Problems with the Genome

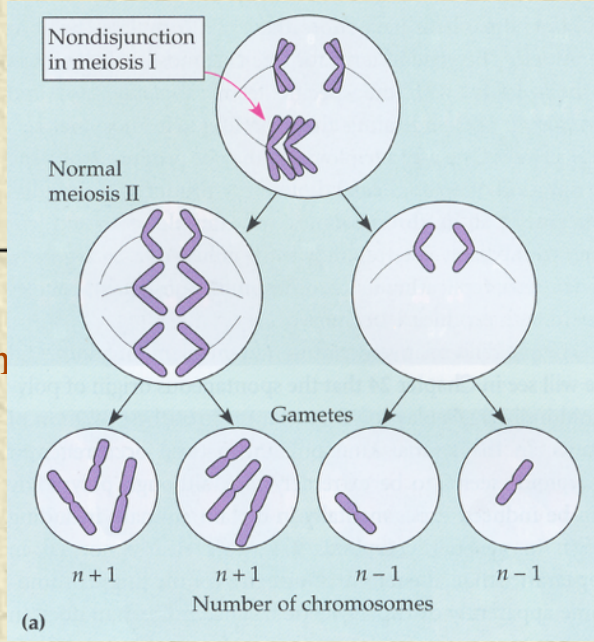
Genetics for Future Medical Doctors

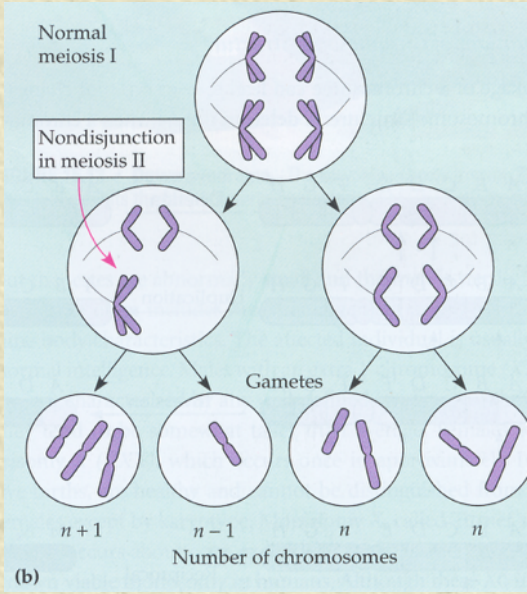
Genetics and Your Health

- Medical science is increasingly coming to understand the genetic root of many maladies in humans. Therefore medical doctors and the public need to know more about these genetic problems.
- So, here are some highlights. . .

Nondisjunction

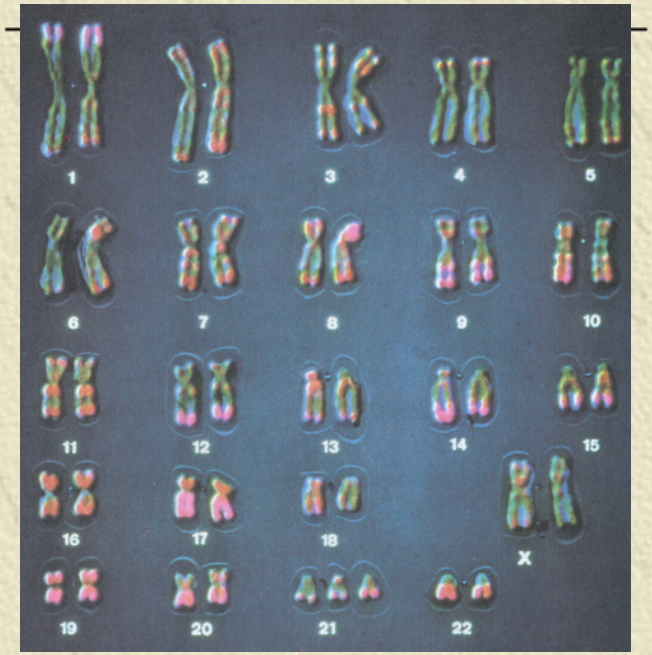
- **Nondisjunction** (2 Possibilities)
  - Sometimes **homologous chromosomes** do not separate in **meiosis I** (illustrated in the upper right)
  - Sometimes **sister chromatids** do not separate in **meiosis II** (illustrated in the lower right)
- Result of Nondisjunction
  - **Aneuploidy**: A cell with more or less than the correct diploid number of chromosomes (either too many or too few)
    - Greek roots: ***an*** = without + ***eu*** = good/true + ***ploidy***="chromosomes"
  - If fertilized eggs have n + 1 chromosomes for a particular chromosome they are said to be **trisomic** for that chromosome
  - If fertilized eggs have n - 1 chromosomes for a particular chromosome they are said to be **monosomic** for that chromosome





Down Syndrome

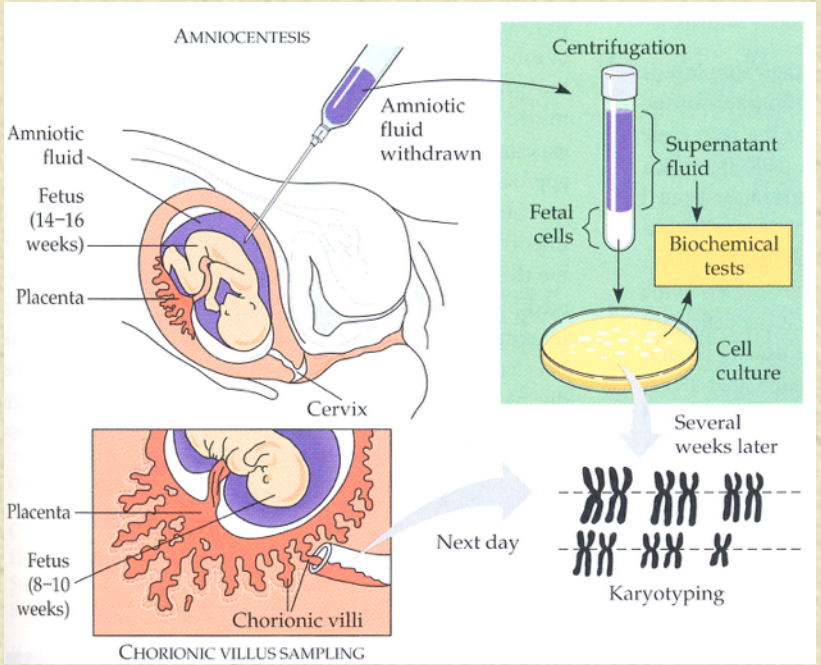
- A result of trisomy in chromosome 21
- Symptoms
  - Characteristic facial features
  - Short stature
  - Heart defects
  - Susceptibility to respiratory infections
  - Low IQ
  - Many are sexually underdeveloped and sterile.



Michael Williams/Mercury Pictures

Prenatal Diagnosis: 2 Different Techniques

- **Amniocentesis**
  - Amniotic fluid is removed, the cells are cultured and then karyotyped
- **Chorionic Villus Sampling**
  - A narrow tube is inserted through the cervix and a small amount of the placenta is removed and the cells are karyotyped



Sex Chromosome Aneuploidy

- XXY (**Klinefelter Syndrome**)
  - Sterile male (has male sex organs)
  - May have female characteristics (some breast development)
  - Normal Intelligence
- XO (**Turner's Syndrome**)
  - Look like females (are females since they have no Y chromosome)
  - Short (average height is 4' 7" tall)
  - Fail to develop secondary sexual characteristics (e.g. breast development)
  - Sterile
  - Normal Intelligence
  - Only known viable example of **monosomy** in humans!
- XYY (No Syndrome)
  - Tend to be taller than normal
- XXX (No Syndrome)
  - Can't tell from appearance

Polyploidy

- Polyploidy is a condition in which an organism has more than 2 complete sets of chromosomes.
  - More common than aneuploidy
- A quick review of what is considered "normal"
  - **Somatic cells** in most organisms have two sets of chromosomes
    - These cells are said to be **diploid** (2n)
      - The chromosomes come in **homologous pairs**.
  - **Sex cells** in all organisms have one set of chromosomes
    - These cells are said to be haploid (n)

Examples of Polyploidy

- **Triploidy** (3n)
  - Possible Causes
    - **Nondisjunction** of all chromosomes leaving an egg with 2n number of chromosomes. This egg is then fertilized by a normal haploid (n) sperm.
    - **Double Fertilization**: Two sperm fertilize one egg resulting in 3n number of chromosomes.
- Tetraploidy (4n)
  - Possible Cause
    - Failure of a zygote to divide after it has replicated its chromosomes (2n->4n) with subsequent mitosis.
    - Very common in plants. In fact, it is believed that over 50% of speciation in plants is due to polyploidy!!!
      - Can be induced by the drug cholchicine

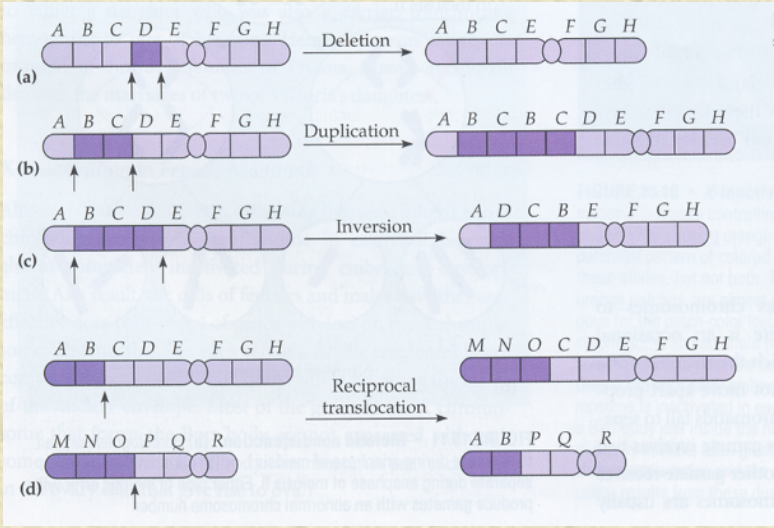
Guinness Book of World Records for Chromosome Number

- What organism has the fewest number of chromosomes and how many chromosomes does it have?
  - There is a species of ant that has 1 chromosome

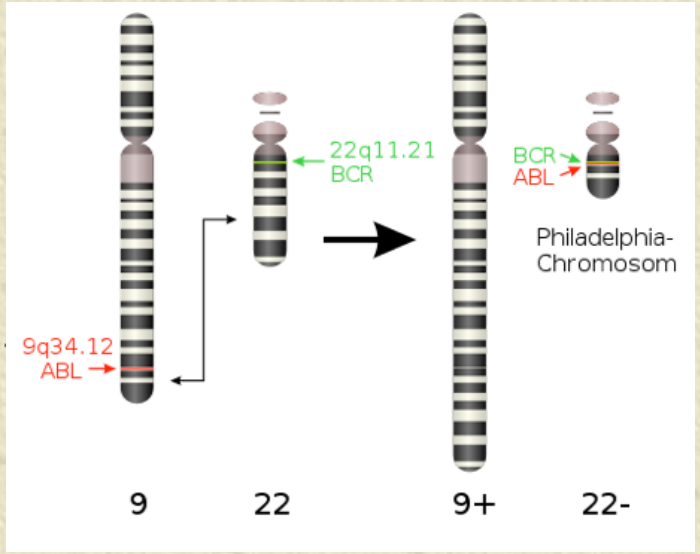
- What organism has the greatest number of chromosomes and how many chromosomes does it have?
  - There is a species of fern that has 1,260 chromosomes per cell!
  - 630 pairs of homologous chromosomes!

Alteration in Chromosome Structure

- **Deletion**
  - Removal of a segment of the chromosome
- **Duplication**
  - Repeating a segment
- **Inversion**
  - Reversal of a segment
- **Translocation (2 Types)**
  - Movement of segment from one chromosome to another non-homologous chromosome
    - Note: If you did this with a homologous chromosome what would it be called?
      - Crossing over!
  - **Reciprocal Translocation**
    - Trading of one chromosome
      - "You give me a piece; I'll give you a piece"
  - **Non-reciprocal Translocation**
    - One way movement
      - No trading of pieces

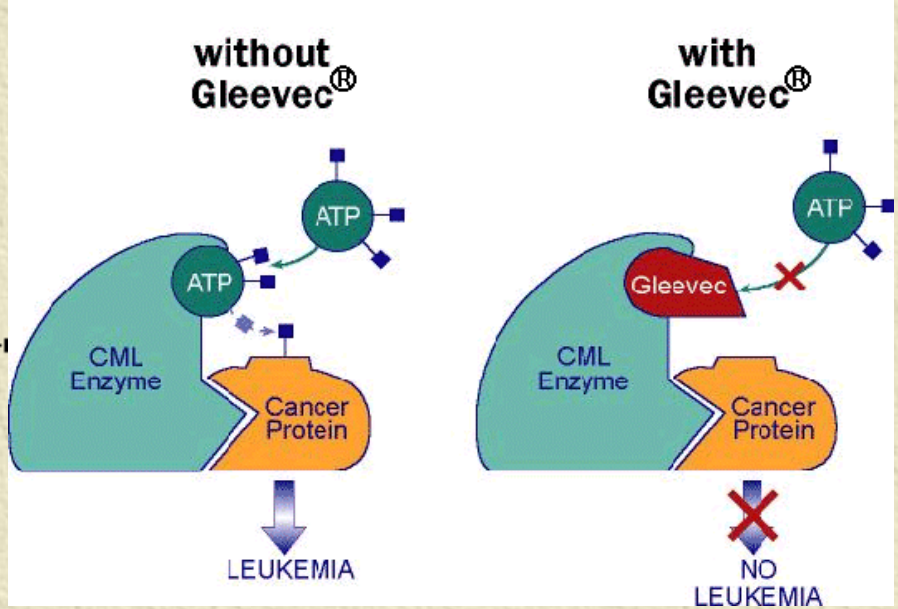


The Philadelphia Chromosome



- **Reciprocal Translocation**
  - A piece of Chromosome 9 & 22 swap places
  - Creates a fusion of two genes ABL and BCR. This "new" gene codes for a protein that unregulates the cell cycle resulting in uncontrolled cell division of white blood cells-> Cancer
  - Chronic Myelogenous Leukemia (CML)

Good News



- A drug was discovered that inhibits the rogue protein (CML Enzyme in this illustration). The active portion of the rogue protein normally binds ATP and activates another protein that causes uncontrolled cell growth of white blood cells. The drug, Gleevec, (in red) blocks the functional part of the protein and renders it harmless.
  - Cell Cycle regulation goes back to normal
  - Uncontrolled cell growth stops
  - Cancer is eliminated!
  - First example of "rational drug discovery"
    - Was a huge breakthrough in cancer therapy

Genomic Imprinting

- In **genomic imprinting** the phenotypic effects of some genes depend on whether they were inherited from the mother or the father.
- Example
  - Deletion on Chromosome 15
    - If the abnormal chromosome is inherited from the father the result is Prader-Wili Syndrome
      - Intellectual disability, obesity, short stature, small hands and feet
    - If the abnormal chromosome is inherited from the mother the result is Angelman Syndrome
      - Spontaneous uncontrollable laughter, jerky body movements
- Genomic Imprinting is only seen in mammals
  - Genes are “imprinted” in some way each generation depending on whether the gene came from the mother or father. Therefore, the phenotypic effect of the gene depends on what parent the gene came from.
    - Same gene, different effect, depending on whether it came from mom or dad.

Barr Body and X-Inactivation in Female Mammals

- Each female somatic cell has two X chromosomes (XX)
- However, one X chromosome in each cell becomes almost completely inactivated during embryonic development
- The inactive X chromosome in each cell of a female condenses into a compact object called a **Barr Body**.
  - It lies along the inside of the nuclear envelope
- Example
  - The X chromosome in cats has a gene controlling fur color- one allele for black, one allele for orange.
  - Male (XY) only inherits one or the other and so is either black or orange
  - Female cats (XX) cat inherit both and are therefore are calico. There are NO male calico cats!