First Lecture **Cytogenetic** **First Semester 2019--2020**

Genetics is the study **of inherited traits and their variation**. Sometimes people confuse genetics with genealogy, which considers relationships but not traits; Genetics is a life science associated with other sciences by one or more than elements and describes the results reveals from their causes.

Scope of Genetics

Genetics as a biological Despines were **branched to:**

1-Cytogenetics

2-Class genetic (Mendial)

3- Molecular genetic

4 – Biochemical genetics

6 – Development genetics

7 – Clinical genetics

8 – Counseling or Behavior genetics

9 – Cytoplasmic genetics

10 – Human genetics

11 – Ecological genetics

12 – Pharmacogenetics

13 – Population genetics

Cytogenetics:

Is one branch of genetics describes **the karyotype of individual** that **reveals stability of number and structure of chromosomes.**

In general , genetics is the study of **inherited traits and their variation** . Some people confuse genetics with genealogy , which consider relationships but not traits.

Genetics is a life science associated with other sciences by one or more than elements and describes the results reveals from their genetics. Genetics is unlike

other life sciences in how directly and intimately it affects our lives. It obviously impacts our health, because we inherit certain diseases and disease susceptibilities. But principles of genetics also touch history, politics, economics, sociology, and psychology, and they force us to wrestle with concepts of benefit and risk.

Genetic Testing:

Although entire human genomes can be sequenced, it is more-cost effective to detect only health related gene variants most likely to be present in a particular individual based on personal health, family history and ethic back-ground.

Levels of Genetics:

There are many levels accomplished to study the genetics represented by:

- DNA & RNA
- Genes , chromosomes and Genomes
- Cells ,Tissues and Organs
- Individual
- Family
- Population
- Evolution

DNA & RNA

Genes consist of sequences of four types of DNA building blocks—adenine, guanine, cytosine, and thymine. Each base bond to a sugar and a phosphate group to form a unit called a nucleotide. DNA bases are also called nitrogenous (nitrogen-containing) bases. DNA bases in a row specify the code for a particular amino acid, and amino acids are the building blocks of proteins.

An intermediate language also encoded in nitrogenous bases is contained in **ribonucleic acid (RNA).** One type of RNA carries a copy of a DNA sequence and presents it to other parts of the cell. In this way, the information encoded in DNA can be used to produce RNA molecules, which are then used to manufacture protein.

Gene, chromosome & Genome

Genes are the units of heredity, the sets of biochemical instructions that tell cells, the basic units of life, how to manufacture certain proteins. These proteins ultimately underlie specific traits; a missing protein blood-clotting factor, for example, causes the inherited disease hemophilia.

A gene is composed of the molecule **deoxyribonucleic acid,** more familiarly known as **DNA.** Some traits are determined nearly entirely by genes; most traits, however, have considerable environmental components.

Individual genes come in variants that differ from each other by small changes in the DNA base sequence. The variants of a gene are called **alleles,** and these changes in DNA sequence arise by a process called **mutation.**

Some mutations are harmful, causing disease; others provide variation, such as freckled skin; and some mutations may actually be helpful. In some people, for example, a rare mutation renders their cells unable to bind HIV, making them resistant to HIV infection.

Chromosome

Genes are part of larger structures called **chromosomes,** which also include proteins that the DNA wraps around. A human cell has 23 pairs of chromosomes. Twenty-two pairs are **autosomes,** or chromosomes that do not differ between the sexes. The autosomes are numbered from 1 to 22, with 1 being the largest. The other two chromosomes, the X and the Y, are **sex chromosomes.**

The **Y chromosome** bears genes that determine maleness. In humans, lacking a Y makes one a female.

Missing even small portions of a chromosome has a devastating effect on health, because many genes are deleted. To detect chromosome abnormalities, geneticists use charts called **karyotypes** that order the chromosome pairs from largest to smallest.

The chromosomes are **stained** with dyes or **fluorescent chemicals** that create different patterns to highlight abnormalities.

Genome, is The complete set of genetic information characteristic of an organism, including protein encoding genes and other DNA sequences, constitutes a **genome.**

Parts of the DNA sequence can vary among individuals, yet not change external appearance or health. A variant in sequence that is present in at least 1 percent of a population is called a **polymorphism.** A polymorphism can occur in a part of the DNA that encodes protein, or in a part that does not encode protein.

“Polymorphism” is a general term that literally means “many forms.” It includes disease-causing variants.

A polymorphism can be helpful, harmful, or, in most instances, have no effect at all (that we know of). The term polymorphism has been part of the language of genetics for decades, but has recently begun to attract a great deal of attention from other fields, such as information technology and medicine.

Researchers have identified more than 3 million **single nucleotide polymorphisms** (SNPs, pronounced "snips"). SNPs are single base sites that differ among individuals. The human genome may include up to 20 million SNPs, or 1 in every 1,250 or so DNA nucleotides, although they are not evenly distributed. DNA microarrays include both disease-causing mutations and SNPs that merely mark places where people differ.

Cells, Tissues, and Organs

A human body consists of **trillions of cells**. Most cells contain all of the genetic instructions, but **cells differ in appearance** and function by using only **some of their genes**, in a process called **differentiation.**

For example: a **muscle cells** manufactures its abundant **protein fiber**, **skin cells** manufacture **keratins, collagen and elastin proteins** characteristic of connective tissue cells.

Specialized cells with **related functions aggregate** and interact to **form tissues**, which in turn form the organs and organ systems of the individual.

Organs also include less specialized cells, called **stem cells,** that retain the ability to differentiate further, should the need arise—perhaps when an injury requires that certain cells be replaced. Some repositories of these replenishing stem cells, including those in the brain, have only recently been discovered. Others, such as the **bone marrow cells that continually replenish the blood,** are better known. A new field called r**egenerative medicine uses stem cells** to replace degenerating cells that cause Conditions such as Parkinson disease and Huntington disease.

Individual

Two terms distinguish between the alleles that are *present* in an individual and the alleles that are *expressed.*

The **genotype** refers to the underlying instructions (alleles present), and the **phenotype** is the visible trait, biochemical change, or effect on health (alleles expressed). Alleles are further distinguished by how many copies it takes to affect the phenotype.

A **dominant** allele produces an effect when present in just one copy (on one chromosome), whereas a **recessive** allele must be present on both chromosomes to be expressed. (Alleles on the Y chromosome are an exception; recessive alleles on the X chromosome in males are expressed because there is no second X chromosome to block expression.)

Family

Individuals are genetically connected into families. Traditionally, the study of traits in families has been called transmission genetics or **Mendelian genetics**.

Molecular genetics, which considers DNA, RNA, and proteins, often begins with transmission genetics, when an interesting trait or illness in a family comes to a researcher's attention. **Charts** called **pedigrees** are **used to represent the members of a family and to indicate** which individuals have **particular inherited traits**. , but an unusual one—a family with identical triplets.

Population

Above the family level of genetic organization is the population. In a strict biological sense, a population is a group of interbreeding individuals. In a genetic sense, a population is a large collection of alleles, distinguished by the frequency of particular alleles. People from Sweden, for example, would have a greater frequency of alleles that specify light hair and skin than people from a population in Ethiopia who tend to have dark hair and skin. The fact that groups of people look different and may suffer from different health problems reflects the frequencies of their distinctive sets of alleles.

All the alleles in a population constitute the **gene pool.** (An individual does not have a gene pool.)

Population genetics is very important in applications such as health care and forensics. It is also the very basis of evolution. In fact, evolution is technically defined as "changing allele frequencies in populations

Evolution

Geneticists have known for decades that comparing DNA sequences for individual genes, or the amino acid sequences of the proteins that the genes encode, can reveal how closely related different types of organisms are. The underlying assumption is that the more similar the sequences are, the more recently two species diverged from a shared ancestor. Such analysis for cytochrome C, a protein essential for extracting energy from nutrients.

Genome wide studies are even more startling than comparing single genes.

Humans, for example, share more than 98 percent of the DNA sequence with chimpanzees. Our genomes differ more in the organization of genes and in the number of copies of genes than in the overall sequence.

Still, learning the functions of the human specific genes may explain the anatomical differences between us and humans also share many DNA sequences with puffer fish, fruit flies, mice, and even bacteria.

Prof. Dr. Mahfoodha A. Umran

20/10/2019

Cell Division and Death

The cell numbers in a human body must be in balance to **develop normally** and **maintain health.** The process of mitotic cell division, or **mitosis,** provides new cells by forming two cells from one. **Mitosis** occurs in **somatic cells** (all cells but the sperm and eggs expection). Although it seems counter intuitive, some cells must die as a body forms, just as a sculptor must take away some clay to shape the desired object. **A foot**, for example, might start out as a webbed triangle of tissue, with digits carved from it **as certain cells die.**

This type of cell death, which is a normal part of development, is called **apoptosis.**
It is a precise, genetically programmed sequence of events, as is mitosis in figure.

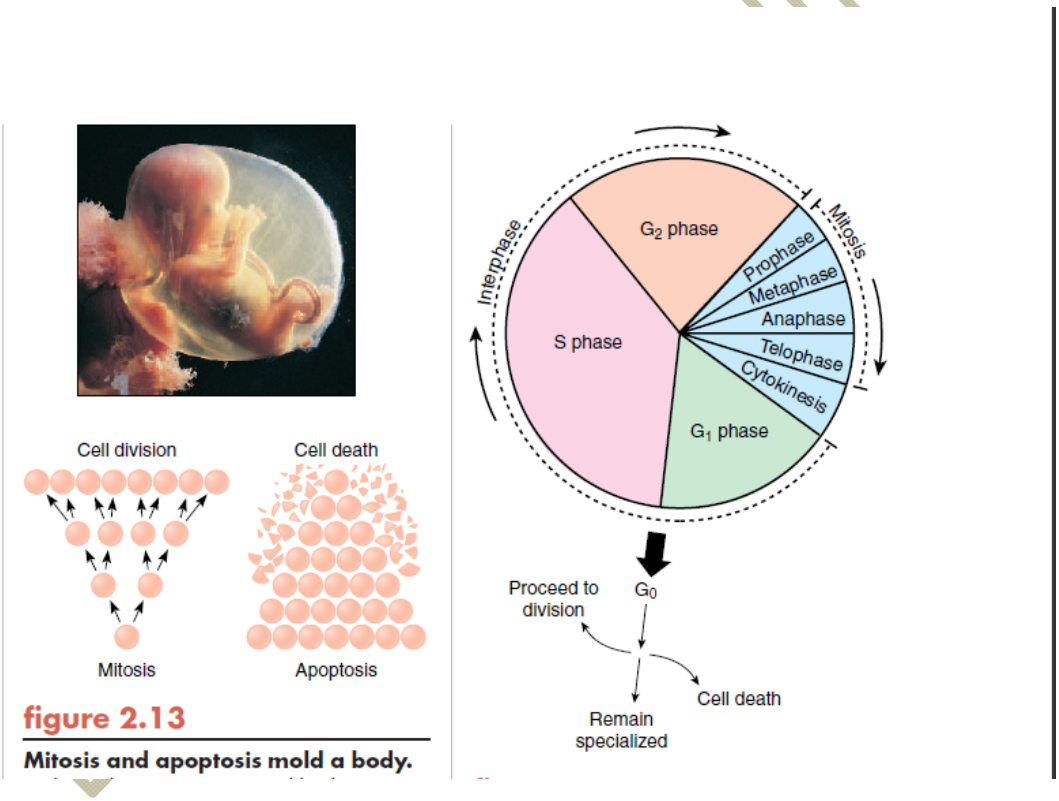


figure 2.13
Mitosis and apoptosis mold a body.

The Cell Cycle

Many cell divisions transform a single fertilized egg into a many-trillion-celled person. A series of events called the **cell cycle** describes when a cell is dividing or not dividing.

Cell cycle rate varies in different tissues at different times.

Are all cells continuous dividing throughout life?

Answer :No, A cell lining the small **intestine's inner wall may divide throughout life**;
a cell in the brain may never divide;
a cell in the deepest skin layer of a 90-yearold may divide more if the person lives long enough. Frequent mitosis enables the embryo and fetus to grow rapidly.

By birth, the mitotic rate slows dramatically. Later, mitosis must maintain the numbers and positions of specialized cells in tissues and organs.

The cell cycle is a continual process, but we divide it into stages based on what we see. The two major stages are **interphase** (not dividing) and mitosis (dividing) (figure 2.14). In **mitosis**, a cell's **replicated chromosomes** are distributed into two daughter cells. This maintains the set of 23 chromosome pairs characteristic of a human somatic cell. Another form of cell division, **meiosis,** produces sperm or eggs. These cells contain half the usual amount of genetic material, or 23 single chromosomes.

Interphase—*A Time of Great Activity*

Interphase is a very active time. The cell continues the basic biochemical functions of life and also replicates its DNA and other subcellular structures for distribution to daughter cells.

Interphase is divided into two **gap (G) phases** and one **synthesis (S) phase.** A cell can exit the cell cycle at G1 to enter **G0, a quiescent phase**. A cell in G0 can maintain its specialized characteristics, but it does not replicate its DNA or divide. It is a cellular "time out."

During the first **gap phase (G1**), the cell **resumes** synthesis of proteins, lipids, and carbohydrates following mitosis. These molecules will surround the two new cells that form from the original one. **G1 is the period of the cell cycle that varies the most in duration among different cell types.**

Slowly dividing cells, such as those in the liver, may exit at G1 and enter G0, where they remain for years. In contrast, the rapidly dividing cells in bone marrow speed through G1 in 16 to 24 hours. Early cells of the embryo may skip G1 entirely.

During the next period of interphase, **S phase**, the cell **replicates its entire genome**, so that each chromosome consists of **two copies joined** at an area called the **centromere .** In most human cells, S phase takes 8 to 10 hours. Many proteins are also synthesized during this phase, including those that form the mitotic **spindle** structure that will pull the chromosomes apart. Microtubules form structures called **centrioles** near the nucleus. Centriole microtubules are oriented at right angles to each other, forming paired oblong structures that organize other microtubules into the spindle.

The second **gap phase, G2**, occurs after the DNA has been replicated but **before mitosis begins.** A cell in this phase synthesizes more proteins. Membranes are **assembled** from molecules made during G1 and stored as small, empty vesicles beneath the cell membrane. These vesicles will be used to enclose the two daughter cells.

Mitosis—*The Cell Divides*

As mitosis begins, the chromosomes are replicated and condensed enough to be visible, when stained, under a microscope. The two long strands of identical chromosomal material of a replicated chromosome are called **chromatids** (figure 2.15). They are joined at their centromeres. At a certain point during mitosis, a replicated chromosome's two centromeres part, allowing each chromatid pair to separate into two individual chromosomes.

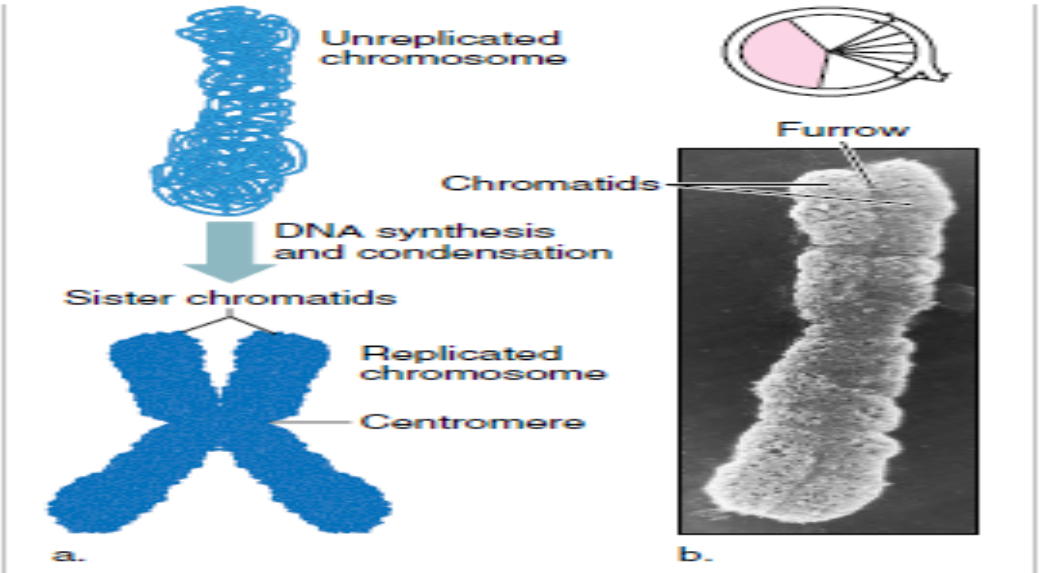
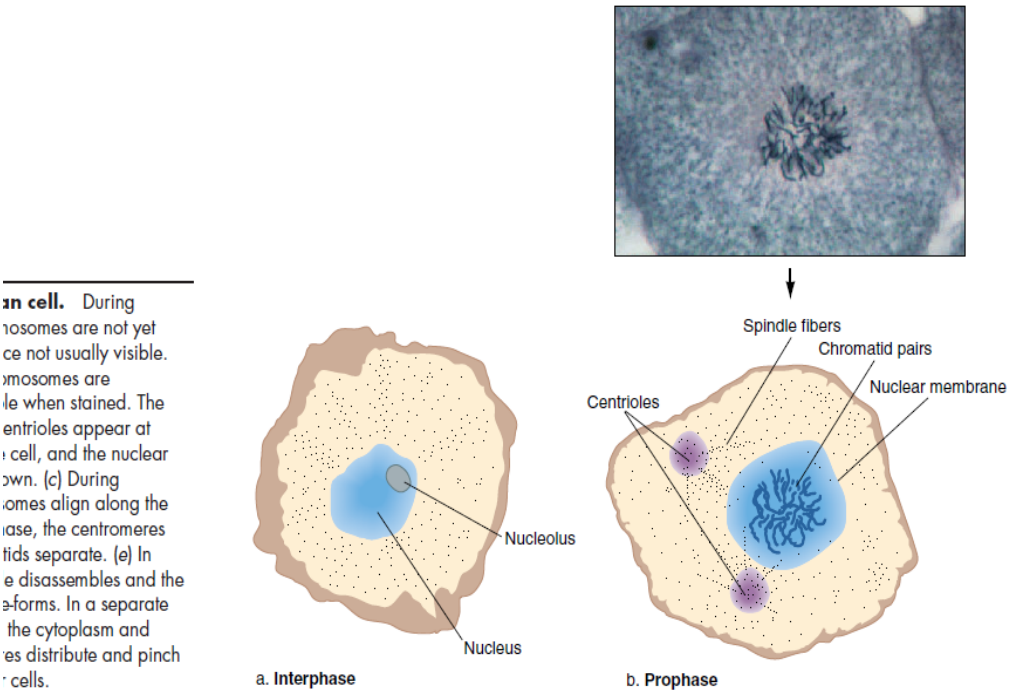


figure 2.15

Replicated and unreplicated chromosomes. Chromosomes are replicated during S phase, before mitosis begins. Two genetically identical chromatids

During **prophase,** the first stage of mitosis,: 1- **DNA coils tightly**, 2- **shortening and thickening the chromosomes,** which enables them to more easily separate (figure 2.16). 3- Microtubules assemble to form the spindle from tubulin building blocks in the cytoplasm. Toward the end of prophase(**Late prophase**), 4- the **nuclear membrane breaks down**. The nucleolus is no longer visible

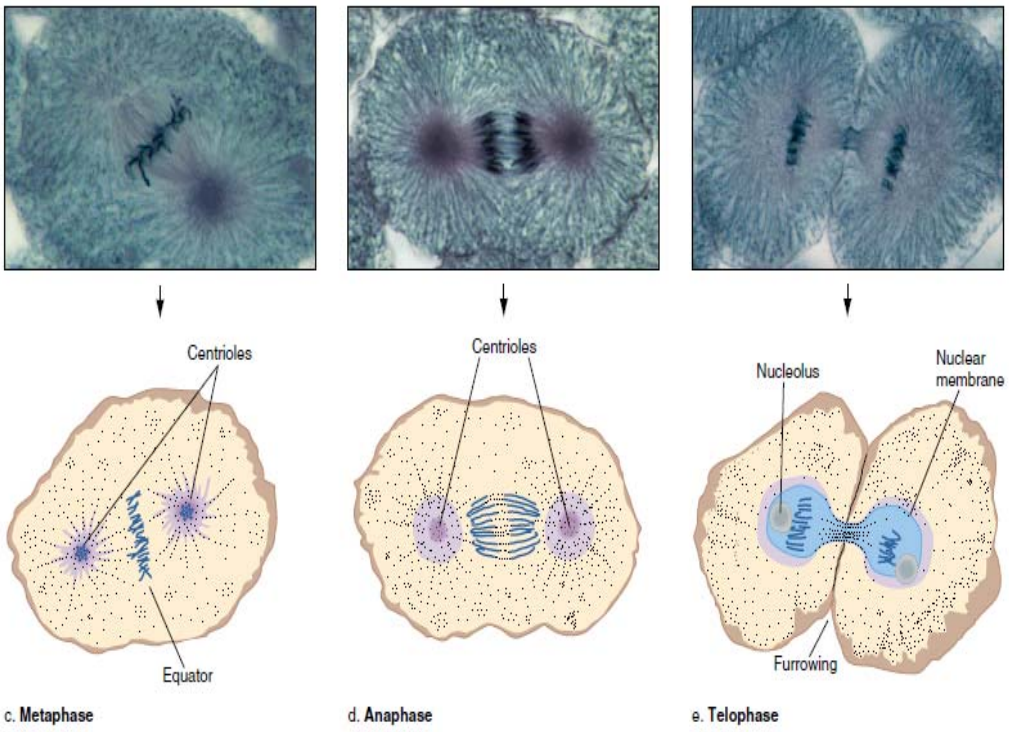


ın cell. During ıosomes are not yet ce not usually visible. ›mosomes are le when stained. The entrioles appear at cell, and the nuclear own. (c) During omes align along the ase, the centromeres tids separate. (e) In e disassembles and the e-forms. In a separate the cytoplasm and es distribute and pinch cells.

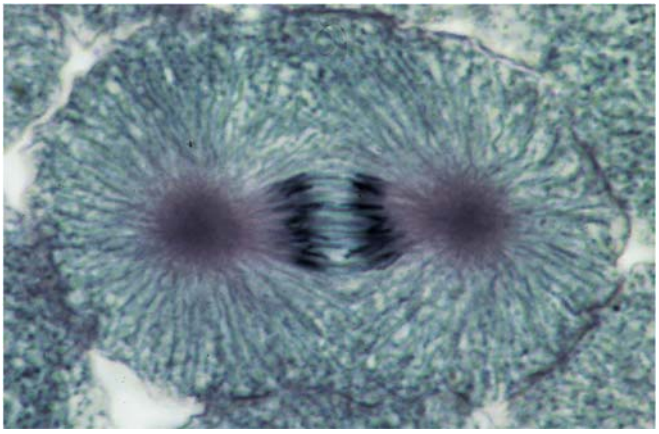
Metaphase follows prophase. Chromosomes attach to the spindle at their centromeres and align along the center of the cell, which is called the equator. When the centromeres part, each daughter cell receives one chromatid from each replicated chromosome. **Metaphase** chromosomes are under **great tension**, but they appear motionless because they are pulled with equal force on both sides, like a tug-of-war rope pulled taut.

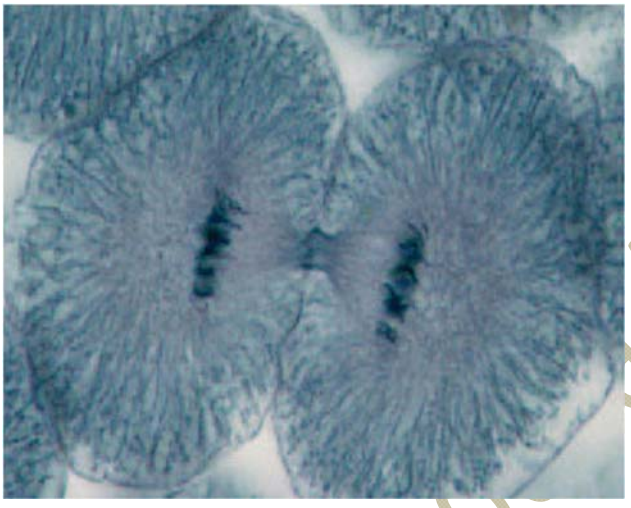
Next, during **anaphase,** the cell membrane indents at the center, where the metaphase chromosomes line up. A band of microfilaments forms on the inside face of the cell membrane, and it constricts the cell down the middle. Then the centromeres part, which **relieves the tension and releases one chromatid from each pair to move to opposite ends of the cell**—like a tug-of-war rope **breaking in the middle and the participants falling into two groups**. Microtubule movements stretch the dividing cell. During the very brief anaphase stage, **a cell temporarily contains twice the normal number of chromosomes** because each chromatid becomes an independently moving chromosome, but the cell has not yet physically divided.

In **telophase,** the final stage of mitosis, the cell looks like a dumbbell with a set of chromosomes at each end. The spindle falls apart, and nucleoli and the membranes around the nuclei re-form at each end of the elongated cell. Division of the genetic material is now complete. Next, during a process called **cytokinesis, organelles and macromolecules are distributed between the two daughter cells.** Finally, the microfilament band contracts like a drawstring, separating the newly formed cells.



c. **Metaphase** d. **Anaphase** e. **Telophase**





Control of the Cell Cycle

When and where a somatic cell divides is crucial to health, and regulation of mitosis is a daunting task. Quadrillions of mitoses occur in a lifetime, and these cell divisions do not occur at random. Too little mitosis, and an injury may go unrepaired; too much, and an abnormal growth forms.

Groups of interacting proteins function at times called **checkpoints** to ensure that chromosomes are faithfully replicated and apportioned into daughter cells (figure 2.17).

1- A "**DNA damage checkpoint**," for example, temporarily pauses the cell cycle while special proteins repair damaged DNA. The cell thus gains time to recover from an injury.

2-An "**apoptosis checkpoint**" turns on as mitosis begins. During this checkpoint, proteins called survivins override signals telling the cell to die, keeping it in mitosis rather than apoptosis.

3- Later during mitosis, the "**spindle assembly checkpoint**" oversees construction of the spindle and the binding of chromosomes to it. Cells obey an internal "clock" that tells them how many times to divide.

Mammalian cells grown (cultured) in a dish divide about **40 to 60 times**. **A connective tissue cell from a fetus,** for example, divides on average about 50 times. But a similar cell from an adult divides only **14 to 29 times**. The number of divisions left declines with age. How can a cell "know" how many divisions it has undergone and how many remain?

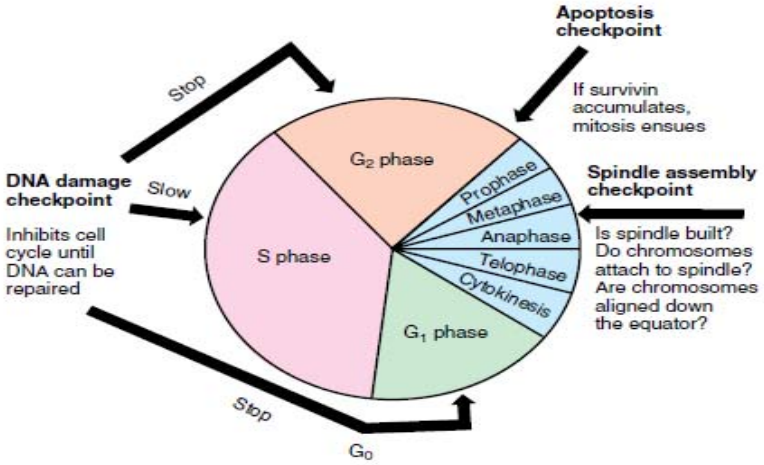


figure 2.17

Cell cycle checkpoints. Checkpoints ensure that events occur in the correct sequence. Many types of cancer result from deranged checkpoints.

The answer of how many chromosomes divided is the tips, called **telomeres** (figure 2.18). Telomeres function like a cellular fuse that burns down as pieces are lost from the very ends.

Telomeres have hundreds to thousands of repeats of a specific six-nucleotide DNA sequence.

At each mitosis, **the telomeres lose 50 to 200 of these nucleotides**, gradually shortening the chromosome like a fuse.

After about **50 divisions**, a critical **amount of telomere DNA is lost**, which signals mitosis to stop. The cell may **remain alive but not divide again**, or it may die. An enzyme called **telomerase** keeps chromosome tips long in **eggs** and **sperm**, in **cancer cells**, and in a **few types of normal cells** (such as bone marrow cells) that must supply many new cells. However, most cells do not produce telomerase, and their chromosomes gradually shrink. Telomerase includes a six-base RNA sequence that functions as a model, or template, used to add DNA nucleotides to telomeres.

Outside factors also affect a cell's mitotic clock. They are:

1- Crowding can slow or halt mitosis. Normal cells growing in culture stop dividing when they form a one-cell-thick layer lining the container. If the layer tears, the cells that border the tear grow and divide to fill in the gap, but stop dividing once it is filled. Perhaps a similar mechanism in the body limits mitosis.

2- Chemical signals control the cell cycle from outside as well as from inside the cell.
Hormones and growth factors are biochemical's from outside the cell that influence mitotic rate. A hormone is a substance synthesized in a gland and transported in the bloodstream to another part of the body, where it exerts a specific effect.

Hormones secreted in the brain, for example, signal the cells lining a woman's uterus to build up each month by mitosis in preparation for possible pregnancy. Growth factors act more locally. Epidermal growth factor, for example, stimulates cell division beneath a scab.

3- Two types of proteins, **cyclins** and **kinases**, interact inside cells to activate the genes whose products carry out mitosis. The two types of proteins form pairs. Levels of cyclins fluctuate regularly throughout the cell cycle, while kinase levels stay the same.

A certain number of cyclin-kinase pairs turn on the genes that trigger mitosis. Then, as mitosis begins, enzymes degrade cyclin. The cycle starts again as cyclin begins to build up during the next interphase.

Apoptosis

Apoptosis rapidly and neatly dismantles a cell into neat, **membrane-bounded pieces** that a phagocyte (a cell that engulfs and destroys another) can mop up. It is a little like taking the contents of a messy room and packaging them into garbage bags—then disposing of it all.

Like mitosis, apoptosis is a continuous process that occurs in a series of steps. It begins when a "death receptor" on the doomed cell's membrane receives a signal to die. Within seconds, enzymes called **caspases** **are activated the cell, stimulating each other and snipping apart various cell components.**

These **killer enzymes** take several actions at once, represented as following:

1• they destroy the cytoskeletal threads that support the nucleus so that it collapses, causing the genetic material within to condense.
2 • demolish the enzymes that replicate and repair DNA.
3 • activate enzymes that chew DNA up into similarly sized small pieces.
4 • tear apart the rest of the cytoskeleton.
5 • destroy the cell's ability to adhere to other cells.
6 • send a certain phospholipid from the cell membrane's inner face to its outer surface, where it attracts phagocytes.

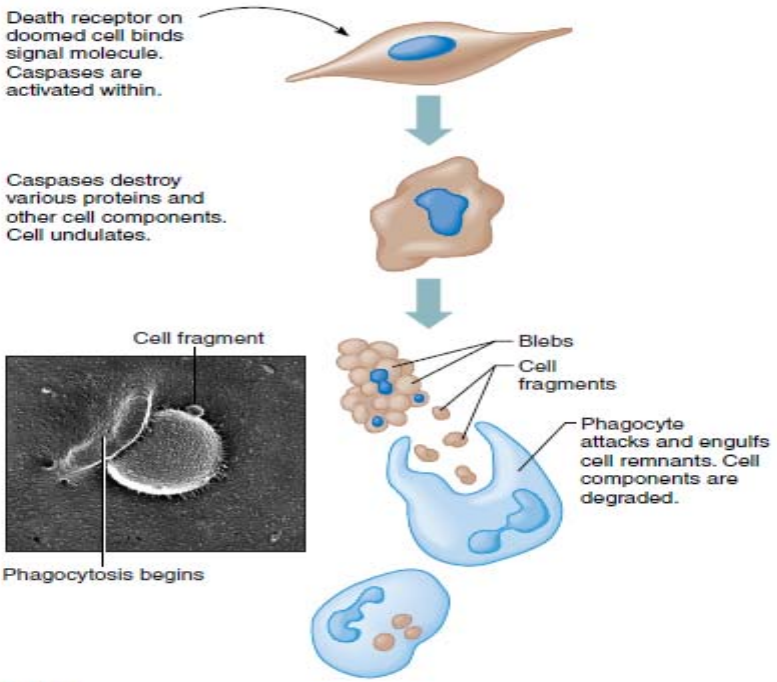


figure 2.19

Death of a cell. A cell undergoing apoptosis loses its characteristic shape, forms blebs, and finally falls apart. Caspases destroy the cell's insides. Phagocytes digest the remains.

Chromosome

Portrait of a Chromosome

Chromosomes are the bearers of genes. A chromosome includes DNA and proteins that enable it to be replicated; information in the form of protein-encoding genes; and DNA sequences that provide stability. The 24 chromosome types in a human cell are distinguished by size, shape, centromere position, and staining patterns. Chromosome charts record health information useful to individuals and families, and can provide clues to exposure to environmental pollution. Comparing chromosomes can reveal evolutionary relationships among species.

Visualizing Chromosomes

Chromosomes can be seen in any cell that has a nucleus. Three techniques are used to obtain fetal cells and observe their chromosomes. Techniques used to visualize chromosomes have evolved from crude stains to highly specific labeled DNA probes.

Abnormal Chromosome Number

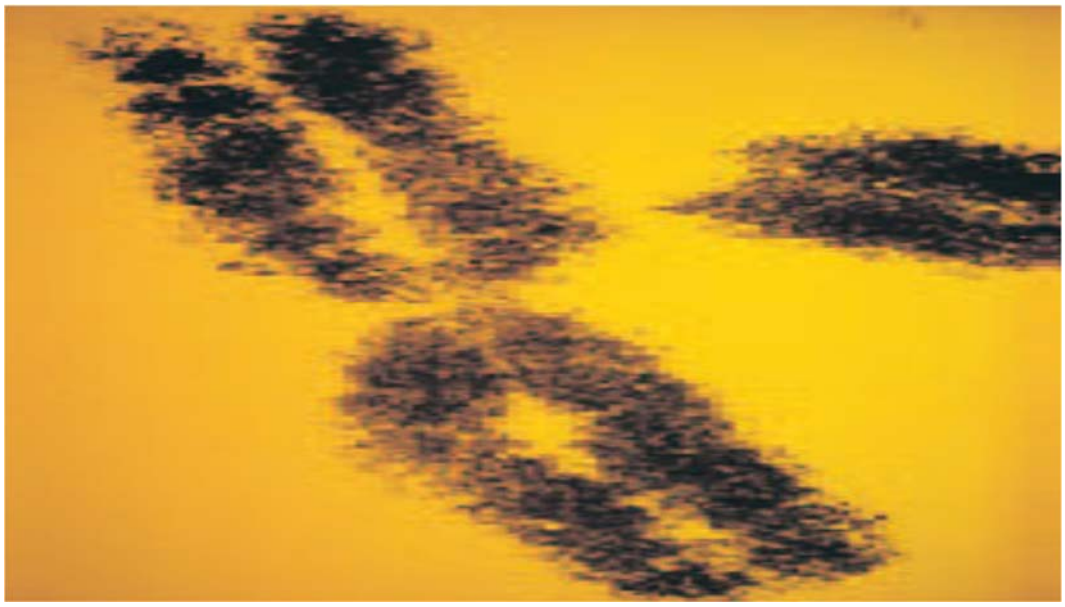
Genetic health is a matter of balance. Extra sets of chromosomes, or missing or extra individual chromosomes, can devastate health. In general, additional genetic material is more tolerable than a deficit. Many embryos with
Abnormalities in chromosome number do not develop for very long.

Abnormal Chromosome Structure

Disruption in the precise sequence of events that occur during meiosis can result in chromosomes that have missing or extra genetic material or that exchange parts. An inverted gene sequence causes loops to form as
Chromosomes pair in meiosis, possibly leading to deletions and duplications of genetic material.

Portrait of a Chromosome

A chromosome is more than a many-million base- long molecule of DNA. It is a structure that consists primarily of DNA and proteins that is duplicated and transmitted, via mitosis or meiosis, to the next cell generation.
Cytogeneticists have long described and distinguished the chromosome types by large-scale differences, such as size and shape. In addition, stains and dyes have traditionally been used to contrast dark **heterochromatin,** which is mostly repetitive DNA sequences, with lighter **euchromatin,** which harbors more protein-encoding genes. Today, geneticists are superimposing information from the human genome sequence onto the existing views of chromosomes.



Telomeres and Centromeres Are Essential

A chromosome must include those structures that enable it to replicate and remain intact—everything else is essentially informational cargo (the protein-encoding genes) and DNA sequences that impart stability to the overall structure. The absolutely essential parts of a chromosome, in terms of navigating cell division, are:

- telomeres
- origin of replication sites, where replication forks begin to form
- the centromere

Telomeres are chromosome tips, each consisting of many repeats of the sequence TTAGGG that are whittled down with each mitotic cell division. The **centromere** is the largest construction of a chromosome, and is where spindle fibers attach. A chromosome without a centromere is no longer a chromosome—it vanishes from the cell as soon as division begins, because it cannot attach to the spindle.

In humans, many of the hundreds of thousands of DNA bases that form the centromere are repeats of a 171-base sequence called an **alpha satellite.** The sequence of the alpha satellites might not be what is important in establishing the centromere, but rather the number of repeats is important.This idea is based on the observation that other species have alpha satellites of about the same repeat length, but with different sequences. The approximate size across

species of about 170 base pairs just about equals the size of a nucleosome , the unit of chromatin that consists of DNA wrapped around octets of histone proteins. Perhaps it is the binding of histones to DNA in a certain pattern that attracts spindle fibers to the centromere.In addition to alpha satellites, which are DNA, centromeres also include **centromere associated proteins.** Some of these are synthesized only when mitosis is imminent. At this time, certain centromere-associated proteins form a structure called a **kinetochore,** which emanates outward from the centromere and contacts the spindle fibers.The kinetochore appears at prophase and vanishes during telophase. Another type of centromere-associated protein, the cohesins, are part of the centromere during interphase. Centromeres are replicated toward the end of S phase, and a protein that may control this process is called centromere protein A, or CENP-A. It resembles a histone,but unlike them, CENP-A remains associated with a chromosome as it is replicated, Between the chromosome's arms where protein-encoding genes lie amidst stretches of repeats and the telomeres are regions appropriately called Looked at from another perspective, these areas extend from 8,000 .**subtelomeres** to 300,000 bases inward toward the centromere from the telomeres. Areas of 50 to 250 bases, right next to the telomeres, indeed consist of 6- base repeats, many of which are very similar to TTAGGG. Then, moving inward from the 6-base buffer zone are many shorter repeats, each present in a few copies. Their function isn't known. Finally the sequence diversifies and protein encoding genes appear.

sub telomere Telomere

centromer

ACACACTTTCGCGAATAAT …
TTAAGGTTAGGGTTAGGGTAAGGG … TTAGGGTTAGGG…
(Telomere) (6-base repeats similar to telomeres)
(Short repeats)

Karyotypes Are Chromosome Charts

Even in this age of genomics, the standard chromosome chart, or **karyotype,** remains a major clinical genetic tool. A karyotype presents chromosomes by size and b
y physical landmarks that appear during mitotic metaphase, when DNA coils especially tightly. The 24 human chromosome types are numbered from largest to smallest—1 to 22—although chromosome 21 is actually the smallest. The other two chromosomes are the X and the Y. Early attempts to sizeorder chromosomes resulted in generalized groupings because many of the chromosomes are of similar size. Centromere position is one distinguishing feature of chromosomes. A chromosome is **metacentric** if the centromere divides it into two arms of approximately equal length. It is **submetacentric** if the centromere establishes one long arm and one short arm, and **acrocentric** if it pinches off only a small amount of material toward one end Some species have **telocentric** chromosomes that have only one arm, but humans do not.

The long arm of a chromosome is designated *q,* and the short arm *p,* where *p* stands for "petite." Five human chromosomes (13, 14, 15, 21, and 22) are distinguished further by bloblike ends, called satellites, that extend from a thinner, stalklike bridge from the rest of the chromosome. (This is a different use of the word "satellite" from the centromeric repeats.) The stalklike regions are areas that do not bind stains well. The stalks carry many repeats of genes coding for ribosomal RNA and ribosoma l proteins, areas called nucleolar organizing regions.

They coalesce to form the nucleolus, a structure in the nucleus where ribosomal building blocks are produced
and assembled.

- Karyotypes are useful at several levels. When a baby is born with the distinctive facial characteristics of Down syndrome, a karyotype confirms the clinical diagnosis.
- Within families, karyotypes are used to identify relatives with a particular chromosomal aberration that can affect health. For example, in one family, several adult members died from a rare form of kidney cancer. Because the cancer was so unusual, researchers karyotyped the affected individuals, and found that they all had an exchange called a **translocation,** between chromosome 3 and 8.When karyotypes showed that two young family members had the translocation,

physicians examined and monitored their kidneys, detecting cancer very early and treating it successfully.

- Karyotypes of individuals from different populations can reveal the effects of environmental toxins, if abnormalities appear only in a group exposed to a particular contaminant. Because chemicals and radiation that can cause cancer and birth defects often also break chromosomes into fragments or rings, detecting this genetic damage can alert physicians to the possibility that certain cancers will appear in the population.
- Karyotypes compared between species can clarify evolutionary relationships. The more recent the divergence of two species from a common ancestor, the more closely related we presume they are, and the more alike their chromosome banding patterns should be. Our closest relative, according to karyotypes, is the pygmy chimpanzee, also known as the bonobo. The human karyotype is also remarkably similar to that of the domestic cat, and somewhat less similar to the karyotypes of mice, pigs, and cows.

:Visualizing Chromosomes

Extra or missing chromosomes are easily detected by counting a number other than 46.

Identifying chromosome rearrangements,such as an inverted sequence or two chromosomes exchanging parts, requires a way to distinguish among the chromosomes. A combination of stains and DNA probes applied chromosomes allows this. A **DNA probe** is a labeled piece of DNA that binds to its complementary sequence on a particular chromosome.

:Obtaining Cells for Chromosome Study

Any cell other than a mature red blood cell (which lacks a nucleus) can be used to examine chromosomes, but some cells are easier to obtain and culture than others. For adults, white blood cells separated from a blood sample or skin

like cells collected from the inside of the cheek are usually the basis of a chromosome test.

A person might require such a test if he or she has a family history of a chromosomal abnormality or seeks medical help because of infertility. For blood-borne cancers (leukemias and lymphomas), cytogeneticists examine chromosomes from bone marrow cells, which give rise to blood cells. DNA microarray tests are replacing karyotypes in matching cancers to the most effective chemotherapies. Chromosome tests are most commonly performed on fetal cells. Couples who receive a prenatal diagnosis of a chromosome abnormality can arrange for treatment of the newborn, if this is possible; learn more about the condition and perhaps contact support groups and plan care; or terminate the pregnancy. These choices are highly individual and personal and are best made after a genetic counselor or physician provides information on the particular medical condition and available treatment options.

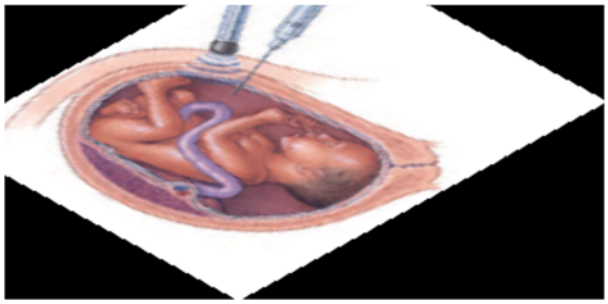
:Amniocentesis

The first successful fetal karyotype was constructed in 1966 by a technique called **amniocentesis.** A doctor removes a small sample of fetal cells and fluids from the uterus with a needle passed through the woman's abdominal wall. The cells are cultured for a week to 10 days, and typically 20 cells are karyotyped. Culturing and staining chromosomes takes a week, but DNA probes can detect chromosomes in a day or two. The sampled amniotic fluid is also examined for deficient, excess, or abnormal biochemical's that could indicate particular inborn errors of metabolism. Amniocentesis takes only a minute or two and guide the needle so it causes only a feeling of pressure. Ultrasound is used to doesn't harm the fetus.

Amniocentesis can detect approximately 400 of the more than 5,000 known chromosomal and biochemical problems. It is usually performed at 15 or 16 weeks gestation, when the fetus isn't yet very large but **240** Part Three DNA and Chromosomes amniotic fluid is plentiful. Amniocentesis can be carried out any time after this point.

Doctors recommend amniocentesis if the risk that the fetus has a detectable condition exceeds the risk that the procedure will cause a miscarriage, which is about 1 in 350. The most common candidate for the test is a pregnant woman over age 35. This "advanced maternal age" statistically increases the risk that the fetus will have an extra or missing chromosome. Amniocentesis is also warranted if a couple has had several spontaneous abortions or children with abnormality. Another reason to seek birth defects or a known chromosome

amniocentesis is if a blood test on the pregnant woman reveals low levels of a fetal liver protein called alpha fetoprotein (AFP) and high levels of human chorionic gonadotropin (hCG). These signs may indicate a fetus with a small liver, which may reflect a condition caused by an extra chromosome, such as Down syndrome. These tests, called **maternal serum marker tests,** may include a third or fourth biochemical too. They are useful for pregnant women younger than 35 who would not routinely undergo age related amniocentesis. Doctors use maternal serum marker tests to screen their patients to identify those who may require genetic counseling and perhaps further, more invasive testing.

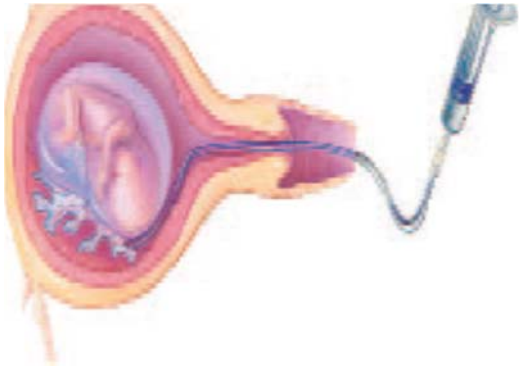


:Chorionic Villus Sampling

During the 10th week of pregnancy, **chorionic villus sampling** (CVS) obtains cells from the chorionic villi, the structures that develop into the placenta . A karyotype is prepared directly from the collected cells, rather than first culturing them, as in amniocentesis.Results are ready in days.Because chorionic villus cells descend from the fertilized ovum, their chromosomes embryo and fetus. Occasionally, a should be identical to those of the chromosomal aberration occurs only in an embryo, or only in chorionic villi. This results in a situation called **chromosomal mosaicism**— that is, the karyotype of a villus cell differs from that of an embryo cell. Chromosomal mosaicism has great clinical consequences. If CVS indicates an aberration in villus cells

that is not also in the fetus, then a couple may elect to terminate the pregnancy based on misleading information—that is, the fetus is actually chromosomally normal, although CVS indicates otherwise. In the opposite situation, the results of the CVS may be normal, but the fetus has a chromosomal problem— leading to an unpleasant surprise at birth or later.

CVS is slightly less accurate than amniocentesis and in about 1 in 1,000 to 3,000 procedures, causes a fatal limb defect. Also, the sampling procedure in CVS does not include amniotic fluid, so the biochemical tests that amniocentesis allows are not possible. Couples expecting a child are sometimes asked to choose between amniocentesis and CVS. The advantage of CVS is earlier results, but it is associated with a greater risk of spontaneous abortion. Although CVS is slightly more invasive and dangerous to the fetus, its greater risk also most spontaneous reflects the fact that CVS is done earlier in pregnancy. Since abortions occur early in pregnancy, more will follow CVS than amniocentesis. The spontaneous abortion rate after the 12th week of pregnancy is about 5 poses is 0.8 percent. In contrast, the percent, and the additional risk that CVS spontaneous abortion rate after the 14th week is 3.2 percent, and amniocentesis adds 0.3 percent to the risk.

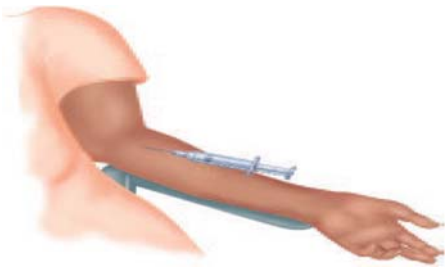


: Fetal Cell Sorting

Fetal cell sorting, a new technique that separates fetal cells from the woman's bloodstream, is safer than amniocentesis and CVS but is still experimental in the United States. The technique traces its rootsto 1957, when a pregnant woman died when cells from a very early embryo lodged in a major blood vessel in her lung, blocking blood flow. The fetal cells were detectable because they were from a male, and were distinguished by the telltale Y chromosome. This meant that fetal cells could enter a woman's circulation. By studying the blood of other pregnant women, researchers found that fetal cells enter the maternal circulation in up to 70 percent of pregnancies. Cells from female embryos, however, cannot be distinguished from the cells of the pregnant woman on the basis of sex chromosome analysis. But fetal cells from either sex

can be distinguished from maternal cells using a device called a fluorescence-activated cell sorter. It separates fetal cells from maternal blood by identifying surface characteristics that differ from those on the woman's cells. The fetal cells are then karyotyped and fetal DNA extracted and amplified for specific gene tests. Rarely, other techniques are used to sample specific fetal tissues, such as blood, skin, liver, or muscle. These biopsy procedures are usually done by using ultrasound to guide a hollow needle through the woman's abdominal wall to reach the fetus.

Such an invasive test is performed if the family has a disease affecting the particular tissue, and a DNA-based test is not available. Instead of examining chromosomes, ultrasound can be used to identify physical features that are part of chromosomal syndromes. For example, ultrasound can detect thickened neck skin and absent or underdeveloped nasal bones that are characteristic of Down syndrome and were part of the initial description in 1866. In one study, 75percent of fetuses with Down syndrome had these characteristics, compared to 0.5 percent of fetuses who did not have Down syndrome. Ultrasound scanning is therefore somewhat imprecise, but it is safer than obtaining chromosomes with amniocentesis or CVS. Combined with maternal serum marker testing, physicians to identify pregnancies in need of ultrasound scans may enable further testing.



:Preparing Cells for Chromosome Observation

Microscopists have tried to describe and display human chromosomes since the late 19th century (figure 12.8 and the Technology Timeline). Then, the prevailing view held that humans had an XO sex determination system, with females system, with females having an extra chromosome (XX).Estimates of the human chromosome number ranged from 30 to 80. In 1923, Theophilus Painter published sketches of human chromosomes from three patients at a

Texas state mental hospital. The patients had been castrated in an attempt to control their abusive behavior, and Painter was able to examine the tissue. He could not at first tell whether the cells had 46 or 48 chromosomes, but finally decided that he saw 48. Painter also showed that both sexes have the same chromosome number. The difficulty in distinguishing between 46 or 48 chromosomes was physical—preparing a cell in which chromosomes do not overlap is challenging. To easily count the chromosomes, scientists had to find a them when they are the most condensed— during cell division— way to capture and also spread them apart. Since the 1950s, cytogeneticists have used colchicines, an extract of the chrysanthemum plant, to arrest cells during division.

:Swelling, Squashing, and Untangling

Ten years later, cell biologists Albert Levan and Joe-Hin Tjio found that when they drew cell-rich fluid into a pipette and dropped it onto a microscope slide prepared with stain, the cells burst open and freed the mass of chromosomes.

Adding a glass coverslip spread the chromosomes enough that they could be counted. Another researcher, a former student of Painter named John Biesele, suggested that Levan and Tjio use cells from tissue culture, and by 1956, they finally settled the matter of how many chromosomes occupy a diploid human cell—46. In the same year, J. L. Hamerton and C. E. Ford identified the expected 23 chromosomes in human gametes. In 1960 came another advance in visualizing chromosomes— through the use of a kidney bean extract called phytohemagglutinin. Originally used to clump red blood cells to separate them from white blood cells, the substance also could stimulate division of white

blood cells. Until recently, a karyotype was constructed using a microscope to locate a cell in which the chromosomes were not touching, photographing the cell, developing a print, and cutting out the individual chromosomes and arranging them into a size-order chart. A computerized approach has largely replaced the cut-and-paste method. The device scans ruptured cells in a drop of stain and selects one in which the chromosomes are the most visible and well spread. Then image analysis software recognizes the band patterns of each stained chromosome pair, sorts the structures into a size-order chart, and prints the karyotype—in minutes. If the software recognizes an abnormal band pattern, a database pulls out identical or similar karyotypes from other patients, providing clinical information on the anomaly. Genome sequence information is also scanned. However, the expert eyes of a skilled technician are still needed to detect subtle abnormalities in chromosome structure.

:Staining

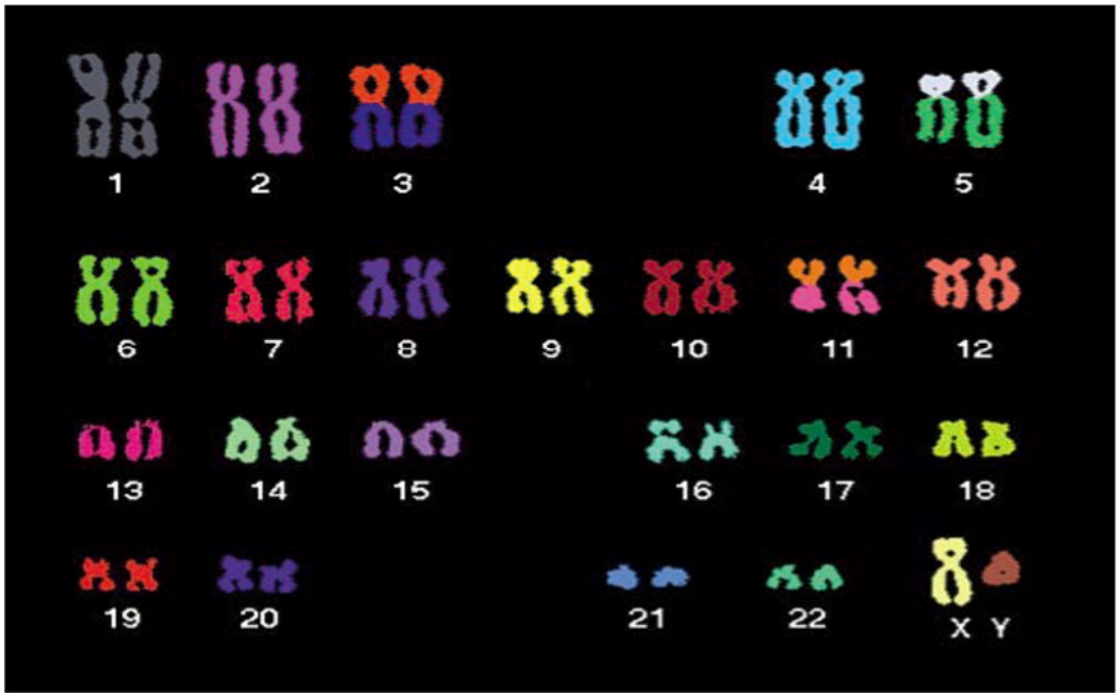
In the earliest karyotypes, dyes stained the chromosomes a uniform color. Chromosomes were grouped into size classes, designated A through G, in decreasing size order. In 1959, scientists described the first chromosomal Abnormalities—Down syndrome (an extra chromosome 21), **Turner syndrome** (also called XO syndrome, a female with only one X chromosome), and **Klinefelter syndrome** (also called XXY syndrome, a male with an extra X chromosome). Before this, women with Turner syndrome were thought to be genetic males because they lack Barr bodies, while men with Klinefelter syndrome were thought to be genetic females because their cells have Barr bodies. The ability to visualize and distinguish the sex chromosomes, even crudely, allowed researchers to determine the causes of these conditions. The first stains that were applied to chromosomes could highlight large deletions and duplications, but more often than not, researchers only vaguely understood the nature of a chromosomal syndrome. In 1967, a mentally retarded child with material missing from chromosome 4 would have been diagnosed as having a “B-group chromosome” disorder. Today the exact genes that are missing can be identified. Describing smaller-scale chromosomal aberrations required better ways to distinguish among the chromosomes. In the1970s, Swedish scientists developed more specific chromosome stains that create banding patterns unique to each chromosome. Combining stains reveals even more bands, making it easier to distinguish chromosomes. Stains are specific for AT-rich or GC-rich stretches of DNA, or for heterochromatin, which stains darkly at the centromere

and telomeres. The ability to detect missing, extra, inverted, or misplaced bands allowed researchers to link many more syndromes with specific chromosome aberrations. In the late 1970s, Jorge Yunis at the University of Minnesota improved chromosome staining further by developing a way to synchronize white blood cells in culture, arresting them in early mitosis. His approach, called high-resolution chromosome banding, revealed many more bands. Today, **fluorescence *in situ* hybridization,** or FISH, is eclipsing even high-resolution chromosome banding, enabling cytogeneticists to focus on individual genes.

:FISHing

One drawback of conventional chromosome stains is that they are not specific to particular chromosomes. Rather, they generate different banding patterns among the 24 human chromosome types. FISH is much more specific because it uses DNA probes that are complementary to DNA sequences found only on one chromosome type. The probes are attached to molecules that fluoresce when illuminated, producing a flash of color precisely where the probe binds to a chromosome in a patient's sample. The technique can reveal a particular extra chromosome in a day or two. FISH is based on a technique, developed in 1970, called *in situ* hybridization, which originally used radioactive labels rather than fluorescent ones. *In situ* hybridization took weeks to work, because it relied on exposing photographic film to reveal where DNA probes bound among the chromosomes. The danger of working with radioactivity, and the crudeness of the results, eventually prompted researchers to seek alternative ways of highlighting bound DNA probes. FISH is used to identify specific chromosomes and to "paint" entire karyotypes, providing a different color for each chromosome. Many laboratories that perform amniocentesis or chorionic villous sampling use FISH probes specific to chromosomes 13, 18, 21, and the sex chromosomes to quickly identify the most common chromosome abnormalities. shows FISH analysis that easily identifies the extra chromosome 21 in cells from a fetus with Down syndrome. In an application of FISH called spectral karyotyping, each chromosome is probed molecules. A computer integrates the images with several different fluorescent and creates a false color for each chromosome. A new approach to prenatal chromosome analysis called quantitative PCR amplifies certain repeated

sequences on chromosomes 13, 18, 21, X, and Y. The technique distinguishes paternally derived from maternally derived repeats on each homolog for these five chromosomes. An abnormal ratio of maternal to paternal repeats indicates a numerical problem, such as two copies of one parent's chromosome 21. Combined with the one chromosome 21 from the other parent, this situation would produce a fertilized ovum with three copies of chromosome 21, which causes Down syndrome. Quantitative PCR is less accurate than culturing cells or FISH to examine chromosomes, but gives results in only hours, which can greatly reduce parental anxiety.



:Chromosomal Shorthand

Geneticists abbreviate the pertinent information in a karyotype. They list chromosome number first, then sex chromosome constitution, then abnormal autosomes. Symbols describe the type of aberration, such as deletion or translocation. Numbers are listed that correspond to specific bands.

A normal male is 46, XY; a normal female is 46, XX. Geneticists use this notation to describe gene locations. For example, the □- globins subunit of hemoglobin is located at 11p15.5. Table 12.3 gives some examples of chromosomal shorthand.

Chromosome information is displayed in an **ideogram,** which is a graphical representation of a karyotype (figure 12.10). Bands appear as stripes, and they are divided into numbered major regions and sub regions. Specific gene loci known from mapping data are listed on the right-hand side with information from the human genome sequence.
Ideograms are becoming so crowded with notations indicating specific genes that they may soon become obsolete.

Ideogram	**Means**
46,XY	Normal male
46,XX	Normal female
45,X	Turner syndrome (female)
47,XXY	Klinefelter syndrome (male)
47,XYY	Jacobs syndrome (male)
46,XY del (7*q*)	A male missing part of the long arm of chromosome 7
47,XX,+21	A female with trisomy 21 Down syndrome
46,XY t (7;9)(*p*21.1; *q*34.1)	A male with a translocation between the short arm of chromosome 7 at band 21.1 and the long arm of chromosome 9 at band 34.1

1923 Theophilus Painter's chromosome sketches are published, human chromosome number thought to be 48

1951 Method to detangle chromosomes discovered by accident

1953 Albert Levan and Joe-Hin Tjio develop "squash and stain" technique for chromosome preparation

1956 Using tissue culture cells, Levan, Tjio, and Biesele determine chromosome number to be 46

1956 J. L.Hamerton and C. E. Ford identify 23 chromosomes in human gametes

1959 First chromosome abnormalities identified

1960 Phytohemagglutinin added to chromosome preparation protocol to separate and stimulate division in white blood cells

1970s Several chromosome stains implemented to improve resolution of karyotypes

1970s FISH developed

1990s Spectral karyotyping combines FISH probes to distinguish each chromosome

.

Subtelomeres. The repetitive sequence of a telomere gradually diversifies toward the centromere. A subtelomere consists of from 8,000 to 300,000 bases from the telomere inward on a chromosome arm.

KEYCONCEPTS

Chromosomes consist of DNA, RNA, histones, and other proteins. A chromosome minimally includes telomeres, origins of replication, and centromeres, which enable the entire structure to replicate.

A centromere consists of alpha satellite repeats and associated proteins, some of which form the kinetochore, to whichspindle fibers attach.

Centromere protein A enables the centromere to replicate.

Subtelomeres contain telomerelike repeats, but also include proteinencoding multigene families.

•

Chromosomes are distinguishable by size, centromere location, the presence of satellites, and differential staining of heterochromatin and euchromatin.

Karyotypes are size-order charts of chromosomes that provide information that is valuable at

The composition of centromeres is still not completely understood, because the techniques used to sequence the human genome, described in chapter 22, do not work on highly repeated sequences. It is known, though, that centromeres lie within vast stretches of heterochromatin, and, gradually, the terrain of the DNA comes to contain protein-encoding sequences with distance from the centromere. Outward from the centromere lie the arms of the chromosomes. Here, gene density varies greatly among the chromosome types, a finding discovered as research groups began to publish whole-chromosome sequences in 1998. Chromosome 21 is described as a “desert,” harboring a million-base stretch with no protein-encoding genes at all. Chromosome 22, in contrast, is a gene jungle.

These two tiniest chromosomes are at opposite ends of the gene-density spectrum. They are remarkably similar in size, but chromosome 22 contains 545 genes to chromosome 21’s 225.

Cytogenetics

Chromosome Six Lecture

Portrait of a Chromosome:

Chromosomes are the bearers of genes. A chromosome includes DNA and proteins that enable it to be replicated; information in the form of protein-encoding genes; and DNA sequences that provide stability. The 24 chromosome types in a human cell are **distinguished** by size, shape, centromere position, and staining patterns. Chromosome charts record health information useful to individuals and families, and can provide clues to exposure to environmental pollution. Comparing chromosomes can reveal evolutionary relationships among species.

Visualizing Chromosomes:

Chromosomes can be seen in any cell that has a nucleus. **Three techniques** are used to **obtain fetal cells** and observe their chromosomes. Techniques used to visualize chromosomes have evolved from **crude stains** to **highly specific labeled DNA probes.**

Abnormal Chromosome Number:

Genetic health is a matter of balance. **Extra sets of chromosomes, or missing or extra individual chromosomes,** can devastate health. In general, additional genetic material is more tolerable than a deficit. Many embryos with Abnormalities in chromosome number do not develop for very long.

Abnormal Chromosome Structure:

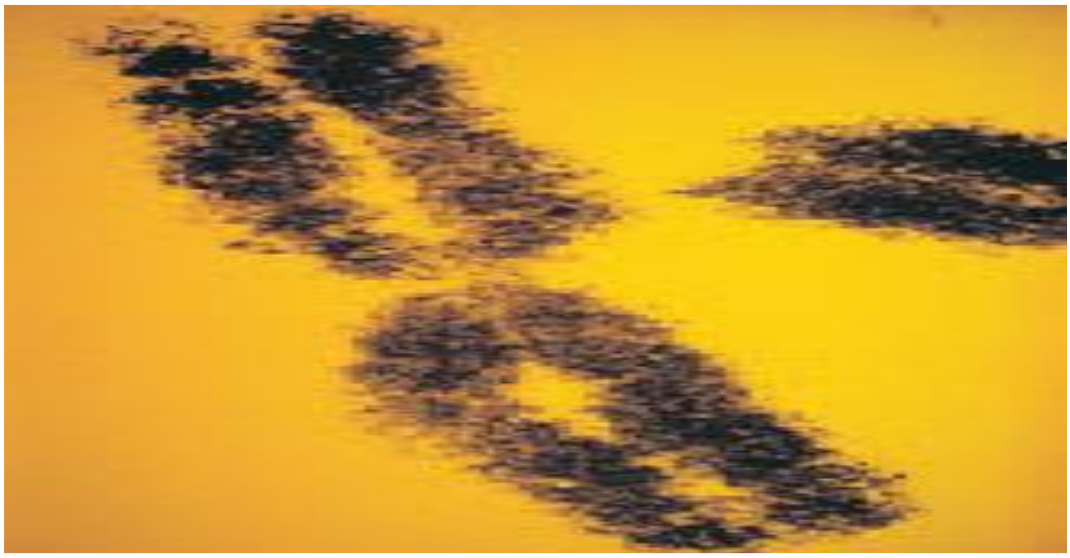
Disruption in the precise sequence of events that occur during meiosis can result in **chromosomes that have missing or extra genetic material** or that **exchange parts**. An **inverted gene sequence** causes loops to form as Chromosomes pair in meiosis, possibly leading to **deletions and duplications of genetic material.**

Portrait of a Chromosome:

A chromosome is more than a many-million base- long molecule of DNA. It is a **structure** that consists primarily of **DNA and proteins** that is duplicated and transmitted, via mitosis or meiosis, to the next cell generation.

Cytogeneticists distinguished the chromosome types by large-scale differences, such as **size** and **shape**. In addition, **stains and dyes** have traditionally been used to contrast dark **heterochromatin,** which is mostly repetitive DNA sequences, with lighter **euchromatin,** which harbors **more protein-encoding genes**. Today,

geneticists are superimposing information from the human genome sequence onto the existing views of chromosomes.



Essential parts of chromosome

Telomeres and Centromeres

A chromosome **must include** those structures that enable it to replicate and remain intact—everything else is essentially informational cargo (the protein-encoding genes) and DNA sequences that impart stability to the overall structure. The absolutely essential parts of a chromosome, in terms of navigating cell division, are:

- Telomeres
- Origin of replication sites, where replication forks begin to form
- The centromere

Telomeres are chromosome tips, each consisting of many repeats of the sequence **TTAGGG** that are whittled down with each mitotic cell division.

The **centromere** is the **largest construction of a chromosome**, and is where spindle fibers attach. A chromosome without a centromere is no longer a chromosome—it vanishes from the cell as soon as division begins, because it cannot attach to the spindle. The structure of centromere included:

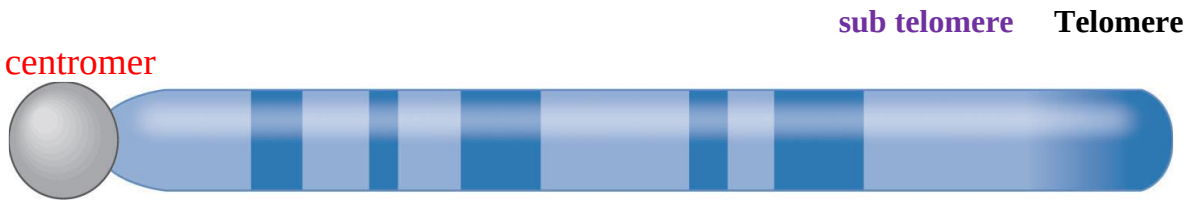
1- **Alpha satellite** In humans, many of the **hundreds of thousands of DNA bases that form the centromere** are repeats of a **171-base sequence** called an**.** The sequence of the alpha satellites might not be what is important in establishing the centromere, but rather **the number of repeats is important**. This idea is based on the observation that other species have alpha satellites of about the same repeat

length, but with different sequences. The approximate size across species of about 170 base pairs just about equals the size of a **nucleosome** , the unit of chromatin that **consists of DNA wrapped around octets of histone proteins**. Perhaps it is the binding of histones to DNA in a certain pattern that attracts spindle fibers to the centromere.

2- Centromere associated proteins, Some of these are synthesized only when mitosis is imminent (about to happen), form a structure called a **kinetochore,** which emanates outward from the centromere and contacts the spindle fibers. The kinetochore appears at **prophase** and vanishes during **telophase**.

Another type of centromere-associated protein, the **cohesins**, is part of the centromere during **interphase**.

Between the chromosome's arms where protein-encoding genes lie amidst stretches of repeats and the telomeres are regions appropriately called **Subtelomeres**. Looked at from another perspective, these areas extend **from 8,000 to 300,000 bases** inward toward the centromere from the telomeres. Areas of 50 to 250 bases, right next to the telomeres, indeed consist of 6- base repeats, many of which are very similar to **TTAGGG**. Then, moving inward from the 6-base buffer zone are many shorter repeats, each present in a few copies. Their function isn't known. Finally the sequence diversifies and protein encoding genes appear.



ACACACTTTCGCGAATAAT ... TTAAGGTTAGGGTTAGGGTAAGGG ... TTAGGGTTAGGG...

(Short repeats) **(6-base repeats similar to telomeres)** **(Telomere)**

Karyotypes Are Chromosome Charts

The standard chromosome chart, or **karyotype,** remains a major clinical genetic tool. A karyotype presents chromosomes by **size** and by **physical landmarks** that **appear during mitotic metaphase**, when DNA coils especially tightly. The 24 human chromosome types are numbered from largest to smallest—1 to 22—

although chromosome 21 is actually the smallest. The other two chromosomes are the X and the Y.

Early attempts to size order chromosomes resulted in generalized groupings because many of the chromosomes are of similar size.

Centromere position is one distinguishing feature of chromosomes. A chromosome is **metacentric** if the centromere divides it into two arms of approximately equal length. It is **submetacentric** if the centromere establishes one long arm and one short arm, and **acrocentric** if it pinches off only a small amount of material toward one end Some species have **telocentric** chromosomes that have only one arm, but humans do not.

The long arm of a chromosome is designated *q*, and the short arm ***p***, where *p* stands for "petite." Five human chromosomes (13, 14, 15, 21, and 22) are distinguished further by **bloblike ends**, called **satellites** that extend from a thinner, **stalklike bridge** from the rest of the chromosome. (This is a different use of the word "satellite" from the centromeric repeats.) The stalklike regions are areas that do not bind stains well. The stalks carry many repeats of genes coding for ribosomal RNA and ribosomal proteins, areas called **nucleolar organizing regions (NOR)**. They coalesce (join to gather) to form the nucleolus, a structure in the nucleus where ribosomal building blocks are produced and assembled.

Importance of Karyotype

Karyotypes are useful at several levels. When

- a **baby is born with the distinctive facial characteristics** of Down syndrome, a karyotype **confirms the clinical diagnosis**.
- Within families, karyotypes are used **to identify relatives with a particular chromosomal aberration** that can affect health. For example, in one family, several adult members died from a rare form of kidney cancer. Because the cancer was so unusual, researchers karyotyped the affected individuals, and found **that they all had an exchange called** a **translocation,** between **chromosome 3 and 8**. When karyotypes showed that two young family members had the translocation; physicians examined and monitored their kidneys, detecting cancer very early and treating it successfully.
- Karyotypes of individuals from different populations can **reveal the effects of environmental toxins**, if abnormalities appear only in a group exposed to a particular contaminant. Because **chemicals and radiation that can cause cancer and birth defects** often also **break chromosomes into fragments or rings**,

detecting this genetic damage can alert physicians to **the possibility that certain cancers will appear in the population**.

- Karyotypes compared between species **can clarify evolutionary relationships**. The more recent the divergence of two species from a common ancestor, the more closely related we presume they are, and the more alike their chromosome banding patterns should be. **Our closest relative**, according to karyotypes, is the **pygmy chimpanzee**, also known as the **bonobo**. The human karyotype is also remarkably similar to that of the **domestic cat**, and somewhat **less similar** to the karyotypes of **mice, pigs, and cows**.

Visualizing Chromosomes:

Extra or missing chromosomes are easily detected by counting a number other than 46.

Identifying chromosome rearrangements, such as an inverted sequence or two chromosomes exchanging parts, requires a way to distinguish among the chromosomes. A combination of stains and DNA probes applied chromosomes allows this. A **DNA probe** is a labeled piece of DNA that binds to its complementary sequence on a particular chromosome.

Obtaining Cells for Chromosome Study:

Any cell other than a mature red blood cell (which lacks a nucleus) can be used to examine chromosomes, but some cells are easier to obtain and culture than others. For adults, **white blood cells** separated from a **blood sample** or **skin** like cells collected from the inside of the cheek are usually the basis of a chromosome test.

A person might require such a test **if he or she has a family history of a chromosomal abnormality or seeks medical help because of infertility**. **For blood-borne cancers (leukemias and lymphomas)**, cytogeneticists examine **chromosomes from bone marrow cells**, which give rise to blood cells. DNA microarray tests are replacing karyotypes in matching cancers to the most effective chemotherapies. Chromosome tests are most commonly performed on **fetal cells**. ***Couples who receive a prenatal diagnosis of a chromosome abnormality can arrange for treatment of the newborn***, if this is possible; learn more about the condition and perhaps contact support groups and plan care; or terminate the pregnancy. These choices are highly individual and personal and are best made

after a genetic counselor or physician provides information on the particular medical condition and available treatment options.

Amniocentesis:

The first successful fetal karyotype was constructed in 1966 by a technique called **amniocentesis.**

1- A doctor removes a small sample of fetal cells and fluids from the uterus with a needle passed through the woman's abdominal wall.

2- The cells are cultured for a week to 10 days, and *typically 20 cells are karyotyped*.

3- Culturing and staining chromosomes takes a week, but DNA probes can detect chromosomes in a day or two.

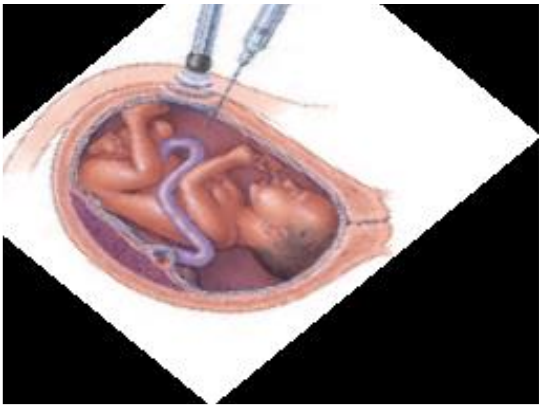
The sampled amniotic fluid is also examined for deficient, excess, or abnormal biochemical's that could indicate particular **inborn errors of metabolism**. Amniocentesis takes only a minute or two and causes only a feeling of pressure. Ultrasound is used to guide the needle so it doesn't harm the fetus.

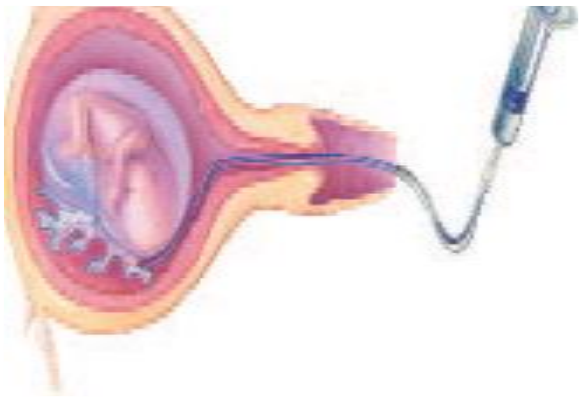
Amniocentesis **can detect approximately 400 of the more than 5,000 known chromosomal and biochemical problems**.

4-It is usually performed at **15 or 16 weeks gestation, when the fetus isn't yet very large** but **240** Part Three DNA and Chromosomes amniotic fluid is plentiful(abundant). Amniocentesis can be carried out any time after this point.

Doctors recommend **amniocentesis if the risk that the fetus has a detectable condition exceeds the risk that the procedure will cause a miscarriage**, which is about 1 in 350.

5- The most **common candidate for the test is a pregnant woman over age 35**. This "advanced maternal age" statistically increases the risk that the fetus will have an extra or missing chromosome. Amniocentesis is also **warranted if a couple has had several spontaneous abortions or children with birth defects or a known chromosome abnormality**. Another reason to seek amniocentesis is **if a blood test on the pregnant woman reveals low levels of a fetal liver protein called alpha fetoprotein (AFP) and high levels of human chorionic gonadotropin (hCG).** These signs may indicate **a fetus with a small liver**, which may reflect a condition caused by an extra chromosome, such as Down syndrome. These tests, called **maternal serum marker tests,** may include a third or fourth biochemical too. They are useful for pregnant women younger than 35 who would not routinely undergo age related amniocentesis. Doctors use maternal serum marker tests to screen their patients to identify those who may require genetic counseling and perhaps further, more invasive testing.





Chorionic Villus Sampling:

During the **10th week of pregnancy**, **chorionic villus sampling** (CVS) obtains cells from the **chorionic villi,** the structures that develop **into the placenta**. A karyotype is prepared: **directly from the collected cells**, rather than **first culturing them, as in amniocentesis.** Results are ready in days. Because chorionic villus cells descend from the fertilized ovum, their chromosomes should be **identical to those of the embryo and fetus**. **Occasionally, a chromosomal aberration occurs** only in an embryo, or only in chorionic villi. This result in a situation called **chromosomal mosaicism**— that is, the karyotype of a villus cell differs from that of an embryo cell. Chromosomal mosaicism has great clinical consequences. If CVS indicates an aberration in villus cells that is not also in the fetus, then a couple may elect to terminate the pregnancy based on misleading information—that is, the fetus is actually chromosomally normal, although CVS indicates otherwise.

In the opposite situation, the results of the CVS may be normal, but the fetus has a chromosomal problem— leading to an unpleasant surprise at birth or later.

CVS is slightly less accurate than amniocentesis and in about 1 in 1,000 to 3,000 procedures, causes a fatal limb defect. Also, the sampling procedure in CVS does not include amniotic fluid, so the biochemical tests that amniocentesis allows are not possible. Couples expecting a child are sometimes asked to choose between amniocentesis and CVS.

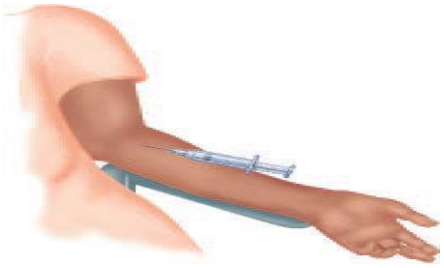
The advantage of CVS is earlier results, but it is associated with a greater risk of spontaneous abortion. Although CVS is slightly more invasive and dangerous to the fetus, its greater risk also reflects the fact that CVS is done earlier in pregnancy. Since most spontaneous abortions occur early in pregnancy, more will follow CVS

than amniocentesis. The spontaneous abortion rate after the 12th week of pregnancy is about 5 percent, and the additional risk that CVS poses is 0.8 percent. In contrast, the spontaneous abortion rate after the 14th week is 3.2 percent, and amniocentesis adds 0.3 percent to the risk.

Fetal Cell Sorting:

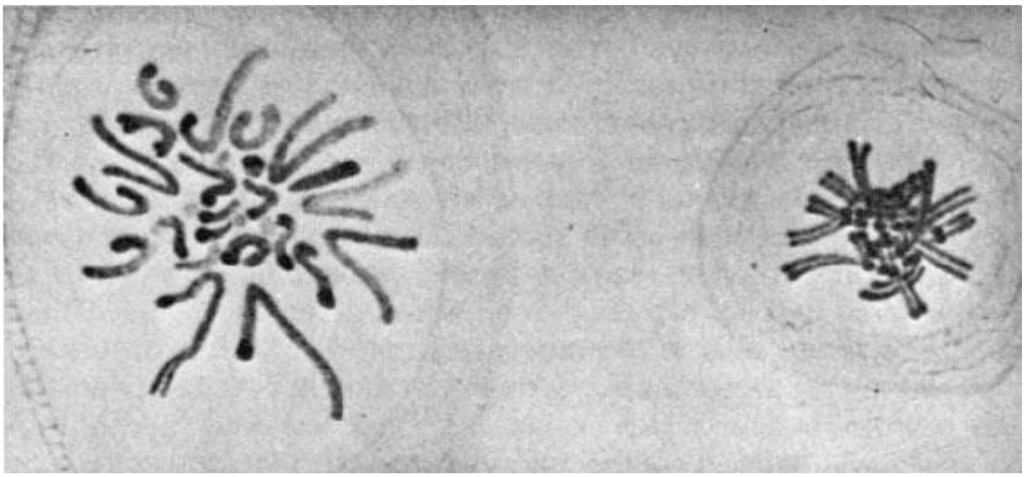
Fetal cell sorting, a new technique that separates fetal cells from the woman's blood stream, is safer than amniocentesis and CVS but is still experimental in the United States. The technique traces its roots to 1957, when a pregnant woman died when cells from a very early embryo lodged in a major blood vessel in her lung, blocking blood flow. The fetal cells were detectable because they were from a male, and were distinguished by the telltale Y chromosome. This meant that fetal cells could enter a woman's circulation. **By studying the blood of other pregnant women, researchers found that fetal cells enter the maternal circulation in up to 70 percent of pregnancies.** Cells from **female embryos**, however, cannot be distinguished from the cells of the pregnant woman on the basis of sex chromosome analysis. But **fetal cells from either sex** can be **distinguished** from **maternal cells** using a device called a **fluorescence-activated cell sorter**. It separates fetal cells from maternal blood by **identifying surface characteristics** that differ from those on the **woman's cells**. The fetal cells are then karyotyped and fetal DNA extracted and amplified for specific gene tests. Rarely, other techniques are used to sample specific fetal tissues, such as blood, skin, liver, or muscle. These biopsy procedures are usually done by using ultrasound to guide a hollow needle through the woman's abdominal wall to reach the fetus.

Such an invasive test is performed if the family has a disease affecting the particular tissue, and a DNA-based test is not available. Instead of examining chromosomes, ultrasound can be used to identify physical features that are part of chromosomal syndromes. For example, ultrasound can **detect thickened neck skin** and absent or **underdeveloped nasal bones** that are characteristic of Down syndrome and were part of the initial description in 1866. In one study, 75percent of fetuses with Down syndrome had these characteristics, compared to 0.5 percent of fetuses who did not have Down syndrome. Ultrasound scanning is therefore somewhat imprecise, but it is safer than obtaining chromosomes with amniocentesis or CVS. Combined with maternal serum marker testing, ultrasound scans may enable physicians to identify pregnancies in need of further testing.



Preparing Cells for Chromosome Observation:

Microscopists have tried to describe and display human chromosomes since the late 19th century (figure 12.8 and the Technology Timeline). Then, the prevailing view held that **humans had an XO sex determination system**, with females system, with females having an extra chromosome (XX).Estimates of the human chromosome number ranged from **30 to 80**. In 1923, **Theophilus Painter** published sketches of human chromosomes from three patients at a Texas state mental hospital. The patients had been castrated in an attempt to control their abusive behavior, and **Painter** was able to examine the tissue. He **could not** at first tell whether the **cells had 46 or 48 chromosomes**, but finally decided that he saw 48. Painter also showed that **both sexes have the same chromosome number**. The difficulty in distinguishing between 46 or 48 chromosomes was **physical—preparing a cell** in which chromosomes do not overlap is challenging. To easily count the chromosomes, scientists had to **find a way to capture** them when they **are the most condensed— during cell division**—and also spread them apart. Since the 1950s, cytogeneticists have used **colchicines**, an extract of the chrysanthemum plant, to arrest cells during division.



Swelling, Squashing, and Untangling:

Ten years later, cell biologists **Albert Levan** and **Joe-Hin Tjio** found that when they drew cell-rich fluid into a pipette and dropped it onto a microscope slide prepared with stain, the **cells burst open** and **freed the mass of chromosomes**. Adding a glass coverslip spread the chromosomes enough that they could be counted. Another researcher, a former student of Painter named John Biesele, suggested that Levan and Tjio use cells from tissue culture, and by 1956, they finally settled the matter of how many chromosomes occupy a diploid human cell—46. In the same year, J**. L. Hamerton** and **C. E. Ford** identified the expected 23 chromosomes in human gametes. In 1960 came another advance in visualizing chromosomes— through the use of a **kidney bean extract called phytohemagglutinin**. Originally used to clump red blood cells to separate them from white blood cells, the substance also could stimulate division of white blood cells. Until recently, a **karyotype was constructed using a microscope to locate a cell in which the chromosomes were not touching, photographing the cell, developing a print, and cutting out the individual chromosomes and arranging them into a size-order chart**. A computerized approach has largely replaced the cut-and-paste method. The device scans ruptured cells in a drop of stain and selects one in which the chromosomes are the most visible and well spread. Then image analysis software recognizes the band patterns of each stained chromosome pair, sorts the structures into a size-order chart, and prints the karyotype—in minutes. If the software recognizes an abnormal band pattern, a database pulls out identical or similar karyotypes from other patients, providing clinical information on the anomaly. Genome sequence information is also scanned. However, the expert eyes of a skilled technician are still needed to detect subtle abnormalities in chromosome structure.

Staining:

In the earliest karyotypes, dyes stained the chromosomes a uniform color. Chromosomes were grouped into size classes, designate Abnormalities—**Down syndrome** (an extra chromosome 21), **Turner syndrome** (also called XO syndrome, a female with only one X chromosome), and **Klinefelter syndrome** (also called XXY syndrome, a male with an extra X chromosome). Before this, women with Turner syndrome were thought to be genetic males because they lack **Barr bodies**, while men with Klinefelter syndrome were thought to be genetic females because their cells have Barr bodies. The ability to visualize and

distinguish the sex chromosomes, even crudely, allowed researchers to determine the causes of these conditions.

The first stains that were applied to chromosomes could highlight large deletions and duplications, but more often than not.

In **1967, a mentally retarded child** with material missing from chromosome 4 would have been diagnosed as having a "B-group chromosome" disorder. Today the exact genes that are missing can be identified. Describing smaller-scale chromosomal aberrations required better ways to distinguish among the chromosomes.

In the1970s, Swedish scientists developed more specific chromosome stains that create banding patterns unique to each chromosome. Combining stains reveals even more bands, making it easier to distinguish chromosomes. Stains are specific for **AT-rich or GC-rich stretches of DNA,** or for heterochromatin, which stains **darkly** at **the centromere and telomeres**. The ability to detect missing, extra, inverted, or misplaced bands allowed researchers to link many more syndromes with specific chromosome aberrations.

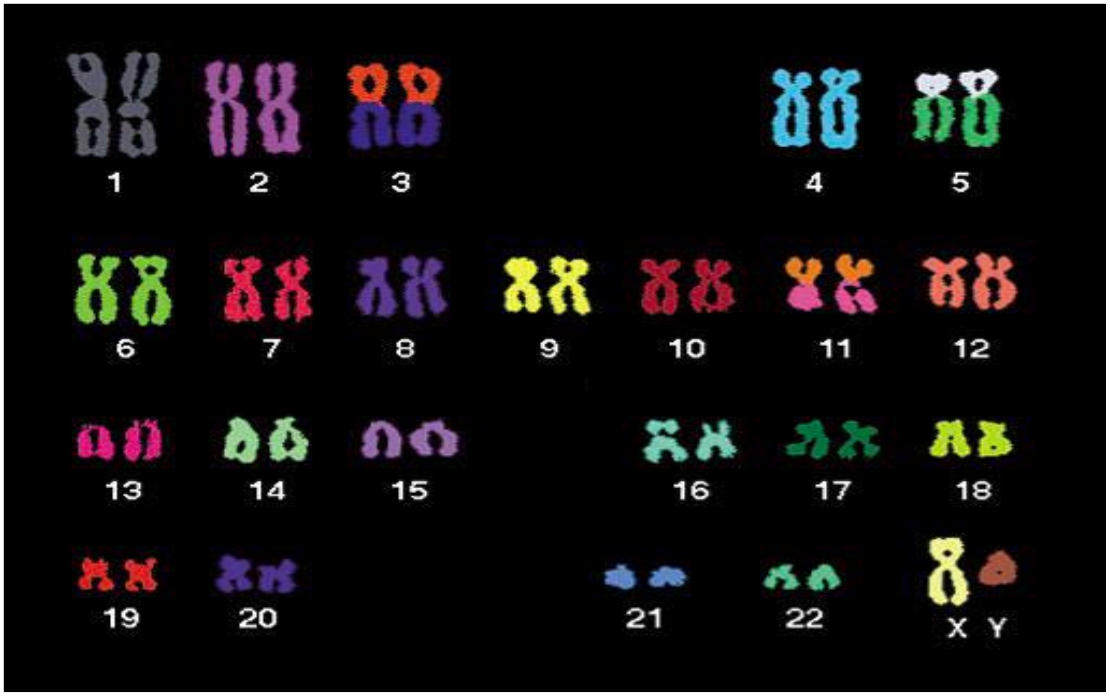
In the late 1970s, Jorge Yunis at the University of Minnesota improved chromosome staining further by developing a **way to synchronize white blood cells in culture**, arresting them in early mitosis. His approach, called high-resolution chromosome banding, revealed many more bands. Today, **fluorescence *in situ* hybridization,** or FISH, is eclipsing even high-resolution chromosome banding, enabling cytogeneticists to focus on individual genes.

FISHing:

One conventional chromosome stains is that they **are not specific to particular chromosomes.** Rather, they generate different banding patterns among the 24 human chromosome types. FISH is much more specific because it uses **DNA probes** that are **complementary to DNA sequences** found only on one chromosome type. The probes are **attached to molecules that fluoresce when illuminated**, producing a **flash of color** precisely where the probe binds to a chromosome in a patient's sample. The technique can reveal a particular extra chromosome in a day or two. FISH is based on a technique, developed in 1970, called *in situ* hybridization, which originally used radioactive labels rather than **fluorescent ones**. *In situ* hybridization took weeks to work, because it relied on exposing photographic film to reveal where DNA probes bound among the chromosomes. The danger of working with radioactivity, and the crudeness of the results, eventually prompted researchers to seek alternative ways of highlighting bound DNA probes. FISH is used to identify specific chromosomes and to "paint"

entire karyotypes, providing a different color for each chromosome. Many laboratories that perform amniocentesis or chorionic villous sampling use FISH probes specific to chromosomes 13, 18, 21, and the sex chromosomes to quickly identify the most common chromosome abnormalities.

A computer integrates the images and creates a false color for each chromosome. A new approach to prenatal chromosome analysis called **quantitative PCR amplifies** certain repeated sequences on chromosomes 13, 18, 21, X, and Y. The technique distinguishes paternally derived from maternally derived repeats on each homolog for these five chromosomes. An abnormal ratio of maternal to paternal repeats indicates a numerical problem, such as two copies of one parent's chromosome 21. Combined with the one chromosome 21 from the other parent, this situation would produce a fertilized ovum with three copies of chromosome 21, which causes Down syndrome. Quantitative PCR is less accurate than culturing cells or FISH to examine chromosomes, but gives results in only hours, which can greatly reduce parental anxiety.



Geneticists abbreviate the pertinent information in a karyotype. They list chromosome number first, then sex chromosome constitution, then abnormal autosomes. Symbols describe the type of aberration, such as deletion or translocation. Numbers are listed that correspond to specific bands.

A normal male is 46, XY; a normal female is 46, XX. Geneticists use this notation to describe gene locations. For example, the λ- globins subunit of hemoglobin is located at **11p15.5.**

Chromosome information is displayed in an **ideogram,** which is a graphical representation of a karyotype (figure 12.10). Bands appear as stripes, and they are divided into numbered **major regions** and **sub regions**. **Specific gene** loci known from mapping data are listed **on the right-hand side** with information from the human genome sequence.

Ideograms are becoming so crowded with notations indicating specific genes that they may soon become obsolete.

Ideogram

Means

46,XY Normal male

46,XX Normal female

45,X Turner syndrome (female)

47,XXY Klinefelter syndrome (male)

47,XYY Jacobs syndrome (male)

46,XY del (7*q*) A male missing part of the long arm of chromosome 7

47,XX,+21 A female with trisomy 21 Down syndrome

46,XY t (7;9)(*p*21.1; *q*34.1) A male with a translocation between the short arm of chromosome 7 at band 21.1 and the long arm of chromosome 9 at band 34.1

Chromosome 21 is described as a "desert," harboring a million-base stretch with no protein-encoding genes at all. Chromosome 22, in contrast, is a gene jungle.

These two tiniest chromosomes are at opposite ends of the gene-density spectrum. They are remarkably similar in size, but chromosome 22 contains 545 genes to chromosome 21's 225.

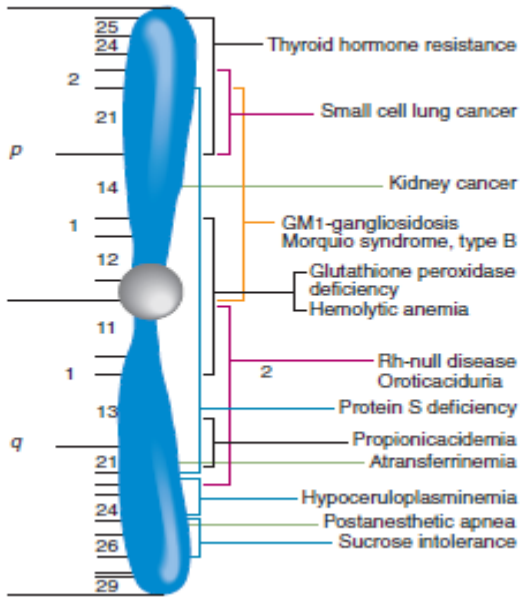


figure 12.10

Ideogram. An ideogram is a schematic chromosome map. It indicates chromosome arm (*p* or *q*), major regions delineated by banding patterns, and the loci of known genes. This is a partial map of human chromosome 3.

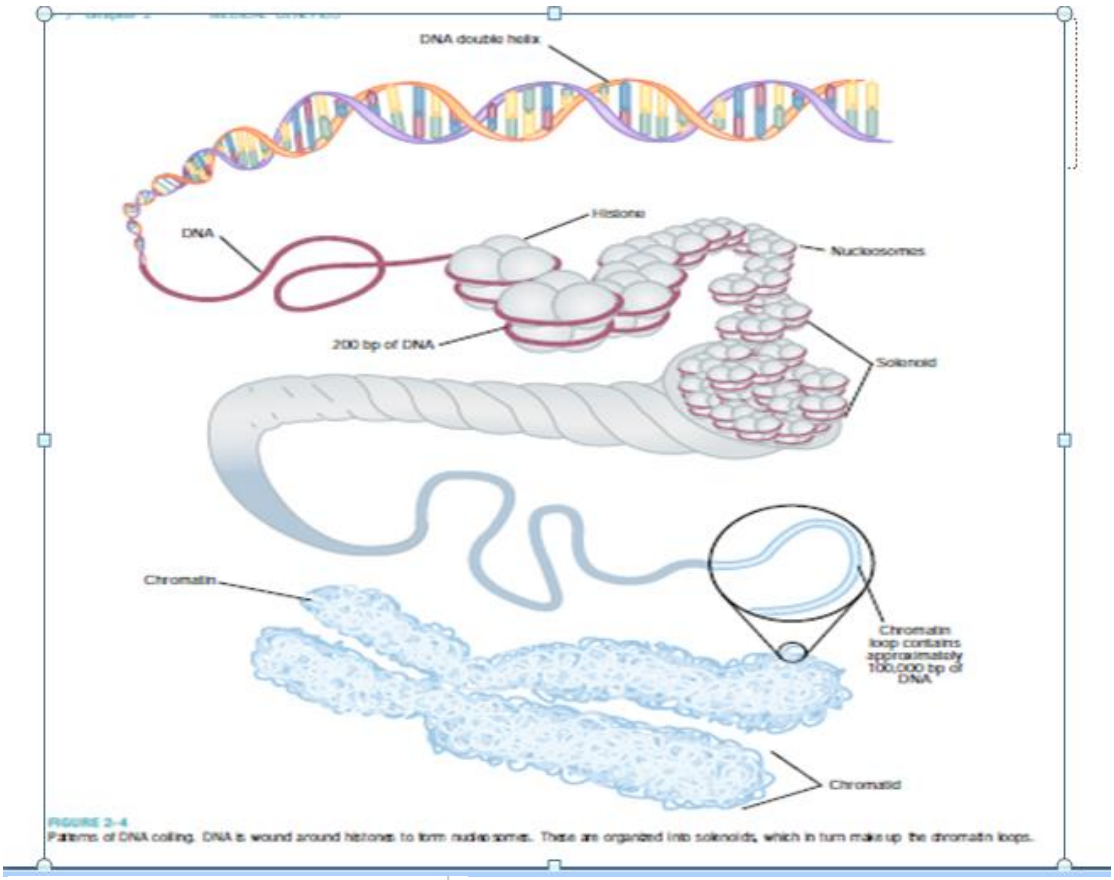


FIGURE 2-4
Patterns of DNA coiling. DNA is wound around histones to form nucleosomes. These are organized into solenoids, which in turn make up the chromatin loops.

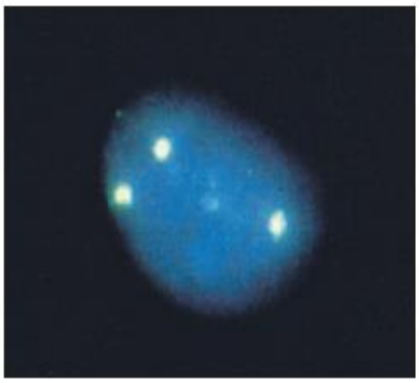
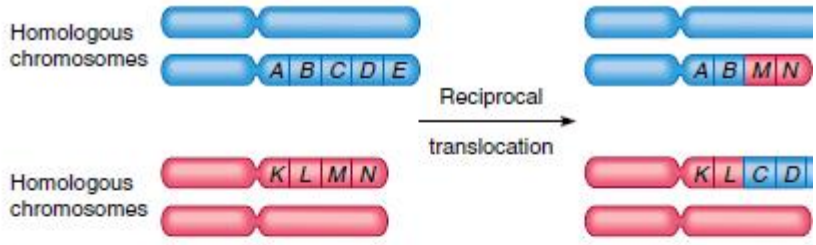
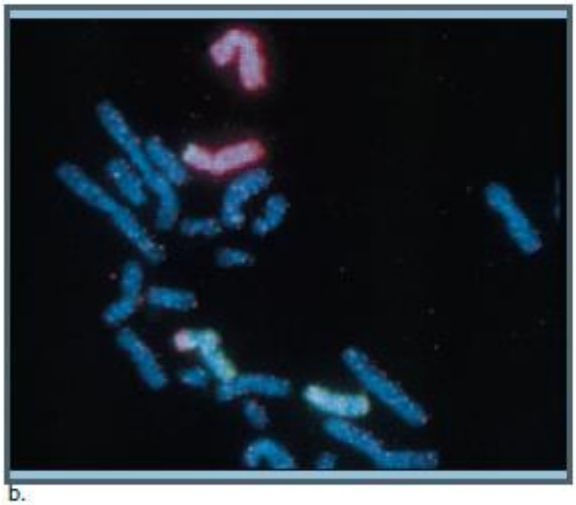


figure 12.9

FISHing for genes and chromosomes. FISH technology clearly shows three fluorescent dots that correspond to the three copies of chromosome 21 in this nucleus of a cell of an individual with Down syndrome.



a.



b.

ure 12.18

ciprocal translocation. In a reciprocal translocation, two nonhomologous
nosomes exchange parts. In (*a*), genes *C*, *D*, and *E* on the blue chromosome ex
ions with genes *M* and *N* on the red chromosome. (*b*) shows a reciprocal transl
s highlighted using FISH. The pink chromosome with the dab of blue, and the bl

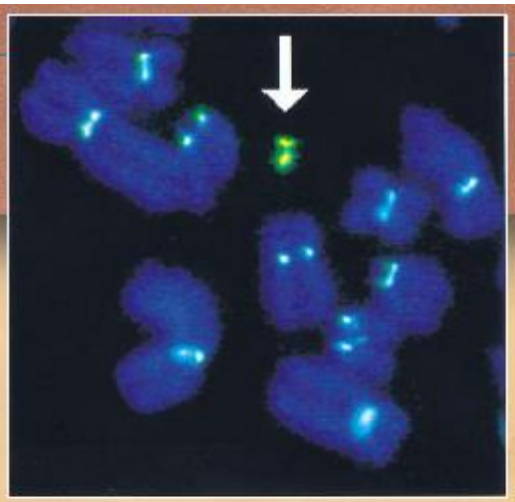
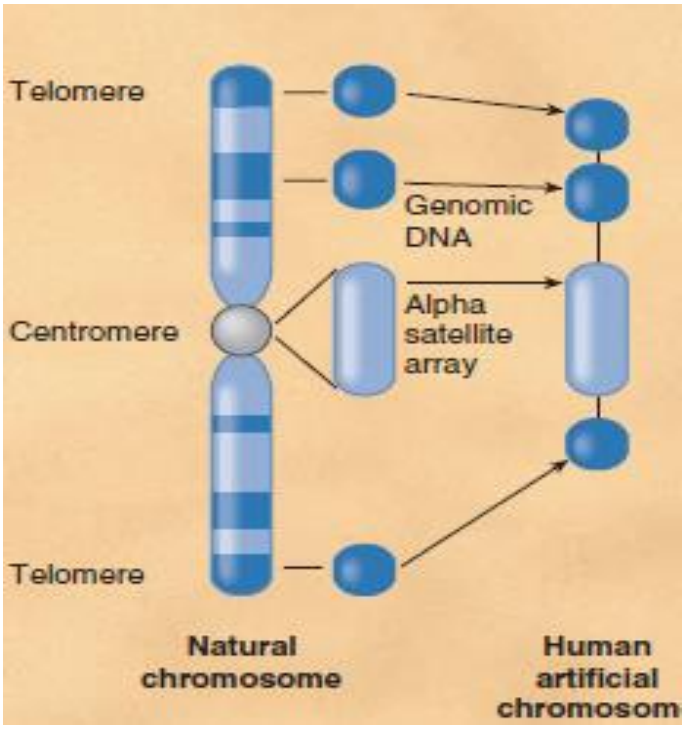


figure 1

HACs. Researchers introduced telomere sequences, centromere sequences, and other DNA pieces into cells in culture. The pieces aligned and assembled into human artificial microchromosomes.

(John Harrington, Huntington Willard, et al. *Nature Genetics* 4:345–55, 1997.)



Abnormal Chromosome Number

A human karyotype is **abnormal** if the number of chromosomes is not 46, or if individual chromosomes have extra, missing, or rearranged genetic material.

Abnormal chromosomes are the most frequent **cause of spontaneous abortion,** accounting for at least 50 percent of them.

Studies of pre implantation embryos cultured in laboratories for *in vitro* fertilization. Yet only 0.5 to 0.7 percent of newborns have abnormal chromosomes. Therefore, most embryos and fetuses with abnormal chromosomes do not develop enough to be born.

Polyploidy

The most drastic upset in chromosome number **is an entire extra set**.

A cell with one or more extra sets of chromosomes is **polyploidy.**

An individual whose **cells have three copies** of **each chromosome** is a **triploid.**

Two-thirds of all **polyploidy** result from:

1- fertilization of an oocyte by two sperm.

2- The other cases of polyploidy arise from formation of a diploid gamete, such as a normal haploid sperm fertilizing a diploid oocyte.

Aneuploidy

Cells missing **a single chromosome or having an extra one** are termed **aneuploid,** which means "not good set." Studies on pre implantation embryos reveal that rare **aneuploids can have a few missing or extra chromosomes, indicating defective meiosis in a parent.**

A normal chromosome number is euploid, which means "good set."

Most autosomal aneuploids are spontaneously aborted. Those that survive have **specific syndromes**, with symptoms depending upon which **chromosomes is missing or extra**. Mental retardation is common in an individual who survives with aneuploidy,.

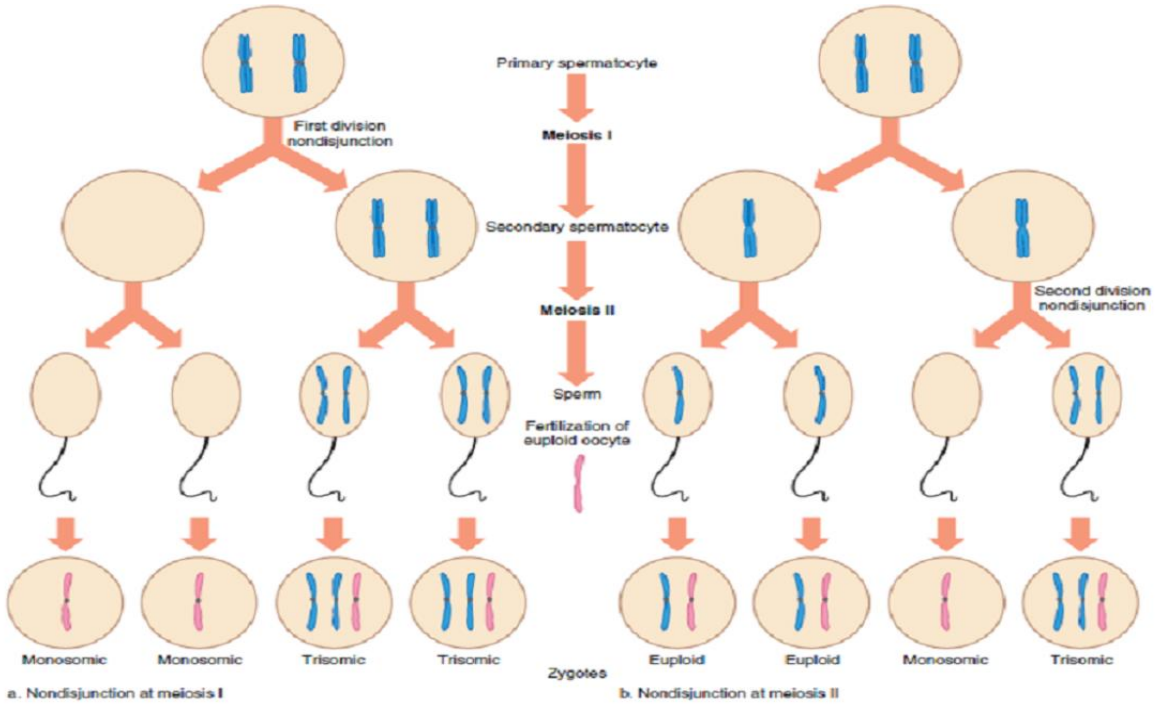
Sex chromosome aneuploidy usually produces less-severe symptoms.

Most children born with the wrong number of chromosomes have an extra chromosome (a trisomy) rather than a missing chromosome (a monosomy).

Most monosomies are so **severe** that an affected embryo ceases developing. Trisomies and monosomies are named according to the chromosome involved, and the associated syndrome has traditionally been named for the investigator who first described it.
For example, Down syndrome can result from an extra chromosome 21 (a trisomy) or a translocation.

The **meiotic error** that causes **aneuploidy** is called **nondisjunction.** Recall that in normal meiosis, homologs separate, and each of the resulting gametes receives only one member of each chromosome pair.

In nondisjunction, a chromosome pair fails to separate at anaphase of either the first or second meiotic division. This produces a sperm or oocyte that has two copies of a particular chromosome, or none, rather than the normal one copy.
Different trisomies are consistently caused **nondisjunction in the male or female, at meiosis I or II**



Extra and missing chromosomes—aneuploidy. Unequal division of chromosome pairs can occur at either the first or second meiotic division. (*a*) A single pair of chromosomes is unevenly partitioned into the two cells arising from meiosis I in a male. The result: two sperm cells have two copies of the chromosome, and two sperm cells have no copies. When a sperm cell with two copies of the chromosome fertilizes a normal oocyte, the zygote is trisomic; when a sperm cell lacking the chromosome fertilizes a normal oocyte, the zygote is monosomic. (*b*) This nondisjunction occurs at meiosis II. Because the two products of the first division are unaffected, two of the mature sperm are normal and two are aneuploid. Oocytes can undergo nondisjunction, leading to zygotes with extra or missing chromosomes when normal sperm cells fertilize them.

A cell can have a missing or extra chromosome in 49 ways—
an extra or missing copy of each of the 22 autosomes, plus

the five abnormal types of sex chromosome combinations (Y, X, XXX, XXY, and XYY). However, only nine types of aneuploids are known in newborns. Others are seen in spontaneous abortions or fertilized ova intended for *in vitro* fertilization.

Most of the 50 percent of spontaneous abortions that result from extra or missing chromosomes are 45,X individuals (missing an X chromosome), triploids, or trisomy 16.

About 9 percent of spontaneous abortions are trisomy 13, 18, or 21. Although these are the most common autosomal aneuploids seen in newborns, more than 95 percent of newborns with abnormal chromosome numbers have an extra 13, 18, or 21, or an extra or missing X or Y chromosome.

Types of chromosome abnormalities seem to differ between the sexes. Abnormal **oocytes** mostly **have extra or missing chromosomes**, whereas **abnormal sperm** more have **structural variants, such as inversions or translocations.**

Aneuploidy and polyploidy also arise during **mitosis**, producing groups of somatic cells with the extra or missing chromosome.

Mosaic is An individual with two chromosomally distinct cell populations. If only a few cells are altered, health may not be affected. However, a mitotic abnormality that occurs early in development, so that many cells descend from the unusual one, can affect health.

A chromosomal mosaic for a trisomy may have a mild version of the condition. This is usually the case for the **1 to 2 percent** of people with Down syndrome who are mosaic.

For example, a person may have the extra chromosome that causes Down syndrome in 5 of 20 sampled fetal cells. This individual would possibly not be as severely mentally impaired as a person who has the extra chromosome in every cell.

The phenotype depends upon which cells have the extra chromosome. A fetus with **affected cells in the brain would later show a greater mental impairment** than a **fetus with the affected cells mostly in the skin**.

Autosomal Aneuploids

Most autosomal aneuploids are very rarely seen in live births, due to the lethality of a large imbalance of genetic material.

Trisomy 21 Down Syndrome The most common autosomal aneuploid among liveborns is trisomy 21. (الى هنا)

Males and females of all ethnic groups can have Down syndrome.

In 1958, improved chromosome visualization techniques revealed 47 chromosomes in cells of a person with trisomy 21 Down syndrome.

In 1960, they discovered Down syndrome caused by a **translocation between chromosome 21** and another chromosome, **and**

in 1961, researchers identified **mosaic Down** syndrome. The affected girl had physical signs of the condition, but normal intelligence.

A child with Down syndrome **is 15 times more li**kely to develop:

1- leukemia than a child who does not have the syndrome,. Many of the medical problems associated with Down syndrome are treatable, so that **more than 70 percent of affected individuals live longer than age 30.**

2- Alzheimer disease is 25 percent, compared to 6 percent for the general population. A gene on chromosome 21 causes one inherited form of Alzheimer disease.

Comparing and Contrasting Trisomies 13, 18, and 21

Type of Trisomy	Incidence at Birth	Percent of Conceptions That Survive 1 Year After Birth
13 (Patau)	1/12,500–1/21,700	<5%
18 (Edward)	1/6,000–1/10,000	<5%
21 (Down)	1/800–1/826	85%

The likelihood of giving birth to a child with **Down syndrome increases dramatically** with the **age of the mother**. The overall frequency of trisomy 21 Down syndrome is 1 in about 800 births. For women under 30 the chances are 1 in 952. But at age 35, the risk is 1 in 378, and at age 40, 1 in 106. By age 45, risk jumps to 1 in 30, and by age 48, it is 1 in 14.

However, 80 percent of children with trisomy 21 are born to women under age 35.

- This is because **younger women are more likely to become pregnant and less likely to undergo amniocentesis**. About **90 percent of trisomy 21** conceptions are **due to nondisjunction during meiosis I in the female.** The 10 percent of cases **due to the male** result from nondisjunction during **meiosis I or II.**
- The chance that **trisomy 21 will recur in a family**, based on empirical data (how often it actually does recur in families), is 1 percent. **Genetic**

counselors consider this figure along with maternal age effects, presenting a worst-case scenario to the expectant couple

- The **age factor** in Down syndrome may reflect **the fact that meiosis in the female is completed only after conception.** The older a woman is, the **longer her oocytes have been arrested on the brink of completing meiosis.** During this time, the oocytes may have been exposed to chromosome-damaging chemicals, viruses, or radiation..
- An **unknown mechanism prevents these abnormal oocytes from maturing**. As a woman ages, selectively releasing normal oocytes each month since puberty, the abnormal ones begin to accumulate, much as black jellybeans accumulate as people preferentially eat the colored ones.

In 1909, a study of 350 affected infants revealed an overrepresentation of older mothers, to attribute the link to "maternal reproductive exhaustion."
In 1930, another study found that the increased risk of Down syndrome correlated **to maternal age, and not to the number of children in the family.**

Trisomy 18—Edward Syndrome

Only 1 in 6,000 to 10,000 newborns has trisomy 18, most affected individuals do not survive to be born. The severe symptoms of trisomy 18 explain why fetuses survive and also make the syndrome relatively easy to diagnose prenatally using ultrasound—yet the **symptoms are presumably milder than those associated with the majority of aneuploids, which are manifest solely as spontaneous abortions.**

After birth, additional anomalies are apparent. These **include overlapping placement of fingers** ,a narrow and flat skull, abnormally shaped and low-set ears, a small mouth and face, unusual or absent fingerprints, short large toes with fused second and third toes, and "rocker-bottom" feet.
Affected children have great physical and mental disabilities, with developmental skills stalled at the six-month level.
Most cases of trisomy 18 are traced to **nondisjunction in meiosis II during oocyte formation.**

Trisomy 13—Patau Syndrome

Trisomy 13 is very rare, but, as is the case with trisomy 18, the number of newborns with the anomaly reflects only a small percentage of affected conceptions. Trisomy 13 has a different set of signs and symptoms than trisomy 18. Most striking, although rare, **is a fusion of the developing eyes, so that a fetus has one large eyelike structure in the center of the face. More common is a small or absent eye.**

Major abnormalities affect the heart, kidneys, brain, face, and limbs. The nose is often malformed, and cleft lip and/or palate is present in a small head. Extra fingers and toes may occur. an ultrasound exam are considered sufficient evidence to pursue chromosome analysis of the fetus to detect trisomy 13. Ultrasound examinations of affected newborns reveal more extensive anomalies, including an extra spleen, abnormal liver structure, rotated intestines, and an abnormal pancreas. A few individuals have survived until adulthood, but they do not progress developmentally beyond the six month level.

Sex Chromosome Aneuploids الى هنا المسائي الثلاثاء

People with sex chromosome aneuploidy have extra or missing sex chromosomes.

How Nondisjunction Leads to Sex Chromosome Aneuploids???

Situation	Oocyte	Sperm	Consequence
Normal	X	Y	46,XY normal male
	X	X	46,XX normal female
Female nondisjunction	XX	Y	47,XXY Klinefelter syndrome
	XX	X	47,XXX triplo-X
		Y	45,Y nonviable
		X	45,X Turner syndrome
Male nondisjunction	X		45,X Turner syndrome
(meiosis I)	X	XY	47,XXY Klinefelter syndrome
Male nondisjunction	X	XX	47,XXX triplo-X
(meiosis II)	X	YY	47,XYY Jacobs syndrome
	X		45,X Turner syndrome

Turner Syndrome (45,X)

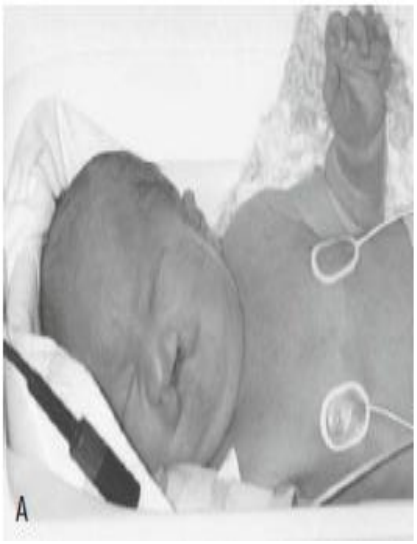
In 1938, at a medical conference, an endocrinologist named Henry Turner described seven young women, aged 15 to 23, who were sexually undeveloped, short, had folds of skin on the back of the neck,. (Eight years earlier, an English physician named Ullrich had described the syndrome in young girls and so it is called Ullrich syndrome in the U.K.) Then it would become known as **Turner syndrome**,

Physicians assumed that a **hormonal insufficiency caused the symptoms**. They were right, but there was more to the story—a chromosomal imbalance caused the hormone deficit.

P. E Polani discovered that cells from Turner patients lacked a Barr body, the dark spot that indicates the presence of a second X chromosome. Might the lack of a sex chromosome cause the symptoms, particularly the failure to mature sexually?

figure 12.13

Trisomy (Edward syndrome). An infant with trisomy 18 clenches its fist in a characteristic manner, with fingers overlapping.



By 1959, karyotyping confirmed the absence of an X chromosome in cells of Turner syndrome patients. It was later learned that only 50 percent of individuals with Turner syndrome are XO. The others have **partial deletions of the X chromosome**, or are **mosaics**,with only some cells affected.

Two X chromosomes are necessary for **normal sexual development in females**.

About half of people with Turner syndrome have impaired hearing and frequent ear infections, due to a small defect in the shape of the cochlea, They cannot hear certain frequencies of sound

At sexual maturity, the girls do not ovulate or menstruate, and they have underdeveloped breasts.
The uterus is very small, but the vagina and cervix are normal.
Intelligence is normal, and these women can lead fairly normal lives if they receive hormone supplements.

Using growth hormone adds up to three inches or so of height. Although women with Turner syndrome are infertile, individuals who are mosaics may have children.

In vitro fertilization (IVF), it can be used to select oocytes that have a normal chromosome number.

Interestingly, Turner syndrome is the only aneuploid condition that seems **unrelated to the age of the mother**.

Having Turner syndrome apparently does affect lifespan. For example, 68 percent of the 156 participants reached age 60, Studies that calculate relative risk for females with Turner syndrome indicate that they are more likely to develop certain disorders than the general population

The many signs and symptoms of Turner syndrome result from the **loss of specific genes.** For example, **loss of a gonadal dysgenesis gene accounts for the ovarian failure,** whereas absence of a homeobox gene causes the characteristic short stature.

Extra X Chromosomes

- About 1 in every 1,000 females has an extra X chromosome in each of her cells, a condition called triplo-X. The only symptom seems to be tallness and menstrual irregularities. Although triplo-X females are rarely mentally retarded, they tend to be less intelligent than their siblings .The lack of symptoms associated with having extra X chromosomes reflects the protective effect of X inactivation—all but one of the X chromosomes is inactivated.

- Klinefelter syndrome (XXY): About 1 in 1,000 males has an extra X chromosome,
- Men severely affected with Klinefelter syndrome are underdeveloped sexually,with rudimentary testes and prostate glands and sparse pubic and facial hair.
- They have very long arms and legs, large hands and feet, and may develop breast tissue. Klinefelter syndrome is the most common genetic or chromosomal cause of male infertility, accounting for 4 to 6 percent of infertile men . Testosterone injections during adolescence can limit limb lengthening and prompt development of secondary sexual characteristics.

Boys and men with Klinefelter syndrome may be slow to learn, but they are usually not ,mentally retarded unless they have more than two X chromosomes,which happens rarely.

XYY Syndrome

Jacobs syndrome : One male in 1,000 has an extra Y chromosome. In 1961, when a tall, healthy, middle-aged man, known for his boisterous behavior, underwent a routine chromosome check after fathering a child with Down syndrome. The man had an extra Y chromosome.

In 1965, researcher Patricia Jacobs published results of a survey among 197 inmates at Carstairs, a high-security prison in Scotland. Of 12 men with unusual chromosomes, seven had an extra Y. **Might their violent or aggressive behavior be linked to their extra Y chromosome.**

History: In 1968, the extra Y of what became known as **Jacobs syndrome**.

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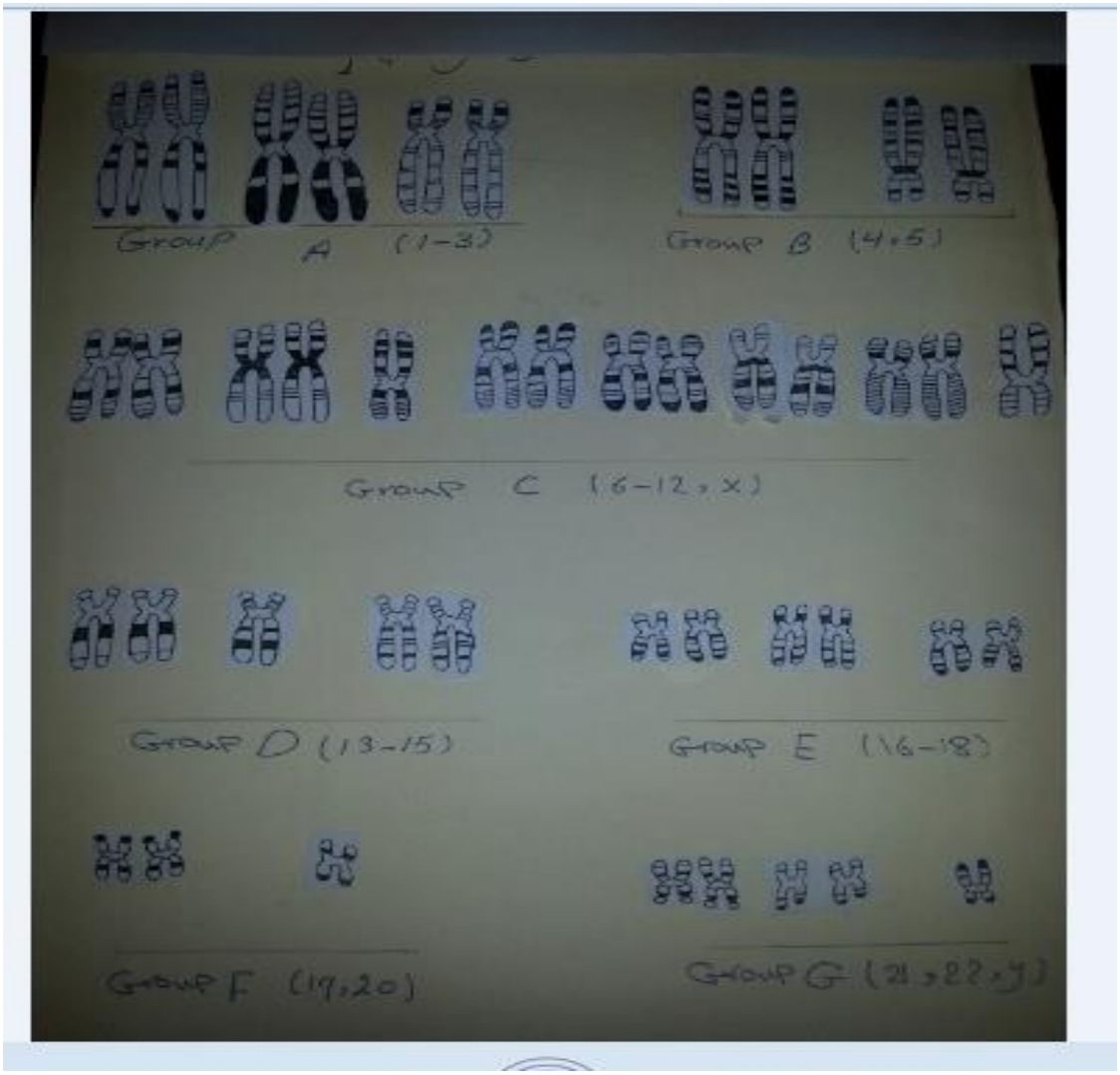
Today, we know that 96 percent of XYY males are **apparently normal**. The only **symptoms** attributable to the extra chromosome may be great **height, acne, and perhaps speech and reading problems.**

Large body size may lead teachers, employers, parents, and others to expect more of these people, and a few of them may deal this stress by becoming aggressive.

Jacobs syndrome can arise from nondisjunction in the male ,producing a sperm with two Y chromosomes that fertilizes an X-bearing oocyte.

Geneticists have never observed a sex chromosome constitution of one Y and no X. Since the Y chromosome carries little genetic material, and the gene-packed X chromosome would not be present, the absence of so many genes makes development beyond a few cell divisions in a YO embryo impossible.


GROUP A (1-3)
GROUP B (4,5)
GROUP C (6-12, X)
GROUP D (13-15)
GROUP E (16-18)
GROUP F (19,20)
GROUP G (21, 22, Y)

Abnormal Chromosome Structure

Structural chromosomal defects include **missing**, **extra**, or **inverted genetic material** **within a chromosome** or **combined** or **exchanged parts of nonhomologs** (translocations)

Deletions and Duplications

A deletion is missing genetic material. Deletions range greatly in size, and the larger ones tend to have greater effects because they remove more genes. Consider cri-du-chat syndrome (French for "cat's cry"), caused by deletion of part of the short arm of chromosome 5 (also called 5p– syndrome). The karyotype is 46,XY,del(5p). Seen in approximately 1 in 50,000 live births, affected children have a high-pitched cry similar to the mewing of a cat and pinched facial features, and are mentally retarded and developmentally delayed. The chromosome region responsible for the catlike cry is distinct from the region that causes mental retardation and developmental delay, suggesting that the deletion can remove more than one gene. A cytogeneticist can determine by examining a detailed karyotype whether a child will have only the catlike cry and perhaps poor weight gain, or will have all of the signs and symptoms, which include low birth weight, poor muscle tone, a small head, and impaired language skills.

Prader–Willi syndrome, a disorder is a good example of a microdeletion syndrome, advanced banding techniques detected a small deletion of chromosome bands 15q11-q13 in about 50% of these patients. With the use of molecular techniques, deletions that were too small to be detected cytogenetically were also discovered. In total, about 70% of Prader–Willi cases are caused by **microdeletions of 15q** .

FISH can detect tiny deletions and duplications that are smaller than the bands revealed by conventional chromosome staining. Small duplications are generally not dangerous, but some "microdeletions" have been associated with a number of syndromes. **Certain microdeletions** in the **short arm of the Y chromosome**, for example, cause **male infertility**.

A duplication *is a region of a chromosome* ***where genes are repeated.*** *Duplications, like deletions, are more likely to cause symptoms if they are extensive.*

For example, **duplications of chromosome 15 do not produce a phenotype unless they repeat several genes.** Another example: three duplicated chromosome **15s**, with increasing amounts of material repeated. Many people have the **first two types of duplications** and have **no symptoms**. However, several unrelated individuals with **the third, larger duplication have seizures and are mentally retarded**.

Duplication elsewhere on chromosome 15 has been associated with **panic attacks** and other **anxiety disorders**.

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Duplications can also be caused by unequal crossover during meiosis, as described for the X-linked color vision loci and for Charcot–Marie–Tooth disease .Duplications tend to produce less serious consequences than deletions, again illustrating the principle that a loss of genetic material is more serious than an excess of genetic material.

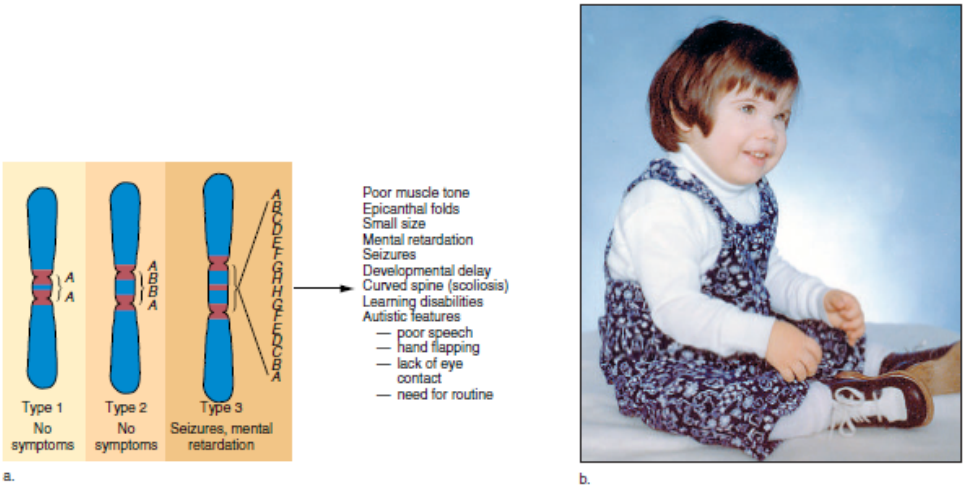


figure 12.16

A duplication. A study of duplications of parts of chromosome 15 revealed that small duplications do not affect the phenotype, but larger ones may. (a) The letters indicate specific DNA sequences, which serve as markers to compare chromosome regions. Note that the duplication is also inverted. (b) This child, who has "inv dup (15) syndrome," appears normal but has minor facial anomalies characteristic of the condition.

Deletions and duplications can arise from chromosome rearrangements, which include translocations, inversions, and ring chromosomes.

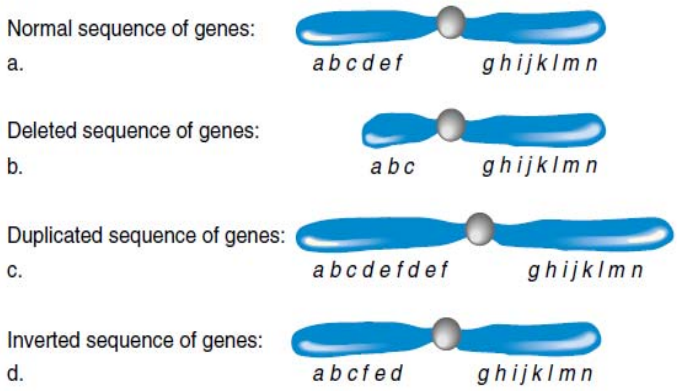


figure 12.15

Chromosome abnormalities. If a hypothetical normal gene sequence appears as shown in (*a*), then (*b*) represents a deletion, (*c*) a duplication, and (*d*) an inversion.

Translocations

In a translocation, **different (nonhomologous)** chromosomes **exchange or combine parts**. Exposure to certain viruses, drugs, and radiation can **cause translocations**, but often they arise for no apparent reason.

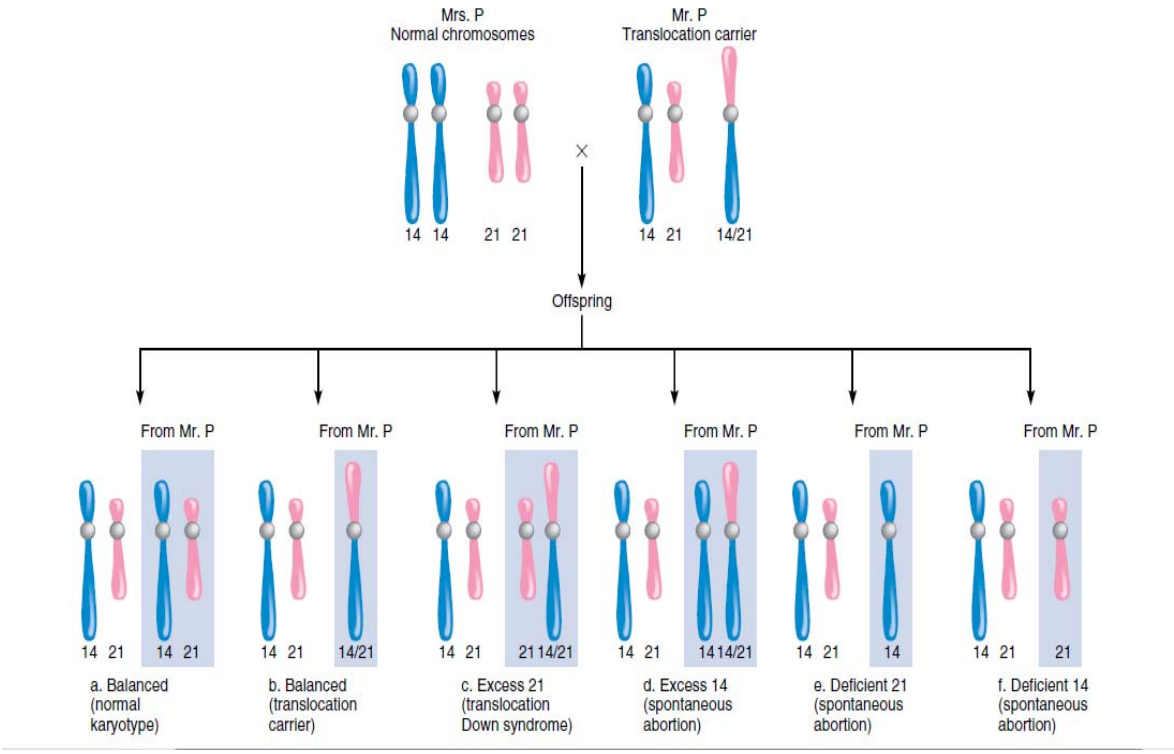
There are two major types of translocations: **In**

1- Robertsonian translocation, the short arms of two different acrocentric chromosomes break, leaving sticky ends that then cause the two long arms to adhere. A new, large chromosome forms from the **long arms of the two different chromosomes**. Because genes on the short arms of the involved chromosomes are repeated elsewhere, their absence in a Robertsonian translocation **does not affect the phenotype**.

The person with the large, translocated chromosome, called a translocation carrier, has 45 chromosomes, but may not have symptoms if a crucial gene has not been deleted or damaged. Even so, he or she may **produce unbalanced gametes**, sperm or oocytes with **too many or too few genes**. This can lead to **reproductive difficulties**, such as spontaneous abortion or birth defects.

One in 20 cases of **Down syndrome** arises because a parent has

a- **Robertsonian translocation between chromosome 21 and another, usually chromosome 14.** The problem arises because the individual with the chromosome produces some gametes that lack either of the involved chromosomes and some gametes that have extra material from one of the translocated chromosomes (figure 12.17).



In such a case a fertilized ovum has a 1 in 2 chance of ending in spontaneous abortion, and a 1 in 6 chance of developing into an individual with Down syndrome. The risk of the couple having a child with Down syndrome is theoretically 1 in 3, because the spontaneous abortions are not counted as births.

However, because some Down syndrome fetuses spontaneously abort, the actual risk of a couple in this situation having a child with Down syndrome is about 15 percent. The other two outcomes—normal chromosomes and a translocation carrier like the parent—have normal phenotypes. Either a male or a female can be a translocation carrier, and the condition is not related to age.

b-The second most common type of **Robertsonian translocation** occurs between **chromosomes 13 and 14,** causing symptoms of Patau syndrome because of an excess of chromosome 13 material. Robertsonian

translocations occur in 1 in 500 births, making them fairly common chromosomal aberrations ,

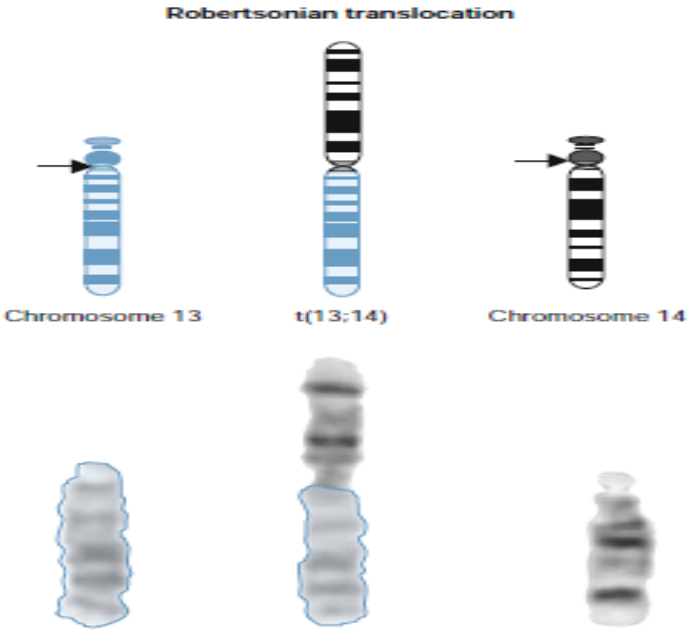


FIGURE 6–15
In a Robertsonian translocation, shown here, the long arms of two acrocentric chromosomes (13 and 14) fuse, forming a single chromosome.

2- In a reciprocal translocation, two different chromosomes exchange parts. FISH can be used to highlight the involved ***chromosomes*** . If the chromosome exchange does not break any genes, then a person who has both translocated chromosomes is healthy and is also a translocation *carrier*. ***He*** or she has the normal amount of genetic material, but it is rearranged.

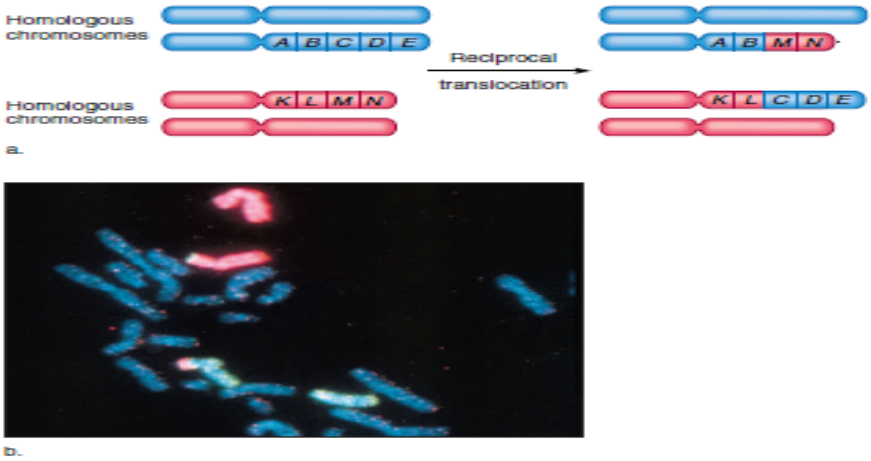


figure 12.18

A reciprocal translocation. In a reciprocal translocation, two nonhomologous chromosomes exchange parts. In (*a*), genes *C*, *D*, and *E* on the blue chromosome exchange positions with genes *M* and *N* on the red chromosome. (*b*) shows a reciprocal translocation that is highlighted using FISH. The pink chromosome with the dab of blue, and the blue chromosome with a small section of pink, are the translocated chromosomes.

A reciprocal translocation carrier can have symptoms if one of the two breakpoints lies in a gene, disrupting its function. Figure 12.19 shows a father and son who have a reciprocal translocation between chromosomes 2 and 20 that causes a condition called Alagille syndrome. Apparently the exchange disrupts a gene on chromosome 20 that causes the condition, because families with the syndrome have deletions in this region of the chromosome.

figure 12.19

A translocation syndrome. In one family with Alagille syndrome, a reciprocal translocation occurs between chromosomes 2 and 20. Distinctive facial features are part of the condition.

Alagille syndrome produces a characteristic face, absence of bile ducts in the liver, abnormalities of the eyes. The father of the young man did not realize he had the syndrome until he had an affected child with a more severe case. For example, **a child was born with a reciprocal translocation between chromosomes 12 and 22**. The distinctive symptoms **of language delay, mild mental retardation, loose joints**, minor facial anomalies, and a narrow, long head matched those of another chromosome problem, called 22q13.3 deletion syndrome,caused absence of a gene (called ProSAP2) that forms scaffolds for neurons in the cerebral cortex and cerebellum, the translocation cuts this gene, abolishing its function just as a deletion does

A translocation carrier produces some **unbalanced gametes—sperm or oocytes that have deletions or duplications of some of the genes in the translocated chromosomes.** The resulting phenotype depends upon the particular genes that the chromosomal rearrangement disrupts or is extra or missing.

A genetic counselor becomes alerted to the possibility of a translocation if a family has had multiple birth defects and spontaneous abortions. People with translocations have been very valuable to medical

genetics research. Studies to identify disease-causing genes often began with people whose translocations pointed the way toward a gene of interest.

Inversions

An inverted sequence of chromosome bands indicates that part of the chromosome has flipped around. **Empirical studies** show that 5 to 10 percent of inversions cause health problems, probably because they **disrupt important genes**. Sometimes inversions are detected in fetal chromosomes, but physician do not know whether symptoms will be associated with the problem. The parents can have their chromosomes checked. If one of them has the inversion and is healthy, then the child will most likely not have symptoms related to the inversion. If neither parent has the inversion, then the anomaly arose in a gamete, and predicting effects may depend on knowing which genes are involved.

Like a translocation carrier, an adult can be **heterozygous** for an inversion and healthy, but have reproductive problems. One woman had an inversion in the **long arm of chromosome 15** and had two **spontaneous abortions**, **two stillbirths**, and **two children with multiple problems** who died within days of birth. She did eventually give birth to a healthy child.

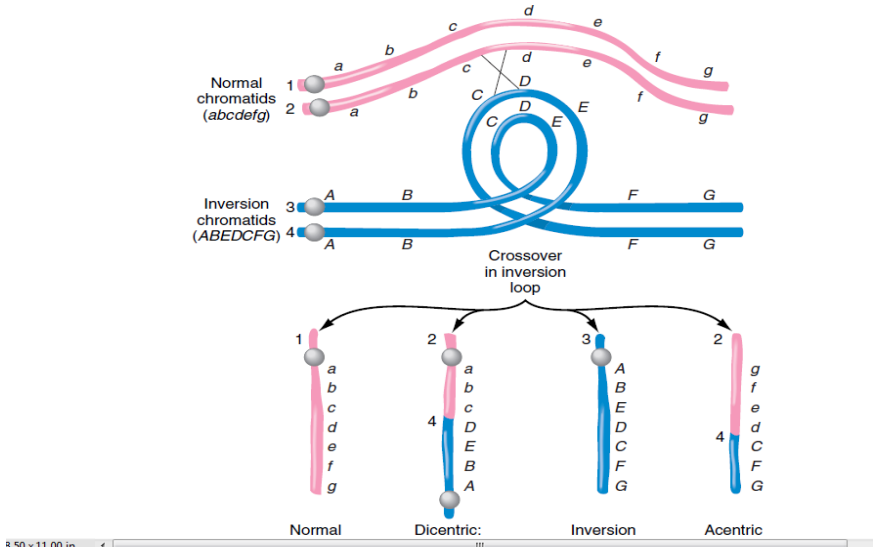
How did the inversion cause these problems?

Inversions with such devastating effects can be **traced to meiosis**, when a crossover occurs between the inverted chromosome segment and the non inverted homolog. To allow the genes to align, the inverted chromosome forms a loop. When crossovers occur within the loop, in the resulting recombinant chromosomes, some areas are duplicated and some deleted. In inversions, the **abnormal chromosomes result from the chromatids that crossed over.**

Two types of inversions are **distinguished** **by the position of the centromere** to the inverted section.

A **paracentric inversion** does **not include the centromere**. A single crossover within the inverted segment gives rise to two very **abnormal chromosomes**. The other **two chromosomes are normal.** One abnormal

chromosome retains both centromeres and is said to be dicentric. When the cell divides, the two centromeres are pulled to opposite sides of the cell, and the chromosome breaks, leaving pieces with extra or missing segments. The second type of **abnormal chromosome resulting from a crossover** within an inversion loop is a small piece that **lacks a centromere**, called an acentric fragment. When the cell divides, the fragment is lost.



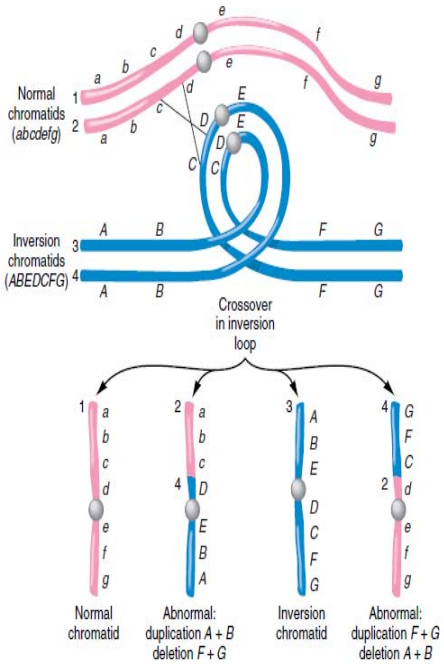
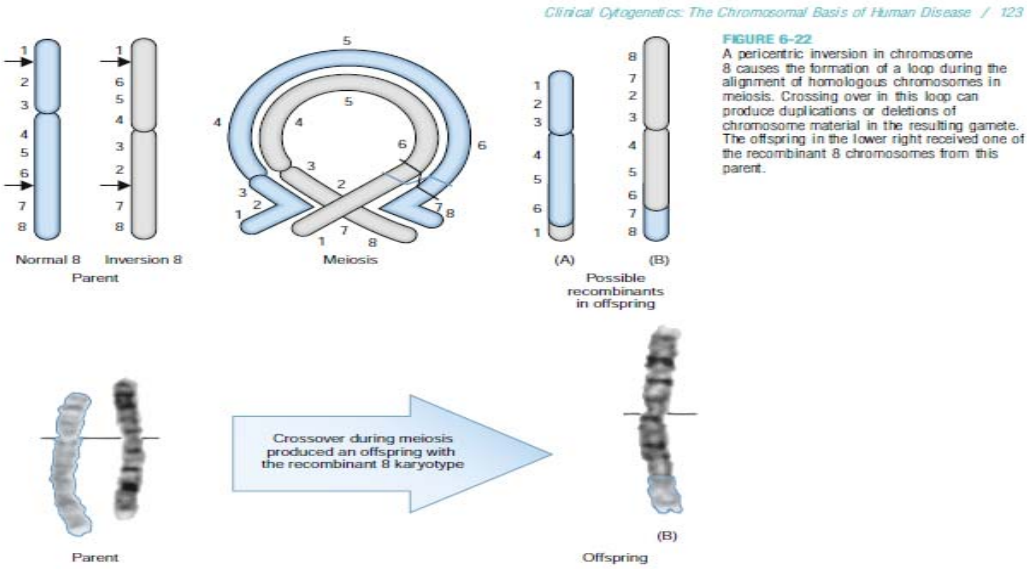


figure 12.21

Pericentric inversion. A pericentric inversion in one chromosome leads to two chromatids with duplications and deletions, one normal chromatid, and one inverted chromatid if a crossover occurs.

A pericentric inversion includes the **centromere within the loop**. A crossover in it produces two chromosomes that **have duplications and deletions,** but one centromere each (figure 12.21).

An example of a pericentric inversion on chromosome (46,XX,inv[8]). About 5% of the offspring of persons who carry this inversion receive a deletion or duplication of the distal portion of 8q. This combination results in the recombinant 8 syndrome, which is characterized by mental retardation, heart defects, seizures, and a characteristic facial appearance.



Clinical Cytogenetics: The Chromosomal Basis of Human Disease / 123

FIGURE 6-22
A pericentric inversion in chromosome 8 causes the formation of a loop during the alignment of homologous chromosomes in meiosis. Crossing over in this loop can produce duplications or deletions of chromosome material in the resulting gamete. The offspring in the lower right received one of the recombinant 8 chromosomes from this parent.

Isochromosomes

Another meiotic error that leads to unbalanced genetic material is the formation of an isochromosome, which is a chromosome that has identical arms. This occurs when, during division, the centromeres part in the wrong plane Isochromosomes are known for chromosomes 12 and 21 and for the long arms of the X and the Y. Some women with Turner syndrome do not have the more common monosomy XO, but an isochromosome in which the long arm of the X chromosome is duplicated but the short arm is absent.

Most isochromosomes observed in live births involve the X chromosome, and babies with isochromosome Xq (46,X,i[Xq]) usually have features of Turner syndrome.
Isochromosome 18q, which produces an extra copy of the long arm of chromosome 18, has been observed in infants with Edwards syndrome.

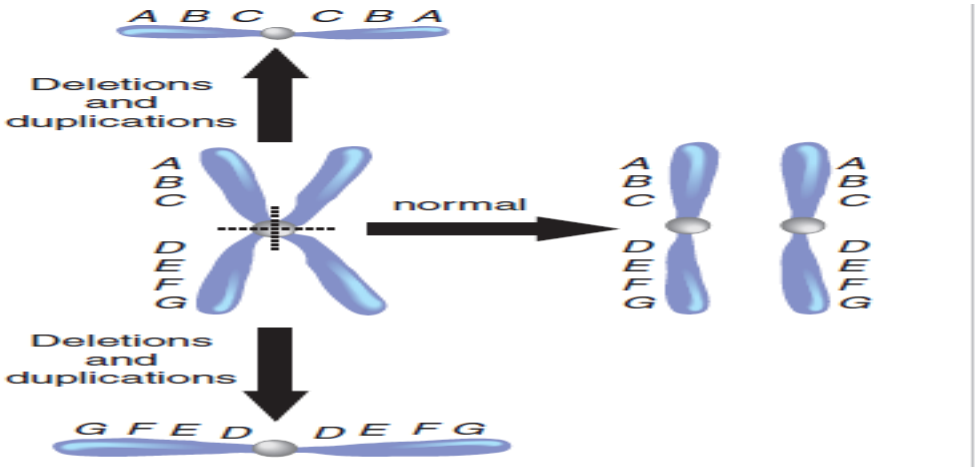


figure 12.22

Isochromosomes have identical arms. They form when chromatids divide along the wrong plane (in this depiction, horizontally rather than vertically).

Ring chromosomes

Chromosomes shaped like rings form in 1 out of 25,000 conceptions. Ring chromosomes may arise when telomeres are ***lost;*** leaving sticky ends that close up. Exposure to irradiation can form rings. They can involve any chromosome, and may occur in addition to a full diploid chromosome set, or account for one of the 46 chromosomes.

The karyotype of a female with a ring X chromosome is 46,X,r(X). If the ring chromosome includes a centromere, it can often proceed through cell division, but its structure can create difficulties. Ring chromosomes are often lost, resulting in monosomy for the chromosome in at least some cells (i.e., mosaicism for the ring chromosome may be seen). Ring chromosomes have been described in at least one case for each of the human autosomes.

Ring chromosomes can produce symptoms when they add genetic material. For example, a small ring chromosome of DNA from chromosome 22 causes cat eye syndrome.

A study from Japan examined 15 women who have a ring X chromosome in some cells, in addition to the other two complete X chromosomes. Nine of the women were mentally retarded, and in all of them, the ring X chromosome did not include the XIST site.

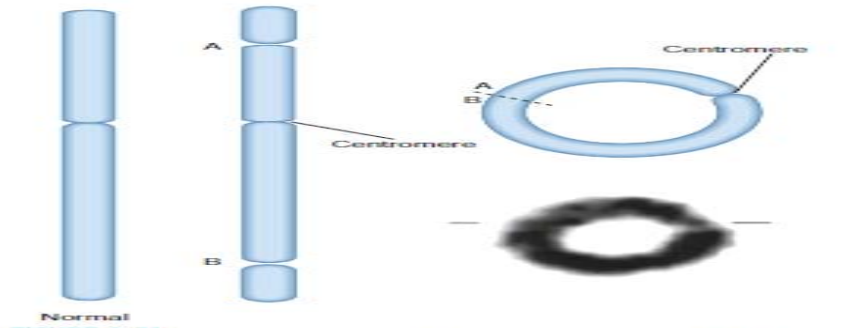


FIGURE 6-21
Both tips of a chromosome can be lost, leaving sticky ends that attach to each other, forming a ring chromosome. A chromosome 12 ring is shown here.

Chromosome rearrangements can cause deletions and duplications. In a Robertsonian translocation, the long arms of two different acrocentric chromosomes join. In a reciprocal translocation, two chromosomes exchange parts. If a translocation lead to a deletion or duplication, or disrupts a gene, symptoms may result. Gene duplications and deletions can occur in **isochromosomes** and **ring chromosomes**, and when crossovers involve **inversions**. An isochromosome has two identical arms, thereby introducing duplications and deletions, and ring chromosomes can add genetic material.

Isochromosomes have identical arms. They form when chromatids divide along the wrong plane (in this depiction, horizontally rather than vertically).

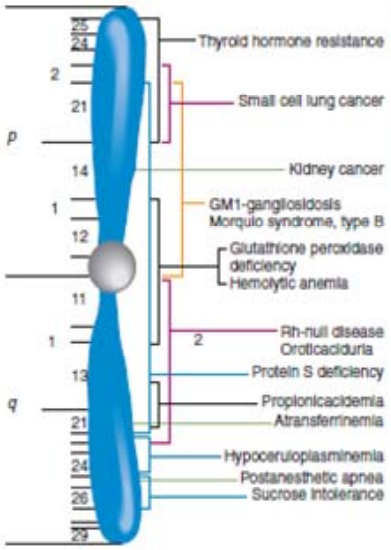


figure 12.10

Ideogram. An ideogram is a schematic chromosome map. It indicates chromosome arm (*p* or *q*), major regions delineated by banding patterns, and the loci of known genes. This is a partial map of human chromosome 3.