosomes still occur in pairs. Note trisomic is different from triploid: trisomic means 3 copies of one type of chromosome, say #2; triploid means three copies of all the chromosomes.

2. How do aneuploidies occur? **Through mistakes in meiosis. We need to go over normal meiosis first, then see how mistakes occur.**

3. What types of aneuploidy survive? Stay tuned! This will be discussed next time after sex chromosomes.

VII. Overview of Meiosis -- See handout 21C.

A. What is meiosis for?

1. Need for meiosis/reduction division -- to keep karyotype & ploidy constant from generation to generation.

Most of the cells of most higher organisms are diploid. Humans, for example, have 46 chromosomes, or 23 pairs, in virtually all of their cells. If eggs and sperm also have 46 chromosomes, the next generation, formed from the fusion of an egg and a sperm, would have 92 chromosomes. But clearly the chromosome # does not double each generation. So the eggs and sperm, unlike all other cells, must have only 23 chromosomes and be haploid. So there must be a way to make haploid cells from diploid cells. There is, and the process is called meiosis. During meiosis, one chromosome from each *pair* is picked at random so that the resulting haploid has 23 chromosomes instead of 23 pairs. Then 2 such haploids fuse, during fertilization, to give you back a diploid with 23 pairs.

2. Why bother with all this? Why sex?

After all, you could start the next generation with one complete diploid cell from either parent and save yourself a lot of trouble! Some organisms do reproduce this way, at least some of the time, but most organisms engage in sexual reproduction. They probably do so because each cycle of meiosis, followed by fusion, allows for a new combination of chromosomes. (Crossing over, which occurs at meiosis, also allows for new combinations of genes within chromosomes as well.) So it looks like sexual reproduction is useful because it allows reshuffling of the genetic material (same argument as for bacteria). Reshuffling is needed to give new variety (for selection to act on) and/or for repair (& replacement) of damaged copies.

3. How reshuffling works

a. Reshuffling Chromosomes.

Suppose one person has 2 identical copies of chromosome #1 and 2 identical copies of chromosome #2. (Draw these chromosomes in one color, say pink.) Another person has 2 copies of chromosome #1 that are the same as each other but different from the copies in the first person, and similarly for chromosome #2. (Draw these chromosomes in another color, say white.) The offspring of these two people will have a mixture of "pink" and "white chromosomes. After several generations, it will be possible to get all conceivable combinations of "pink" and "white" chromosomes. **(See problem 8-4 parts A & B or wait until after 'life cycles'.)**

b. Reshuffling genes:

In addition to reshuffling whole chromosomes, equivalent parts of chromosomes can be reshuffled or exchanged. Homologous chromosomes pair and can exchange equivalent sections during meiosis by crossing over. (This is equivalent to what happens to bacteria during transformation, transduction, etc., but in eukaryotes the process is restricted to prophase I of meiosis.) See Sadava figs. 11.16 & 11.17 (11.17 & 11.18) or Becker fig 25-16 (20-16). Note: the term "genetic recombination" usually refers to reshuffling of genes by crossing over. It is sometimes used in a more inclusive sense to mean all kinds of reshuffling (of genes and/or chromosomes) whether crossing over is involved or not.

B. How many chromosomes, chromatids & cells during meiosis? What happens if there is one pair of homologs?

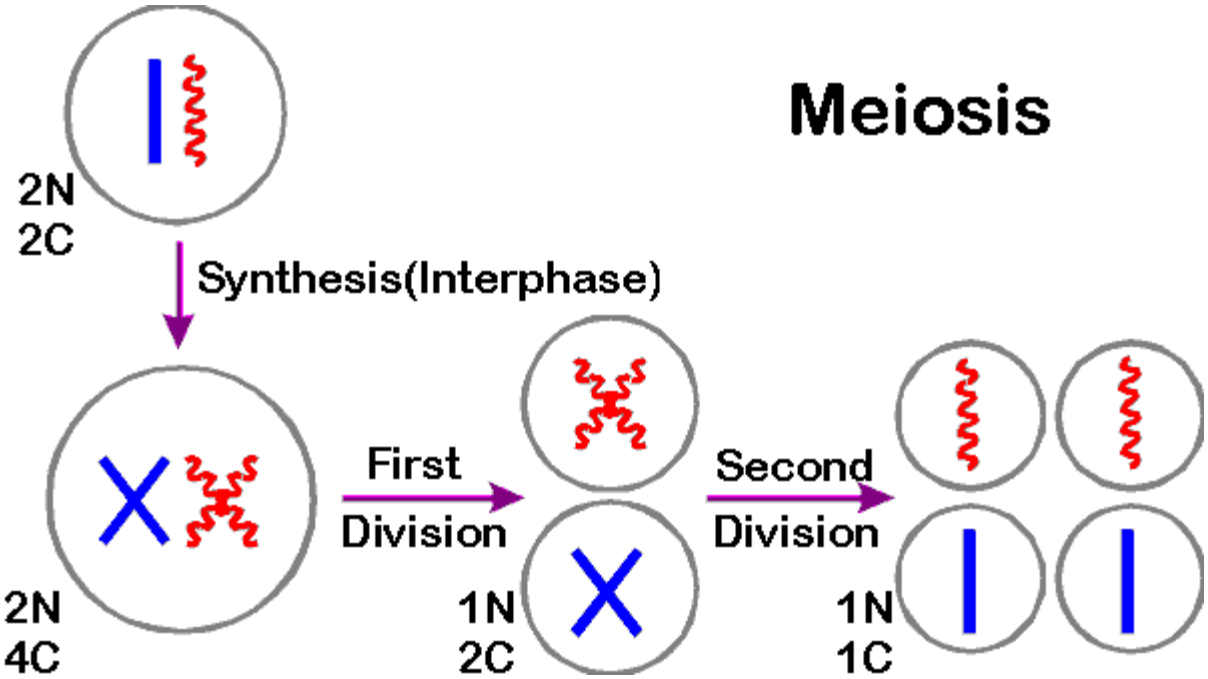
Picture below (or nondisjunction handout) shows what happens to ***one pair*** of chromosomes. It shows **all cells** at each stage -- before DNA synthesis, after S, after 1st div, and after 2nd div. See Becker fig. 25-1 (20-3) for a similar diagram of meiosis in a cell with ***2 pairs*** of chromosomes.

1. DNA synthesis occurs first -- before division. Meiosis is preceded by DNA duplication just as mitosis is. During the S before meiosis (or mitosis) the cell doubles the DNA content and # of chromatids per chromosome. So cell starts with pairs of doubled chromosomes = 4 copies of each chromosome.

2. Number of Products: There are 4 products, each haploid (from meiosis), instead of 2 products, each diploid (from mitosis).

3. Number of divisions: To cut the number of copies of each chromosome from 4 to one requires 2 divisions, not one. The first division of meiosis separates homologs; the second division of meiosis separates sister chromatids. (Mitosis has only one division.)

4. What happens to N, C and # of chromatids/chromosome? The first division cuts the chromosome number per cell in half from 2N to N and cuts the DNA content per cell in half from 4C to 2C ("C" is defined below). The second division halves the DNA content per cell (from 2C to C), halves the number of chromatids/chromosome (from 2 to 1) and halves the total chromatid # per cell (from 2N to N). What happens to a cell with one pair of chromosomes is as follows:



C. What happens to chromosomes ***per cell*** during meiosis?

The diagram above shows all cells at each stage. What about the number of chromosomes, the number of chromatids, and the DNA content **per cell** at each stage? Recitation problem set #13 will include a chart with this info (the chromosome cycle) for cells with one chromosome pair (N = 1) & for 3 pairs (N = 3). Space will be provided for you to fill in the values expected for any general value of N.

D. Definition of c

"C" or 'c' is a measure of DNA content per cell, not the number of chromosomes or chromatids.

C = minimum DNA content per haploid cell of an organism = DNA content of haploid cell before S (with unreplicated chromosomes) = DNA content of one set of chromatids.

C is NOT equal to N; C is the DNA content of N chromosomes (with one chromatid/chromosome).

N & C are constants for each species. The multiple of C in each cell (1C, 2C, etc.) and the number of chromatids/per cell (1N, 2N, etc.) vary during the cell cycle, and during cell division (mitosis & meiosis). The multiple of N (1N, 2N, etc., meaning the number of chromosomes/cell) changes during meiosis, but not during mitosis. The values of C and N do not change during interphase or cell division..

Values of C (in picograms)

- 1 picogram of DNA ≈ 10^9 BP. Therefore the aprox. value of C in picograms) = #BP (per haploid, unreplicated genome) /10^9 .
- The C content of humans is about 3 picograms (about 3 X 10^9 BP). For a comparison of genome sizes, see Becker fig. 21-12 (18-11) or table 21-2 (18-2). Note that the C value does not correlate with the number of genes or the complexity of the organism, because much euk. DNA has no known function.

VII. The Mechanism of Meiosis -- see handout 21A.

A. Steps: These are diagrammed in detail in parallel to the steps of mitosis on handout 21A. For similar diagrams of mitosis vs. meiosis see Sadava fig. 11.18 (11.19) or Becker fig. 25-6 (20-8). For nicer pictures of meiosis see Sadava 11.15 (11.16) or Becker figs. 25-3 & 25-4 (20-5 & 20-6). A summary table comparing meiosis and mitosis is below (for you to fill in).

B. What if N >1? Handout 21A shows what will happen to a cell with 1 pair of chromosomes. (2N cell, N =1.) If there are additional chromosome pairs (N > 1), each pair will line up independently at metaphase I. This has important genetic implications, as will be discussed later.

C. Prophase I -- Some Differences from Mitosis

1. Crossing over. This is the time when recombination occurs by a "cut & rejoin" mechanism, which switches equivalent sections of chromosomes between 2 members of a pair. Recombination requires pairing, so homologous chromosomes are paired in pro. I of meiosis but not mitosis. More details to follow. (Pictures of pairing are shown in the texts.)

2. Duration. Prophase I in meiosis is generally much longer and more complex than prophase in mitosis. (Both texts divide prophase into early, mid and late substages; Becker fig. 25-4 (20-6) has even more details if you are curious.) Pro. I can be very prolonged -- in human females, it lasts from before birth to the time the egg is shed. Consequences of this very long pro. I are discussed below.

3. Recombination vs Splicing vs Restriction. Crossing over (recombination) involves cutting and rejoining of double stranded DNA molecules; production of mRNA (splicing) involves cutting and rejoining of single stranded RNA molecules. Restriction involves cutting of double stranded DNA at specific sites. All these process involve cutting and/or rejoining of poly nucleotides. However, three ***different*** sets of enzymes are involved in these processes -- splicing, crossing over, and restriction.

D. Products of human meiosis (see Sadava fig. 42.4 (43.3) or Becker fig. 25-8 (20-9))

1. In Females: When female germ cells go through meiosis, the equivalent of 4 haploid nuclei are formed, but only one ends up in an egg. The genetic material that would end up in the "other 3" nuclei is shunted aside --it forms small structures called polar bodies. The egg contains (at least) the amount of cytoplasm that would be sufficient for 4 meiotic products and the genetic information of only one.

2. In males: When male germ cells go through meiosis, 4 sperm are formed.

To review Meiosis, and compare to Mitosis, fill in table on the next page, and do or finish problems 8-1, 8-2 (parts A to E), 8-3, & 8-8 (parts A-D & G).

To review Meiosis vs Mitosis:

Question	Mitosis	Meiosis
What lines up at Metaphase I? Individual chromosomes or pairs of homologs?		
What happens to centromeres at Anaphase I? Split or not?		
Does pairing and crossing-over occur at prophase?		
Is there a second division?		
How many daughter cells (if all survive)?		
Ploidy of daughter cells (relative to that of parents)?		
DNA/ daughter cell (relative to that of parents)?		
# chromosomes/daughter cell (relative to that of parents)?		
Are all daughter cells the same?		

VIII. Nondisjunction -- Handout 21C (bottom)

A. Where do gametes with missing and extra chromosomes come from?

Answer: Mistakes in Meiosis. Two types of mistakes:

- Homologs can fail to separate (fail to "disjoin") properly at first division (= 1st div. nondisjunction), or
- Sister chromatids can fail to separate properly at second division (= 2nd div. ND).

Note that the sisters or homologs do separate eventually -- they just do it later than normal.

Either way, nondisjunction produces gametes with extra and/or missing chromosomes (aneuploidy). See handout 21C, bottom half of page. (Note: If you turn handout 21C 90^{o} -- if you look at it in landscape, not portrait orientation -- the diagram of normal meiosis is the same as the one in the notes above.)

On handout 21C: Note that the "empty" cells are not really empty -- they are only missing a chromosome from the pair involved in ND. They have all the other chromosomes, but the others are not shown to keep the picture as simple as possible. ND is a rare error that generally affects only one event at a time -- one pair of chromatids or one pair of homologs fails to separate at one stage of meiosis. Two or more mistakes in a single meiosis are extremely unlikely. In the rare event of a ND there is usually only one event (separation) that fails to occur -- usually all other separations of chromosomes and chromatids proceed normally. See Sadava fig. 11.19 (11.20).

B. Where do multicellular, diploid individuals with missing and extra chromosomes come from?

When an aneuploid gamete (= gamete with missing or extra chromosomes) from one parent meets a normal gamete from another parent, then a monosomic or trisomic diploid cell (the zygote) is formed. (Nondisjunction is so rare, that it is unusual for two aneuploid gametes to meet up.) The zygote then divides by mitosis to produce a multicellular, aneuploid, individual. To see how this works, see 'Life cycles' below.

C. What types of aneuploidy are (relatively) common?

Aneuploid zygotes containing missing or extra autosomes usually do not develop into viable individuals, but aneuploid zygotes containing missing or extra sex chromosomes (XO, XXY, XXX etc.) are usually viable as long as there is at least one X. (Why is this? Stay tuned!.) The only trisomies that survive early infancy at a reasonable rate are:

1. Trisomy 21.

2. Aneuploidy of the sex chromosomes.

To review Nondisjunction, try 8-8E & 8-9.

X. Life Cycles -- How do meiosis and mitosis fit together?

Handouts 21C & 21D. Or how does 1 multicellular organism give 2? Or better, for diploid organisms engaging in sexual reproduction, how do 2 (parents) give 1 (offspring)?

A. Supercycle -- Handout 21C (breakdown into individual cycles is on 21D)

1. General idea -- Overview

Many different life cycles are possible, depending on the number of mitotic divisions that follow meiosis and/or fusion. Three possibilities are shown on handout 21D.

The 'Supercycle' on the top of handout 21C shows a generalized life cycle that includes all possible stages = it's what you get if you superimpose all 3 diagrams on handout 21D. (Sadava fig. 11.14 (11.15) or 27.6 (28.6) is equivalent; Becker fig. 25-2 (20-4) is similar.) Each case on handout 21D will be discussed briefly, and then you can see how each fits into the supercycle on 21C.

2. Haploid vs Diploid Life Cycles

a. Diploid Life Cycle. (Middle case on 21D). What you get if meiosis → gametes. An organism can skip most of the stages on the left half of the supercycle diagram and go directly from germ cells to gametes. Such an organism has a basically diploid life cycle, as humans do. See Becker, fig. 25-4 (d) [20-4 (d)].

b. Haploid Life Cycle (Bottom case on 21D). What you get if the zygote divides immediately by meiosis, not mitosis. An organism can skip most of the right half of the diagram if the zygote divides immediately by meiosis, not mitosis. Such an organism has a basically haploid life cycle. Some simple algae are like this. See Becker fig. 25-2 (b) [20-4 (b)].

3. Alternation of Generations What you get if you don't skip any stages; common in plants. See Sadava fig. 28.6 (28.3) **Top case on 21D.**

a. Most plants go through both haploid and diploid phases, with mitotic divisions of both haploids and diploids. However the haploid phase is so short (involves so few mitotic divisions) that the haploid form of the organism is usually not visible to the naked eye.

b. Both phases may be visible. A few of the simpler plants, such as moss, produce both haploid and diploid forms that are visible to the naked eye. See Sadava fig. 27.7 (28.7) and/or Becker fig. 25-2 (c) [20-4 (c)]. You can see both of them -- both the sporophyte (diploid, spore bearing form of plant) and the gametophyte (haploid, gamete bearing form of plant).

c. Moss Life Cycle. For moss, the green fuzzy stuff is haploid and produces gametes, so it is called the gametophyte = gamete-bearing plant. Two gametes fuse to form a zygote, which divides by mitosis to produce the brown stalks (diploid) on top of the green mat. Some cells of the stalk go through meiosis to produce haploid spores (inside the capsule at the end of the stalk), so the stalk is called a sporophyte = spore-bearing plant. (There are many diagrams and videos of the moss life cycle online and in your texts.)

4. Gametes and Spores -- Terminology

a. Two ways to get gametes -- by meiosis of 2N or specialization of N cells. Moss produces gametes by specialization of haploid cells; humans produce gametes by meiosis of diploids.

b. Products of meiosis are always haploid, but they can be called spores or gametes. Depends on what the products of meiosis will do next.

c. Gametes vs spores: If meiotic products will never divide by mitosis, but simply fuse to form a zygote, then they are called gametes. If the meiotic products are going to divide by mitosis, then they are called spores. {Q&A}

d. In moss: The products of meiosis are called spores, not gametes, because the meiotic products are going to divide by mitosis (before specializing to make gametes). In humans, the products of meiosis are called gametes.

5. Super cycle can reduce to haploid or diploid life cycle

a. Diploid Life Cycle. If meiosis → gametes. No mitotic division of haploids. No spores. In the diploid life cycle, the only haploid stage is the gamete.

b. Haploid Life Cycle. If zygote → immediate meiosis. (Meiosis → spores, not gametes.) No mitotic division of diploids. No germ cells. In the haploid life cycle, the only diploid stage is the zygote.

B. Some implications of this cycle (the mitotic part):

1. The Problem of Development. If zygote→ us by mitosis; how does development work? If all cells have the same DNA, why do cells make different proteins? In other words, why are the genes 'expressed' differently in different cell types? What sets and maintains the switches? How differential gene expression is set up and maintained is not entirely understood, but will be discussed some more next term.

2. Forensics. Virtually all the cells of the adult have the same DNA. Therefore you can compare DNA from a suspect to DNA found at the scene of the crime. It doesn't matter what type of cells the DNA comes from -- hair, saliva, blood sperm, etc.

Note: From blood, you need WBC (white blood cells). RBC (red blood cells) have lost their organelles and DNA during development,

3. PGD & Amniocentesis. If all cells of embryo & fetus have same genes/DNA/chromosomes, you can test the DNA or chromosomes of any cell to look for abnormalities, even if the gene involved only affects (makes proteins in) certain specialized tissues.

a. Testing embryonic cells (PGD) -- one cell can be removed from an 8 cell embryo without damaging the ability of the remaining cells to develop into a normal individual. Fertilization must take place *in vitro*. One cell can be removed from the resulting embryo and the DNA of the cell can be tested. If the cell does not have a disease genotype, the remaining 7 cells can be implanted in the womb and development can proceed normally. This is called pre-implantation genetic diagnosis (PGD).

b. Testing fetal cells (Amniocentesis, etc.) If you identify a fetus that will have sufficiently serious disabilities, you have the option to consider a therapeutic abortion. There are several current ways to test fetal cells, and more ways are under development. The most common current method is amniocentesis (testing fetal cells from amniotic fluid).

4. What you can detect by amniocentesis, PGD, etc. These examples will not be discussed in class but are included for reference.

a. Chromosome Mutations. Since you can do banding, you can tell all the chromosomes and chromosome regions apart. Therefore you can detect large abnormalities affecting whole chromosomes and/or large blocks of genes (so called "chromosomal" mutations) from looking at karyotypes as discussed previously.

b. Gene Mutations. You can look at DNA sequence (by PCR, use of probes, sequencing, etc.) for smaller changes affecting one or a few genes and/or nucleotides (so called "gene" mutations). Sometimes you can look at the protein the gene makes as in amniocentesis for case (1) below, and sometimes you look at the DNA instead as in case (2). Some examples:

(1). Tay-Sachs disease*.** The gene that causes Tay-Sachs disease (when mutant) codes for an enzyme. The enzyme is made in many cell types, including the cells in the amniotic fluid. Using amniotic fluid cells, you can look at the DNA ***or measure the enzymatic activity of the protein made from the gene. In embryonic cells, you have to look at the DNA.

(2). PKU. The gene that causes phenylketonuria or PKU (when mutant) codes for an enzyme (PAH) that is made only in liver cells. So using amniotic fluid cells, you can't measure the activity of the enzyme. But you can test the state of the gene itself (in embryonic or amniotic fluid cells) to see if the gene is normal or mutant.

To review life cycles, cell cycle, etc. and how they all fit together, try 8-11 and/or 8-14.