- Bleeding in muscles and joints can be painful and can lead to serious damage.

- Today, people with hemophilia can be treated with intravenous injections of the missing protein.
- Although female mammals inherit two X chromosomes, only one X chromosome is active.
- Therefore, males and females have the same effective dose (one copy) of genes on the X chromosome.
  - During female development, one X chromosome per cell condenses into a compact object called a **Barr body.**
  - Most of the genes on the Barr-body chromosome are not expressed.
- The condensed Barr-body chromosome is reactivated in ovarian cells that produce ova.
- Mary Lyon, a British geneticist, demonstrated that selection of which X chromosome will form the Barr body occurs randomly and independently in embryonic cells at the time of X inactivation.
- As a consequence, females consist of a *mosaic* of two types of cells, some with an active paternal X chromosome, others with an active maternal X chromosome.
  - After an X chromosome is inactivated in a particular cell, all mitotic descendants of that cell will have the same inactive X.
  - If a female is heterozygous for a sex-linked trait, approximately half her cells will express one allele, and the other half will express the other allele.
- In humans, this mosaic pattern is evident in women who are heterozygous for an X-linked mutation that prevents the development of sweat glands.
  - A heterozygous woman will have patches of normal skin and skin patches lacking sweat glands.
- Similarly, the orange-and-black pattern on tortoiseshell cats is due to patches of cells expressing an orange allele while other patches have a nonorange allele.
- X inactivation involves modification of the DNA by attachment of methyl (—CH_3) groups to cytosine nucleotides on the X chromosome that will become the Barr body.
- Researchers have discovered a gene called *XIST* (X-inactive specific transcript).
  - This gene is active *only* on the Barr-body chromosome and produces multiple copies of an RNA molecule that attach to the X chromosome on which they were made.
  - This initiates X inactivation.
  - The mechanism that connects *XIST* RNA and DNA methylation is unknown.
- What determines which of the two X chromosomes has an active *XIST* gene is also unknown.

C. Errors and Exceptions in Chromosomal Inheritance

- Physical and chemical disturbances can damage chromosomes in major ways.
- Errors during meiosis can alter chromosome number in a cell.
- Plants tolerate genetic defects to a greater extent that do animals.

1. Alterations of chromosome number cause some genetic disorders.

- **Nondisjunction** occurs when problems with the meiotic spindle cause errors in daughter cells.
  - This may occur if tetrad chromosomes do not separate properly during meiosis I.
  - Alternatively, sister chromatids may fail to separate during meiosis II.

- As a consequence of nondisjunction, one gamete receives two of the same type of chromosome, and another gamete receives no copy.
- Offspring resulting from fertilization of a normal gamete with one produced by nondisjunction will have an abnormal chromosome number, a condition known as **aneuploidy.**
  - **Trisomic** cells have three copies of a particular chromosome type and have $2n + 1$ total chromosomes.
  - **Monosomic** cells have only one copy of a particular chromosome type and have $2n - 1$ chromosomes.
- If the organism survives, aneuploidy typically leads to a distinct phenotype.
- Aneuploidy can also occur during failures of the mitotic spindle.
- If this happens early in development, the aneuploid condition will be passed along by mitosis to a large number of cells.
  - This is likely to have a substantial effect on the organism.
- Organisms with more than two complete sets of chromosomes are **polyploid.**
- This may occur when a normal gamete fertilizes another gamete in which there has been nondisjunction of all its chromosomes.
  - The resulting zygote would be *triploid* ($3n$).
- Alternatively, if a $2n$ zygote failed to divide after replicating its chromosomes, a *tetraploid* ($4n$) embryo would result from subsequent successful cycles of mitosis.
- Polyploidy is relatively common among plants and much less common among animals, although it is known to occur in fishes and amphibians.
  - The spontaneous origin of polyploid individuals plays an important role in the evolution of plants.
  - Both fishes and amphibians have polyploid species.
  - Recently, researchers in Chile have identified a new rodent species that may be tetraploid.
- Polyploids are more nearly normal in phenotype than aneuploids.
  - One extra or missing chromosome apparently upsets the genetic balance during development more than does an entire extra set of chromosomes.

2. Alterations of chromosome structure cause some genetic disorders.

- Breakage of a chromosome can lead to four types of changes in chromosome structure.
  - A **deletion** occurs when a chromosome fragment lacking a centromere is lost during cell division.
    - This chromosome will be missing certain genes.
  - A **duplication** occurs when a fragment becomes attached as an extra segment to a sister chromatid.
    - Alternatively, a detached fragment may attach to a nonsister chromatid of a homologous chromosome.
    - In this case, the duplicated segments will not be identical if the homologues carry different alleles.
  - An **inversion** occurs when a chromosomal fragment reattaches to the original chromosome, but in the reverse orientation.
  - In **translocation,** a chromosomal fragment joins a nonhomologous chromosome.

- Deletions and duplications are especially likely to occur during meiosis.
  - Homologous chromatids may break and rejoin at incorrect places during crossing over, so that one chromatid loses more genes than it receives.
  - The products of such a *nonreciprocal* crossover are one chromosome with a deletion and one chromosome with a duplication.
- A diploid embryo that is homozygous for a large deletion or a male with a large deletion to its single X chromosome is usually missing many essential genes.
  - This is usually lethal.
- Duplications and translocations are typically harmful.
- Reciprocal translocation or inversion can alter phenotype because a gene's expression is influenced by its location among neighboring genes.

3. Human disorders are due to chromosome alterations.

- Several serious human disorders are due to alterations of chromosome number and structure.
- Although the frequency of aneuploid zygotes may be quite high in humans, most of these alterations are so disastrous to development that the embryos are spontaneously aborted long before birth.
  - Severe developmental problems result from an imbalance among gene products.
- Certain aneuploid conditions upset the balance less, making survival to birth and beyond possible.
  - Surviving individuals have a set of symptoms—a syndrome—characteristic of the type of aneuploidy.
  - Genetic disorders caused by aneuploidy can be diagnosed before birth by fetal testing.
- One aneuploid condition, **Down syndrome,** is due to three copies of chromosome 21 or *trisomy 21.*
  - It affects one in 700 children born in the United States.
- Although chromosome 21 is the smallest human chromosome, trisomy 21 severely alters an individual's phenotype in specific ways.
  - Individuals with Down syndrome have characteristic facial features, short stature, heart defects, susceptibility to respiratory infection, mental retardation, and increased risk of developing leukemia and Alzheimer's disease.
  - Most are sexually underdeveloped and sterile.
- Most cases of Down syndrome result from nondisjunction during gamete production in one parent.
- The frequency of Down syndrome increases with the age of the mother.
  - This may be linked to some age-dependent abnormality in the spindle checkpoint during meiosis I, leading to nondisjunction.
- Trisomies of other chromosomes also increase in incidence with maternal age, but it is rare for infants with these autosomal trisomies to survive for long.
- Nondisjunction of sex chromosomes produces a variety of aneuploid conditions in humans.
- This aneuploidy upsets the genetic balance less severely that autosomal aneuploidy.
  - This may be because the Y chromosome contains relatively few genes and because extra copies of the X chromosome become inactivated as Barr bodies in somatic cells.
- An XXY male has *Klinefelter's syndrome*, which occurs once in every 2,000 live births.

- These individuals have male sex organs, but have abnormally small testes and are sterile.
- Although the extra X is inactivated, some breast enlargement and other female characteristics are common.
- Affected individuals have normal intelligence.

- Males with an extra Y chromosome (XYY) tend to be somewhat taller than average.
- Trisomy X (XXX), which occurs once in every 2,000 live births, produces healthy females.
- Monosomy X or *Turner syndrome* (X0) occurs once in every 5,000 births.
  - This is the only known viable monosomy in humans.
  - X0 individuals are phenotypically female but are sterile because their sex organs do not mature.
  - When provided with estrogen replacement therapy, girls with Turner syndrome develop secondary sex characteristics.
  - Most are of normal intelligence.
- Structural alterations of chromosomes can also cause human disorders.
- Deletions, even in a heterozygous state, can cause severe problems.
- One syndrome, *cri du chat*, results from a specific deletion in chromosome 5.
  - These individuals are mentally retarded, have small heads with unusual facial features, and have a cry like the mewing of a distressed cat.
  - This syndrome is fatal in infancy or early childhood.
- Chromosomal translocations between nonhomologous chromosomes are also associated with human disorders.
- Chromosomal translocations have been implicated in certain cancers, including *chronic myelogenous leukemia (CML).*
  - CML occurs when a large fragment of chromosome 22 switches places with a small fragment from the tip of chromosome 9.
  - The resulting short, easily recognized chromosome 22 is called the *Philadelphia chromosome.*

4. The phenotypic effects of some mammalian genes depend on whether they are inherited from the mother or the father.

- For most genes, it is a reasonable assumption that a specific allele will have the same effect regardless of whether it is inherited from the mother or father.
- However, for a few dozen mammalian traits, phenotype varies depending on which parent passed along the alleles for those traits.
  - The genes involved are not necessarily sex linked and may or may not lie on the X chromosome.
- Variation in phenotype depending on whether an allele is inherited from the male or female parent is called **genomic imprinting.**
- Genomic imprinting occurs during formation of gametes and results in the silencing of certain genes.
  - Imprinted genes are not expressed.
- Because different genes are imprinted in sperm and ova, some genes in a zygote are maternally imprinted, and others are paternally imprinted.

- These maternal and paternal imprints are transmitted to all body cells during development.
- For a maternally imprinted gene, only the paternal allele is expressed.
- For a paternally imprinted gene, only the maternal allele is expressed.

- Patterns of imprinting are characteristic of a given species.
- The gene for insulin-like growth factor 2 (*Igf2*) is one of the first imprinted genes to be identified.
- Although the growth factor is required for normal prenatal growth, only the paternal allele is expressed.
- Evidence that the *Igf2* allele is imprinted initially came from crosses between wild-type mice and dwarf mice homozygous for a recessive mutation in the *Igf2* gene.
  - The phenotypes of heterozygous offspring differ, depending on whether the mutant allele comes from the mother or the father.
  - The *Igf2* allele is imprinted in eggs, turning off expression of the imprinted allele.
  - In sperm, the *Igf2* allele is not imprinted and functions normally.
- What exactly is a genomic imprint?
- In many cases, it consists of methyl (—CH_3) groups that are added to the cytosine nucleotides of one of the alleles.
- The hypothesis that methylation directly silences an allele is consistent with the evidence that heavily methylated genes are usually inactive.
  - Other mechanisms may lead to silencing of imprinted genes.
- Most of the known imprinted genes are critical for embryonic development.
- In experiments with mice, embryos engineered to inherit both copies of certain chromosomes from the same parent die before birth, whether their lone parent is male or female.
- Normal development requires that embryonic cells have one active copy of certain genes.
- Aberrant imprinting is associated with abnormal development and certain cancers.

5. Extranuclear genes exhibit a non-Mendelian pattern of inheritance.

- Not all of a eukaryote cell's genes are located on nuclear chromosomes, or even in the nucleus.
- *Extranuclear genes* are found in small circles of DNA in mitochondria and chloroplasts.
- These organelles reproduce themselves and transmit their genes to daughter organelles.
  - Their cytoplasmic genes do not display Mendelian inheritance, because they are not distributed to offspring according to the same rules that direct distribution of nuclear chromosomes during meiosis.
- Karl Correns first observed cytoplasmic genes in plants in 1909 when he studied the inheritance of patches of yellow or white on the leaves of an otherwise green plant.
  - He determined that the coloration of the offspring was determined by only the maternal parent.
  - These coloration patterns are due to genes in the plastids that are inherited only via the ovum, not via the sperm nucleus in the pollen.
- Because a zygote inherits all its mitochondria from the ovum, all mitochondrial genes in mammals demonstrate maternal inheritance.

- Several rare human disorders are produced by mutations to mitochondrial DNA.
  - These primarily impact ATP supply by producing defects in the electron transport chain or ATP synthase.
  - Tissues that require high energy supplies (the nervous system and muscles) may suffer energy deprivation from these defects.
  - For example, a person with *mitochondrial myopathy* suffers weakness, intolerance of exercise, and muscle deterioration.
  - Other mitochondrial mutations may contribute to diabetes, heart disease, and other diseases of aging.