**Chromosome Theory of Inheritance**

Sutton and Boveri in 1902 correlated Mendel's conclusions about genes (or inherited traits) to the behavior of chromosomes during mitosis and meiosis.

Sutton is credited with first proposing the chromosome theory of inheritance:
- Chromosomes are in pairs
- Homologous Chromosomes separate during meiosis so that alleles are segregated
- Meiotic products have one of each homologous chromosome but not both
- Fertilization restores the pairs of chromosomes
  - And -- Genes are located on chromosomes

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From the time of Sutton's deduction, genetic research had a problem. There are far more genetic traits than chromosome pairs. And Mendelian inheritance patterns require genes to be inherited independently of each other. In the early 1900's researchers raced to find explanations, even as the explanation was "at hand".
Gene Linkage
In 1908, researchers discovered a dihybrid cross in sweet peas that did not give the predicted Mendelian ratio of 9:3:3:1. They could not explain why their results were closer to 75% and 25% (the 3:1 ratio expected for a monohybrid cross).

Ultimately it was shown that the flower color and pollen length (the genes observed) were on the same chromosome. Since we inherit entire chromosomes rather than independent genes, all genes on one chromosome are inherited together as a single unit (called the linkage group), and we should expect a 3:1 inheritance ratio for the linkage group. This was just the first time someone had seen this.

Following this discovery with peas, researchers in inheritance went forth to find genes that were linked. They would take two traits, do an inheritance test, and if the inheritance ratio was 9:3:3:1, they would conclude the genes were on separate chromosomes, and followed Mendel’s independent assortment. If the ratio was 3:1, they would conclude the genes were on the same chromosome, and linked.
**Discovery of Crossing-Over and Recombination**

But a funny thing happened some of the time. Sometimes with a cross involving linked genes, the researchers would get a few individuals that "mixed" – or a cross that had purple flowers with short pollen or white flowers with long pollen. What happened? Recall that during our discussion of meiosis that **crossing over** occurs which results in the exchange of bits and pieces of DNA between homologous pairs of chromosomes at the chiasmata during prophase I. This process of **recombination** results in gametes (or meiotic products) that are not identical; some of the linkage groups have been changed by the crossing-over.

When **recombination** takes place the expected inheritance ratio for linked genes is altered slightly by the recombinant gametes. This frequency of recombination can be measured (very tediously) for a number of pairs of genes and used to locate the relative positions of genes on their respective chromosomes. This process of pin-pointing specific genes on the chromosome is called **chromosome mapping**. Each map unit, called a **centimorgan**, is defined as the distance within which a cross-over is expected in 1% of the gametes. Your text has more detailed information about recombination rates and genetic mapping.
Chromosome mapping using recombination data was used extensively in the earlier part of the 20\textsuperscript{th} century. Today we have much more sophisticated methods of dealing with chromosome mapping using DNA probes, where a known DNA fragment is used to compare with an unknown chromosome region. If the probe matches we can identify the region. The genomes of a number of organisms have now been completed, including \textit{Arabidopsis}, \textit{E coli}, the common yeast, the fruit fly and, of course, the human genome. We will return to this subject later.

**Sex-Linkage and Sex-determining Chromosomes**

By the early 1900's it was known that males and females of most species have one pair of "not-exactly-matching" homologous chromosomes, which determine the gender of the individual. These chromosomes are called the \textbf{sex chromosomes}. (The truly matching chromosomes are the \textbf{autosomes}.)

For many species, the gender-determining chromosomes will be truly homologous for one sex, usually female, and are conventionally called XX, while the male will have two unmatched chromosomes (XY). At meiosis, all eggs will contain an X chromosome, but half the sperm gametes will have a Y chromosome and the other half will have an X chromosome.

Some species, including birds, have a reverse pattern of sex chromosomes (male = ZZ and female = ZW (just to not confuse letters)), and some species have one gender (female) with a pair of chromosomes and one gender (male) with a single unmatched chromosome (XX and X0 (OK to be confused with the letters)). In all cases the gender with the dissimilar pattern will determine the gender of the offspring. And some insects, including bees, have haploid males and diploid females.

Sex-determining chromosomes have information that determines the sex of the individual. In humans the gene that triggers the hormonal conditions for the development of the testes is located on the Y chromosome. This gene, called the SRY gene, is activated in the embryo at about 2 months. Some other genes needed for normal male development are on the Y chromosome; others are on autosomes. In some species, the activation of the SRY gene is influenced by environmental conditions that can change how this gene gets expressed, hence altering the gender of the developing individual.
Sex-Linked Genes
Yet no one thought these chromosomes would have genes that coded for somatic traits until Thomas Hunt Morgan "accidentally" discovered this. Morgan spent much of his career studying inheritance patterns of the fruit fly, *Drosophila melanogaster*.

Fruit flies are good organisms to work with in inheritance studies. They:
- have a short generation time (important for research spanning a number of generations)
- are small and easy to keep in a laboratory
- produce reasonably good numbers of offspring
- have a number of easy to see inheritable characteristics
- have a chromosome number of 8 (4 pairs of chromosomes)

Morgan was perhaps the first to take full advantage of the fruit fly in genetics. One of the things he did was to actively seek varieties of flies different from the normal, or "wild" type. While doing so, he happened upon a "new" trait: white eye. Morgan made several crosses using his white-eyed male, expecting the standard Mendelian results. He did not get them. While the ratio of 3:1 was obtained, all of the white-eyed second generation offspring were male flies. All females had red eyes (and 25% of the males also had red eyes). Morgan concluded that eye color was related to sex, and proceeded to investigate how.
Chromosomes and Inheritance

To do so, he had to apply knowledge about sex-determining chromosomes to the inheritance of non sex-related genes. Morgan did a series of reciprocal crosses of white-eye males with red-eye females and red-eye males with white-eye females. He concluded that the gene for eye color in the fruit fly was located on the X chromosome. Males passed the trait to their daughters (on their solitary X chromosome) and mothers passed the trait to sons. White eyed females could also pass the white eye allele to their daughters, but if the father fly had red eyes, the eye color of the daughters would be red, while the eye color of the sons of white-eyed females would always be white.

Morgan demonstrated that the sex-determining chromosomes also carry other genetic information. The other traits are said to be sex-linked because they are inherited along with the sex of the individual. Because the X and Y chromosome are not exactly matching, the X chromosome can have genes that are not located on the Y chromosome, and vice-versa. Some of these genes are unrelated to the sexual characteristics, but are inherited with the sex-determination. This is referred to as sex-linkage.

Some human sex-linked traits are
- Hemophilia (X)
- Hairy ear rims (Y)
- Red-green color blindness (X)
- Duchenne muscular dystrophy (protein dystrophin on X)

A special feature of the sex chromosomes – The Barr Body
Females have two X-chromosomes. In cells, one of them is deactivated during embryonic development and forms a tightly condensed object that lines the nuclear membrane, the so-call Barr body. Transcription does not occur on the Barr body except in certain cells (Barr bodies in ovary cells that do meiosis, for example.) The choice of which X gets condensed for a given cell line appears to be random, although there is evidence that a specific gene coding for a special RNA molecule is responsible for the X inactivation producing the Barr body.

The pattern of the calico cat is an example of Barr body expression. Both orange and black pigment alleles are on the X chromosome. The black patches of fur are from cell lines where the orange X chromosome is a Barr body. Orange patches of fur result when the black X chromosome becomes the Barr body. The patches of white fur are the expression of a different gene.
Chromosomes and Inheritance

A **mutation** is any change in the DNA. Mutations occur naturally, caused by errors in DNA duplication, errors in processing DNA, and errors in meiosis and mitosis. Physical damage and chemical damage can induce mutations as well, and are used by researchers to study mutations.

When mutations involve chromosomes or numbers of chromosomes they are referred to as **chromosomal mutations**. Mutations involving single genes or nucleotides will be discussed in our section on molecular DNA. We will just briefly mention some terms here, and focus on chromosome changes at this time.

**Chromosomal Mutations**  
As expected, there is a vocabulary associated with chromosomal mutations to present first:

**Deletions**  
A chromosomal deletion is a loss of the chromosome or a large portion of the chromosome (generally a fragment without a centromere). The remainder of the chromosome, with the centromere intact has the deletion.

**Duplications**  
A deleted chromosome fragment can attach to its homologue, thereby duplicating a region of genes on the chromosome to which it attaches.

**Translocations**  
A part of a chromosome is transferred to a different chromosome. Jumping genes or transposons, which will be discussed later, may facilitate this "mutation". Reciprocal translocations involve exchange of genes between non-homologous chromosomes.

**Inversions**  
A portion of a chromosome is inverted 180° from normal, so that a gene sequence may be read A B C H G F E D I J K, etc.
Aneuploidy
The chromosome number is different from normal. For reasons not understood, occasionally, a homologous chromosome pair or a replicated chromosome will fail to separate during meiosis, resulting in a gamete (or spore) with one more or one fewer than the normal complement of chromosomes (trisomy or monosomy). In general, we call this process a non-disjunction and the change in chromosome number that results an aneuploidy.

Most often, a non-disjunction results in a gamete that does not survive; in some cases, however, some gametes do survive, producing individuals with abnormal chromosome numbers. Most of these non-disjunctions have serious genetic consequences. A non-disjunction can affect either the sex-determining chromosomes or autosomes. We will mention a few human examples.

Non-disjunction of Autosomes
Survival with an autosomal non-disjunction is rare.
- Trisomy G or 21 or Down syndrome
  As many as 1 in 20 eggs produced after the age of 40 may carry this chromosome abnormality.
  Characteristics:
  Poor muscle tone, including heart muscle
  Tongue and mouth not proportioned, affecting speech
  Common mental retardation
  Immune system weak
- Trisomy of chromosome 13 and 18 also occur.
Non-disjunction of sex chromosomes

- Monosomy X0 = Turner syndrome
  Symptoms include absence of secondary sexual development and sterility. They do not produce Barr bodies.
- Monosomy Y0
  Lethal in embryonic development
- Trisomy XXX (female)
  No detectable problems. Females are usually fertile and bear normal XX or XY children. It may be related to the Barr body.
- Trisomy XXY (male) (and other multiples with both X and Y, except XYY) = Kleinfelter syndrome
  Mixed secondary sexual development at puberty and sterility
  Have normal intelligence testing
- Trisomy XYY (male) = Jacob's syndrome
  Increased vertical stature

Other Chromosome Differences

Polyploidy

- Increase in the number of sets of chromosomes, usually resulting from the formation of diploid gametes.
- Occurs naturally in many plants and may produce larger, hardier individuals. A naturally occurring tetraploid rat is found in Argentina.
- If the diploid gamete unites with a normal haploid gamete, the triploid hybrid is sterile (no homologous matches at meiosis).
- If both gametes are diploid, the individuals are often fertile.
- Polyploidy is used extensively in developing agricultural varieties.

The impacts of these chromosomal alterations vary, depending on when and where. In some cases, the cell will not work, and dies. In gametes, they will be carried in all cell lines, and there is some evidence that some chromosomal alterations may activate oncogenes, or cancer causing genes. One form of leukemia is known to be caused by a translocation.
Selective Phenotypic Expression of Parental Autosomes

We are comfortable with the idea that there are differences in the sex chromosomes. There are differences in parental autosomes, too. In some cases, it makes a difference which gamete provided the chromosome.

Imprinting is gender specific and appears to be caused by actions on chromosomes during the process of meiosis and gamete maturation. Certain genes get "imprinted" at this time, by adding methyl groups to specific nucleotides at certain gene loci. These genes are differentially imprinted in males and females. Most of the time imprinting deactivates the affected gene so that the offspring that develop after fertilization express just the allele it inherited from the other parental gamete. More than 20 genes affected by imprinting have been identified in humans, most of which affect embryonic development.

It is interesting to note that the imprinting affects the gamete and zygote development after fertilization. Both sexes are impacted the same way by the imprinted genes. However, in the reproductive organs of that individual the imprinting is "erased", and those cells can do meiosis producing imprinted genes according to the sex of the individual. For example, two genetic disorders, Angelman and Prader-Willi syndromes, can arise from gene imprinting at meiosis. A child will exhibit Prader-Willi syndrome if he/she inherited the imprinted gene from the father's gamete. A child will get Angelman syndrome if he or she inherits the imprinted gene from the mother's gamete. When the affected individuals do meiosis, sons can make gametes that will have Prader-Willi imprints, but daughters will imprint genes with Angelman syndrome no matter which disorder the affected individual has.

The fragile X syndrome, which causes serious mental retardation, and results from a CGG triplet repeat hundreds of times in the X chromosome, is one in which the gene imprint appears to activate the chromosome rather than deactivate it. Fragile X syndrome is more commonly inherited from mothers than from fathers.

Extra-nuclear gene expression

And for our final note on transmission of characteristics from generation to generation, Mendelian inheritance addresses the behavior of genes on chromosomes.

Organelles, such as mitochondria and chloroplasts (and all plastids) have small circular pieces of DNA, and that DNA is transcribed and translated within the organelle. Mitochondria and chloroplasts are self-replicating. In sexual reproduction, only the egg cell's cytoplasm is passed to the zygote, so only maternal mitochondrial and chloroplast DNA will be transmitted from generation to generation. Some genetic disorders are traced to mutations in mitochondrial DNA that codes for proteins in the electron transport chain. Mutations in mitochondrial DNA may be one reason cells age. Some variegated leaf patterns are caused by mutations in chloroplast DNA.