A. Outline:
1. Pedigree analysis
2. Extensions and exceptions to Mendel's laws
   Material from Human Genetics, 7th edition by Ricki Lewis

B. Reading assignment:
Read Lewis Human Genetics Chapter 4, pages 88-91, reading 7.1 and Figure 7.6, pages 142-143; Chapter 5, pages 95-101
Cartoon Guide, pages 162-163

C. Suggested practice questions:
Pedigree analysis: Chapter 4 Applied questions: 8, 9, 11, 14-18
Extensions and exceptions to Mendel's laws: Chapter 5 Review questions: 1-5; Applied questions: 1, 5

1. Pedigree analysis
If members of a family are afflicted with the same disease, it may suggest that the disease is inherited. Geneticists and doctors will look at a family tree or a pedigree to aid in determining if the disease has a genetic basis.

   Pedigrees depict family relationships and the transmission of inherited traits
   - Used to predict modes of inheritance in families
   - keeps track of relationships and traits
   - display laws revealed by Mendel for single gene traits
   - often pedigrees are incomplete because it is difficult to get information about some relatives

   Symbols
Squares represent males and circles represent females
Symbols for heterozygotes are half-shaded, and for individuals with a particular phenotype, completely shaded
open circle - unaffected female; filled circle - affected female; half-filled circle - carrier female
open square - unaffected male; filled square - affected male; half-filled square - carrier male

Lines
Horizontal lines indicate parents, vertical lines show generations, and siblings are connected to each other by a horizontal line above the symbols and to the parents by a vertical line

Do the practice problems (Chapter 4 Applied questions: 8, 9, 11, 14-18) to make sure you understand how to read a pedigree.
Extensions and exceptions to Mendel's laws

Mendel chose traits in peas that showed two distinct forms. Not all genes exhibit such simple inheritance.

1. Alleles interact
2. Genes interact
3. Non-nuclear genes
4. Segregation of genes on same chromosome

A. Lethal allele combinations - these are genotypes or combinations of alleles that are lethal. Some genotypes cause death before birth.

Lethal genotypes remove expected progeny from a cross resulting in changes in observed ratios of progeny.

- **Recessive allele example** - Humans - **Tay-Sachs** - metabolic disorder, brain deterioration death by age 3-5, others may cause death while the fetus is still in the uterus.

- **Dominant allele example** - **Achondroplasia**

Mexican hairless dogs result from a mutation in a gene that shows lethality

<table>
<thead>
<tr>
<th>Allele</th>
<th>Phenotype</th>
</tr>
</thead>
<tbody>
<tr>
<td>hh</td>
<td>hairy</td>
</tr>
<tr>
<td>Hh</td>
<td>hairless</td>
</tr>
<tr>
<td>HH</td>
<td>dies</td>
</tr>
</tbody>
</table>

B. Multiple alleles - A gene may exist in more than two allelic forms in a population. Genes can mutate in many ways at any nucleotide in their DNA sequence. In these cases, variations in phenotype or severity of a disease can be detected among affected individuals.

Examples:

- **PKU** - phenylketonuria - inborn error of metabolism inherited as an autosomal recessive trait - more than 300 alleles have been identified, there are 4 classes of PKU of varying severity of the disease.

- **CF** - cystic fibrosis - inborn error of metabolism inherited as an autosomal recessive trait. The deltaF508 allele causes 70% of the cases in the population (most severe form when homozygous recessive) but over 400 other alleles have been reported - many impart differing degrees of severity
• **white** locus in *Drosophila melanogaster* - white is recessive - homozygous recessive fly has white eyes - over 100 alleles of white exist that give a range of eye colors in flies.

**Dominance Relationships**

**Complete dominance** - Mendel traits followed this - one allele is expressed while the other is not.

**Incomplete dominance** - the heterozygote phenotype is intermediate between that of the homozygous dominant and homozygous recessive - a lack of dominance.

Example of an *incompletely dominant* trait in plants: Snapdragon flower color

- RR = Red - full amount of pigment
- Rr = pink - partial amount of pigment
- rr = white - no pigment

Example of an *incompletely dominant* trait in humans: Familial hypercholesterolemia – inherited form of high cholesterol disease

- FF = normal number of LDL receptors on liver
- Ff = one-half the number of LDL receptors on liver
- ff = no LDL receptors on liver

**Codominant** - alleles that are both expressed when in the heterozygous state - neither allele is dominant

*ABO blood groups* - illustrates both *multiple alleles* and *codominance* principles. Alleles for A and B type blood are codominant (both are expresses in people who have both alleles (AB blood type) and the allele for type O blood is recessive. There will be a group presentation of blood-type genetics. For more information, see the Cartoon Guide p162-163 and Human Genetics, 7th Ed. p97-98.
Epistasis - from the Greek word for stoppage - when one gene affects or masks the expression of another gene
Mendel's rule do not fit when 1 gene masks or affects the expression of different gene - crosses involving two genes that are subject to epistasis give rise to modified dihybrid phenotypic ratios.

Example: mouse coat color
At the A locus:
Inheritance of Agouti AA or Aa leads to a grayish coat, wild-type phenotype
Inheritance of aa - black coat, recessive

At the B locus:
Inheritance of BB or Bb allows pigment to be expressed
Inheritance of bb leads to albinism - eliminates all pigment regardless of inheritance of A or a

P1 = AABB (agouti) x aabb (albino)
F1 = AaBb (agouti)
F1 X F1 - AaBb (agouti) X AaBb (agouti)

<table>
<thead>
<tr>
<th>Genotype</th>
<th>Frequency</th>
<th>Phenotype</th>
</tr>
</thead>
<tbody>
<tr>
<td>A_B_</td>
<td>9/16</td>
<td>agouti</td>
</tr>
<tr>
<td>A_bb</td>
<td>3/16</td>
<td>albino</td>
</tr>
<tr>
<td>aaBb</td>
<td>3/16</td>
<td>black</td>
</tr>
<tr>
<td>aabb</td>
<td>1/16</td>
<td>albino</td>
</tr>
</tbody>
</table>

9 agouti, 3 black and 4 albino

Inheritance of bb masks expression of the A allele
b is epistatic to A
A is hypostatic to b

The determination of fruit color in summer squash is another example where epistasis is apparent.

More genetic terms:
Penetrance
Some allele combinations can produce different degrees of a phenotype in different individuals. This reflects the fact that genes do not act alone. The differences might reflect environmental or additional genetic factors. Penetrance = the percentage of individuals that show some degree of the phenotype.
**Completely penetrant** - everyone who inherits the allele combination is affected. Example: Tay-Sachs - homozygous recessive allele combination is 100 percent penetrant.

**Incomplete penetrance** - some individuals who inherit certain alleles do not express the phenotype or have no symptoms.

The percentage of people who express disease symptoms is expressed as **percentage penetrant**. For example, if 8 of 10 people with the allele combination express symptoms, the disease is said to be **80 percent penetrant**. Example: polydactyly.

**Expressivity**

**Variable expression** - phenotype varies in intensity among affected individuals - variation caused by influence of other genes and/or environment. Examples: polydactyly (one or both hands affected, etc), familial hypercholesterolemia (affected by age, diet, exercise, medicine).

**Pleiotrophy** - one gene controls expression of many symptoms and the symptoms may be variably expressed.

Example: porphyria variegata (King George example in Human Genetics book) and Marfan syndrome (fibrillin defect - affects many parts of the body).

**Phenocopy** - when an environmentally caused trait mimics an inherited disease - similar symptoms.

Example - thalidomide poisoning - limb defects were mistaken for those of a rare Mendelian disorder called phocomelia. Children with AIDS from parents with AIDS - HIV positive children were most likely infected by virus - did not inherit it from parents.

**Genetic heterogeneity** - when different genes cause the same symptoms. For example, there are greater than 130 genes associated with deafness, several with cleft palate, and several with albinism. Genes that encode enzymes that act in one or more biosynthetic pathways - disruption of the pathway may have one phenotype but it can be caused by mutation in one of many genes.