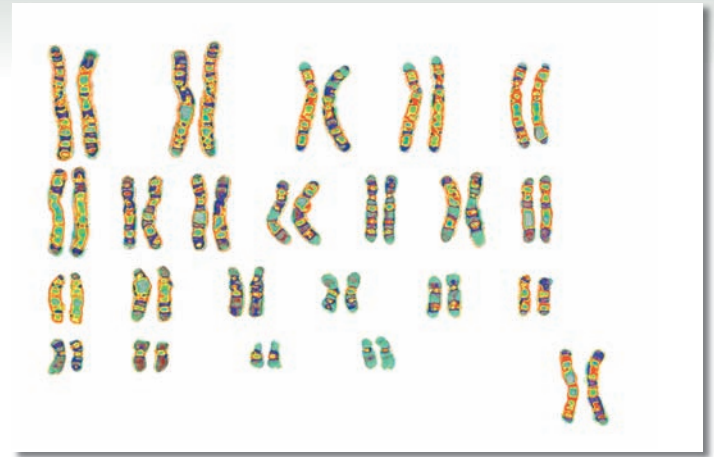


CHAPTER OUTLINE

- 8.1 Variation in Chromosome Structure
- 8.2 Variation in Chromosome Number
- 8.3 Natural and Experimental Ways to Produce Variations in Chromosome Number



The chromosome composition of humans. Somatic cells in humans contain 46 chromosomes, which come in 23 pairs.

8

VARIATION IN CHROMOSOME STRUCTURE AND NUMBER

The term **genetic variation** refers to genetic differences among members of the same species or between different species. Throughout Chapters 2 to 7, we have focused primarily on variation in specific genes, which is called **allelic variation**. In Chapter 8, our emphasis will shift to larger types of genetic changes that affect the structure or number of eukaryotic chromosomes. These larger alterations may affect the expression of many genes and thereby influence phenotypes. Variation in chromosome structure and number are of great importance in the field of genetics because they are critical in the evolution of new species and have widespread medical relevance. In addition, agricultural geneticists have discovered that such variation can lead to the development of new crops, which may be quite profitable.

In the first section of Chapter 8, we begin by exploring how the structure of a eukaryotic chromosome can be modified, either by altering the total amount of genetic material or by rearranging the order of genes along a chromosome. Such changes may often be detected microscopically. The rest of the chapter is concerned with changes in the total number of chromosomes. We will explore how variation in chromosome number occurs and consider examples in which it has significant phenotypic consequences. We will also examine how changes in chromosome number can be induced

through experimental treatments and how these approaches have applications in research and agriculture.

8.1 VARIATION IN CHROMOSOME STRUCTURE

Chromosomes in the nuclei of eukaryotic cells contain long, linear DNA molecules that carry hundreds or even thousands of genes. In this section, we will explore how the structure of a chromosome can be changed. As you will see, segments of a chromosome can be lost, duplicated, or rearranged in a new way. We will also examine the cellular mechanisms that underlie these changes in chromosome structure. Unusual events during meiosis may affect how altered chromosomes are transmitted from parents to offspring. Also, we will consider many examples in which chromosomal alterations affect an organism's phenotype.

Natural Variation Exists in Chromosome Structure

To appreciate changes in chromosome structure, researchers need to have a reference point for a normal set of chromosomes. To determine what the normal chromosomes of a species look like, a **cytogeneticist**—a scientist who studies chromosomes microscopically—examines the chromosomes from several members of

a given species. In most cases, two phenotypically normal individuals of the same species have the same number and types of chromosomes.

To determine the chromosomal composition of a species, the chromosomes in actively dividing cells are examined microscopically. **Figure 8.1a** shows micrographs of chromosomes from

three species: a human, a fruit fly, and a corn plant. As seen here, a human has 46 chromosomes (23 pairs), a fruit fly has 8 chromosomes (4 pairs), and corn has 20 chromosomes (10 pairs). Except for the sex chromosomes, which differ between males and females, most members of the same species have very similar chromosomes. For example, the overwhelming majority of

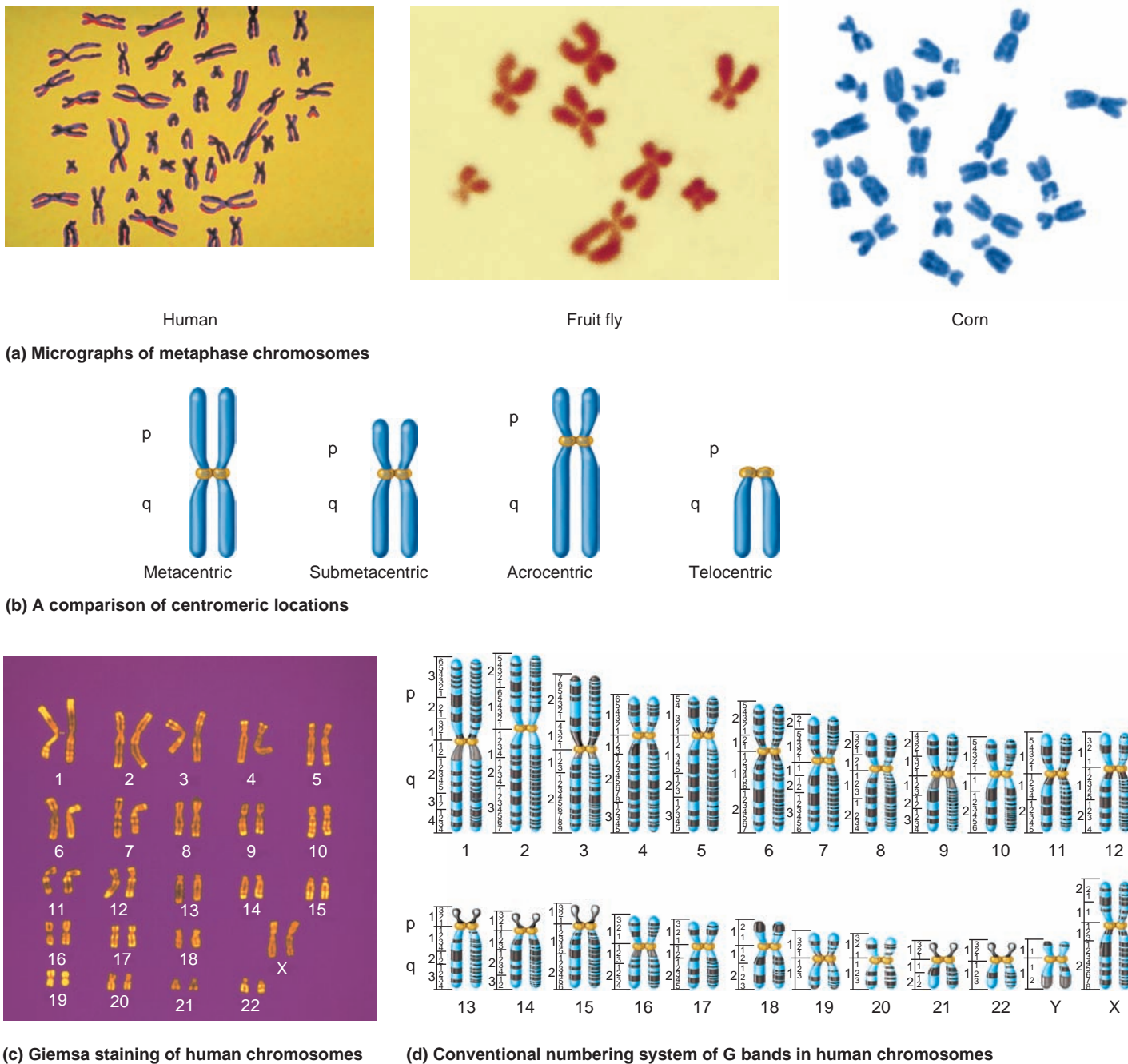


FIGURE 8.1 Features of normal chromosomes. (a) Micrographs of chromosomes from a human, a fruit fly, and corn. (b) A comparison of centromeric locations. Centromeres can be metacentric, submetacentric, acrocentric (near one end), or telocentric (at the end). (c) Human chromosomes that have been stained with Giemsa. (d) The conventional numbering of bands in Giemsa-stained human chromosomes. The numbering is divided into broad regions, which then are subdivided into smaller regions. The numbers increase as the region gets farther away from the centromere. For example, if you take a look at the left chromatid of chromosome 1, the uppermost dark band is at a location designated p35. The banding patterns of chromatids change as the chromatids condense. The left chromatid of each pair of sister chromatids shows the banding pattern of a chromatid in metaphase, and the right side shows the banding pattern as it would appear in prometaphase. Note: In prometaphase, the chromatids are more extended than in metaphase.

people have 46 chromosomes in their somatic cells. By comparison, the chromosomal compositions of distantly related species, such as humans and fruit flies, may be very different. A total of 46 chromosomes is normal for humans, whereas 8 chromosomes is the norm for fruit flies.

Cytogeneticists have various ways to classify and identify chromosomes. The three most commonly used features are location of the centromere, size, and banding patterns that are revealed when the chromosomes are treated with stains. As shown in **Figure 8.1b**, chromosomes are classified as **metacentric** (in which the centromere is near the middle), **submetacentric** (in which the centromere is slightly off center), **acrocentric** (in which the centromere is significantly off center but not at the end), and **telocentric** (in which the centromere is at one end). Because the centromere is never exactly in the center of a chromosome, each chromosome has a short arm and a long arm. For human chromosomes, the short arm is designated with the letter p (for the French, *petite*), and the long arm is designated with the letter q. In the case of telocentric chromosomes, the short arm may be nearly nonexistent.

Figure 8.1c shows a human karyotype. The procedure for making a karyotype is described in Chapter 3 (see Figure 3.2). A **karyotype** is a micrograph in which all of the chromosomes within a single cell have been arranged in a standard fashion. When preparing a karyotype, the chromosomes are aligned with the short arms on top and the long arms on the bottom. By convention, the chromosomes are numbered roughly according to their size, with the largest chromosomes having the smallest numbers. For example, human chromosomes 1, 2, and 3 are relatively large, whereas 21 and 22 are the two smallest. An exception to the numbering system involves the sex chromosomes, which are designated with letters (for humans, X and Y).

Because different chromosomes often have similar sizes and centromeric locations (e.g., compare human chromosomes 8, 9, and 10), geneticists must use additional methods to accurately identify each type of chromosome within a karyotype. For detailed identification, chromosomes are treated with stains to produce characteristic banding patterns. Several different staining procedures are used by cytogeneticists to identify specific chromosomes. An example is **G banding**, which is shown in Figure 8.1c. In this procedure, chromosomes are treated with mild heat or with proteolytic enzymes that partially digest chromosomal proteins. When exposed to the dye called Giemsa, named after its inventor Gustav Giemsa, some chromosomal regions bind the dye heavily and produce a dark band. In other regions, the stain hardly binds at all and a light band results. Though the mechanism of staining is not completely understood, the dark bands are thought to represent regions that are more tightly compacted. As shown in Figure 8.1c and d, the alternating pattern of G bands is a unique feature for each chromosome.

In the case of human chromosomes, approximately 300 G bands can usually be distinguished during metaphase. A larger number of G bands (in the range of 800) can be observed in prometaphase chromosomes because they are more extended than metaphase chromosomes. **Figure 8.1d** shows the conventional numbering system that is used to designate G bands along a set of human chromosomes. The left chromatid in each pair of sister chromatids shows the expected banding pattern during

metaphase, and the right chromatid shows the banding pattern as it would appear during prometaphase.

Why is the banding pattern of eukaryotic chromosomes useful? First, when stained, individual chromosomes can be distinguished from each other, even if they have similar sizes and centromeric locations. For example, compare the differences in banding patterns between human chromosomes 8 and 9 (Figure 8.1d). These differences permit us to distinguish these two chromosomes even though their sizes and centromeric locations are very similar. Banding patterns are also used to detect changes in chromosome structure. As discussed next, chromosomal rearrangements or changes in the total amount of genetic material are more easily detected in banded chromosomes. Also, chromosome banding can be used to assess evolutionary relationships between species. Research studies have shown that the similarity of chromosome banding patterns is a good measure of genetic relatedness.

Changes in Chromosome Structure Include Deletions, Duplications, Inversions, and Translocations

With an understanding that chromosomes typically come in a variety of shapes and sizes, let's consider how the structures of normal chromosomes can be modified. In some cases, the total amount of genetic material within a single chromosome can be increased or decreased significantly. Alternatively, the genetic material in one or more chromosomes may be rearranged without affecting the total amount of material. As shown in **Figure 8.2**, these mutations are categorized as deletions, duplications, inversions, and translocations.

Deletions and duplications are changes in the total amount of genetic material within a single chromosome. In Figure 8.2, human chromosomes are labeled according to their normal G-banding patterns. When a **deletion** occurs, a segment of chromosomal material is missing. In other words, the affected chromosome is deficient in a significant amount of genetic material. The term **deficiency** is also used to describe a missing region of a chromosome. In contrast, a **duplication** occurs when a section of a chromosome is repeated compared with the normal parent chromosome.

Inversions and translocations are chromosomal rearrangements. An **inversion** involves a change in the direction of the genetic material along a single chromosome. For example, in Figure 8.2c, a segment of one chromosome has been inverted, so the order of four G bands is opposite to that of the parent chromosome. A **translocation** occurs when one segment of a chromosome becomes attached to a different chromosome or to a different part of the same chromosome. A **simple translocation** occurs when a single piece of chromosome is attached to another chromosome. In a **reciprocal translocation**, two different types of chromosomes exchange pieces, thereby producing two abnormal chromosomes carrying translocations.

Figure 8.2 illustrates the common ways that the structure of chromosomes can be altered. Throughout the rest of this section, we will consider how these changes occur, how the changes are detected experimentally, and how they affect the phenotypes of the individuals who inherit them.

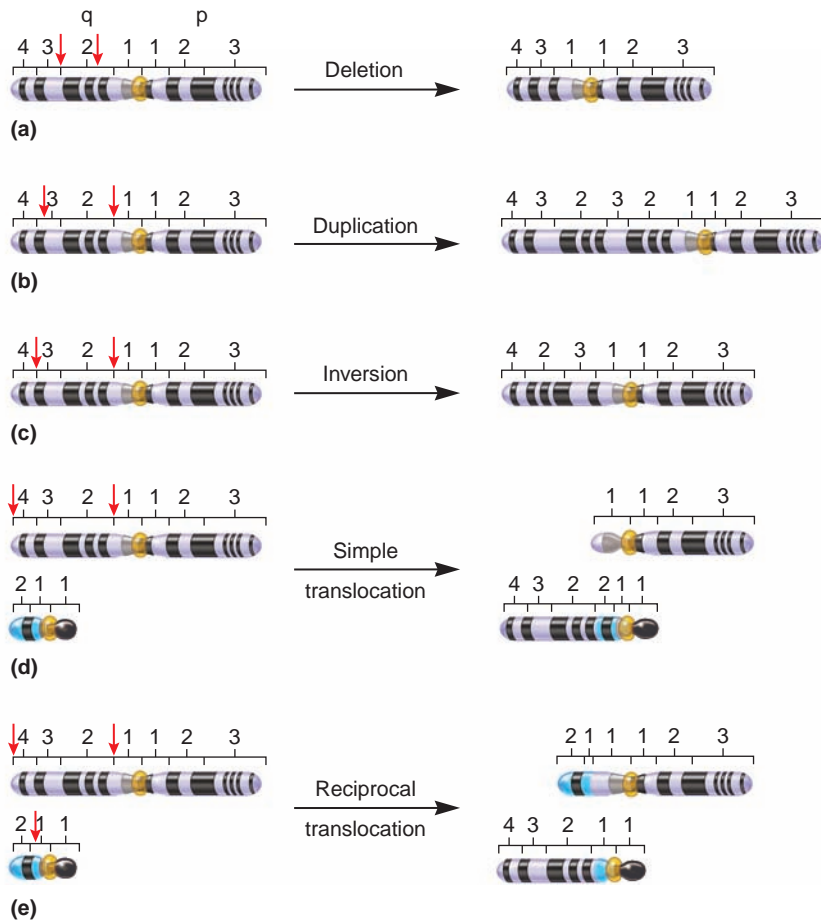


FIGURE 8.2 Types of changes in chromosome

structure. The large chromosome shown throughout is human chromosome 1. The smaller chromosome seen in (d) and (e) is human chromosome 21. (a) A deletion occurs that removes a large portion of the q2 region, indicated by the red arrows. (b) A duplication occurs that doubles the q2–q3 region. (c) An inversion occurs that inverts the q2–q3 region. (d) The q2–q4 region of chromosome 1 is translocated to chromosome 21. A region of a chromosome cannot be inserted directly to the tip of another chromosome because telomeres at the tips of chromosomes prevent such an event. In this example, a small piece at the end of chromosome 21 must be removed for the q2–q4 region of chromosome 1 to be attached to chromosome 21. (e) The q2–q4 region of chromosome 1 is exchanged with most of the q1–q2 region of chromosome 21.

The Loss of Genetic Material in a Deletion Tends to Be Detrimental to an Organism

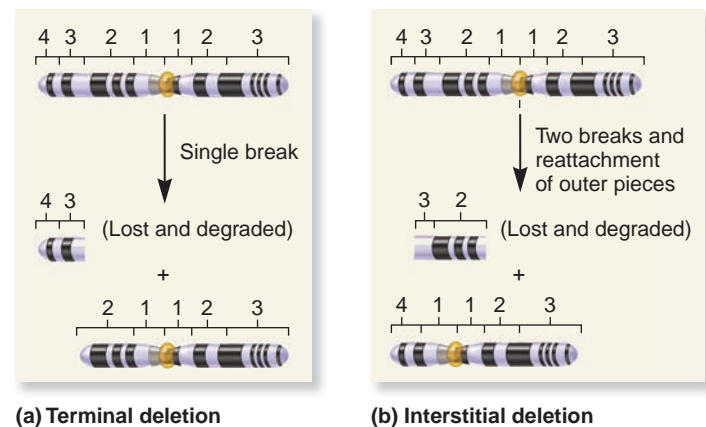
A chromosomal deletion occurs when a chromosome breaks in one or more places and a fragment of the chromosome is lost. In **Figure 8.3a**, a normal chromosome has broken into two separate pieces. The piece without the centromere is lost and degraded. This event produces a chromosome with a **terminal deletion**. In **Figure 8.3b**, a chromosome has broken in two places to produce three chromosomal fragments. The central fragment is lost, and the two outer pieces reattach to each other. This process

has created a chromosome with an **interstitial deletion**. Deletions can also be created when recombination takes place at incorrect locations between two homologous chromosomes. The products of this type of aberrant recombination event are one chromosome with a deletion and another chromosome with a duplication. This process is examined later in this chapter.

The phenotypic consequences of a chromosomal deletion depend on the size of the deletion and whether it includes genes or portions of genes that are vital to the development of the organism. When deletions have a phenotypic effect, they are usually detrimental. Larger deletions tend to be more harmful because more genes are missing. Many examples are known in which deletions have significant phenotypic influences. For example, a human genetic disease known as cri-du-chat, or Lejeune, syndrome is caused by a deletion in a segment of the short arm of human chromosome 5 (**Figure 8.4a**). Individuals who carry a single copy of this abnormal chromosome along with a normal chromosome 5 display an array of abnormalities including mental deficiencies, unique facial anomalies, and an unusual catlike cry in infancy, which is the meaning of the French name for the syndrome (**Figure 8.4b**). Two other human genetic diseases, Angelman syndrome and Prader-Willi syndrome, which are described in Chapter 5, are due to a deletion in chromosome 15.

Duplications Tend to Be Less Harmful Than Deletions

Duplications result in extra genetic material. They are usually caused by abnormal events during recombination. Under normal circumstances, crossing over occurs at analogous sites between homologous chromosomes. On rare occasions, a crossover may occur



(a) Terminal deletion

(b) Interstitial deletion

FIGURE 8.3 Production of terminal and interstitial deletions. This illustration shows the production of deletions in human chromosome 1.

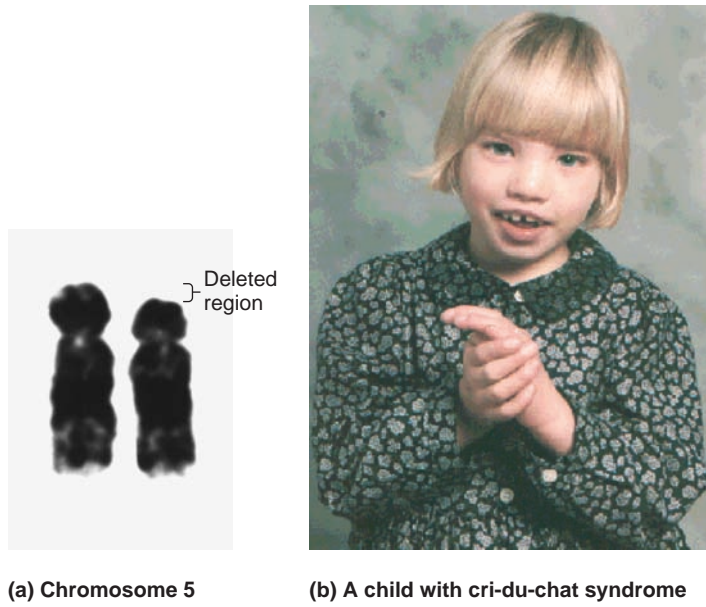


FIGURE 8.4 Cri-du-chat syndrome. (a) Chromosome 5 from the karyotype of an individual with this disorder. A section of the short arm of chromosome 5 is missing. (b) An affected individual.

Genes → Traits Compared with an individual who has two copies of each gene on chromosome 5, an individual with cri-du-chat syndrome has only one copy of the genes that are located within the missing segment. This genetic imbalance (one versus two copies of many genes on chromosome 5) causes the phenotypic characteristics of this disorder, which include a catlike cry in infancy, short stature, characteristic facial anomalies (e.g., a triangular face, almond-shaped eyes, broad nasal bridge, and low-set ears), and microencephaly (a smaller than normal brain).

at misaligned sites on the homologs (**Figure 8.5**). What causes the misalignment? In some cases, a chromosome may carry two or more homologous segments of DNA that have identical or similar sequences. These are called **repetitive sequences** because they occur multiple times. An example of repetitive sequences are transposable elements, which are described in Chapter 17. In **Figure 8.5**, the repetitive sequence on the right (in the upper chromatid) has lined up with the repetitive sequence on the left (in the lower chromatid). A crossover then occurs. This is called **nonallelic homologous recombination** because it has occurred at homologous sites (i.e., repetitive sequences), but the alleles of neighboring genes are not properly aligned. The result is that one chromatid has an internal duplication and another chromatid has a deletion. In **Figure 8.5**, the chromosome with the extra genetic material carries a **gene duplication**, because the number of copies of gene *C* has been increased from one to two. In most cases, gene duplications happen as rare, sporadic events during the evolution of species. Later in this section, we will consider how multiple copies of genes can evolve into a family of genes with specialized functions.

Like deletions, the phenotypic consequences of duplications tend to be correlated with size. Duplications are more likely to have phenotypic effects if they involve a large piece of the chromosome. In general, small duplications are less likely to have harmful effects than are deletions of comparable size. This observation suggests that having only one copy of a gene is more

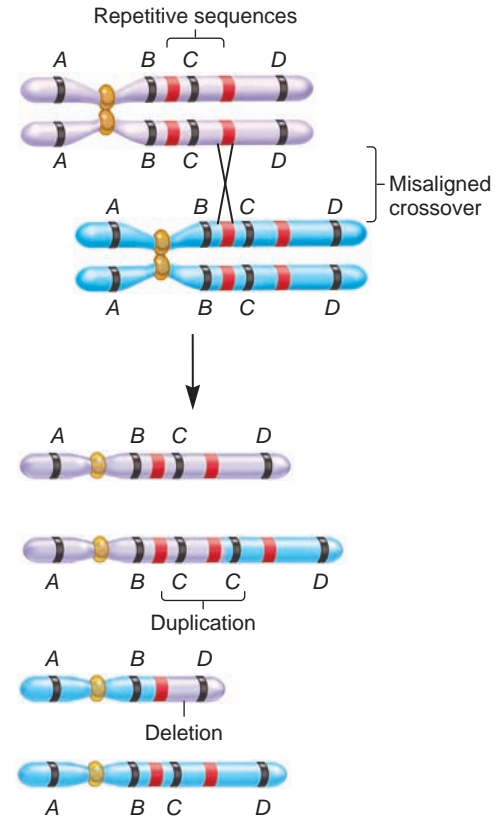


FIGURE 8.5 Nonallelic homologous recombination, leading to a duplication and a deletion. A repetitive sequence, shown in red, has promoted the misalignment of homologous chromosomes. A crossover has occurred at sites between genes *C* and *D* in one chromatid and between genes *B* and *C* in another chromatid. After crossing over is completed, one chromatid contains a duplication, and the other contains a deletion.

harmful than having three copies. In humans, relatively few well-defined syndromes are caused by small chromosomal duplications. An example is Charcot-Marie-Tooth disease (type 1A), a peripheral neuropathy characterized by numbness in the hands and feet that is caused by a small duplication on the short arm of chromosome 17.

Duplications Provide Additional Material for Gene Evolution, Sometimes Leading to the Formation of Gene Families

In contrast to the gene duplication that causes Charcot-Marie-Tooth disease, the majority of small chromosomal duplications have no phenotypic effect. Nevertheless, they are vitally important because they provide raw material for the addition of more genes into a species' chromosomes. Over the course of many generations, this can lead to the formation of a **gene family** consisting of two or more genes that are similar to each other. As shown in **Figure 8.6**, the members of a gene family are derived from the same ancestral gene. Over time, two copies of an ancestral gene can accumulate different mutations. Therefore, after many generations, the two genes will be similar but not identical. During

evolution, this type of event can occur several times, creating a family of many similar genes.

When two or more genes are derived from a single ancestral gene, the genes are said to be **homologous**. Homologous genes within a single species are called **paralogs** and constitute a gene family. A well-studied example of a gene family is shown

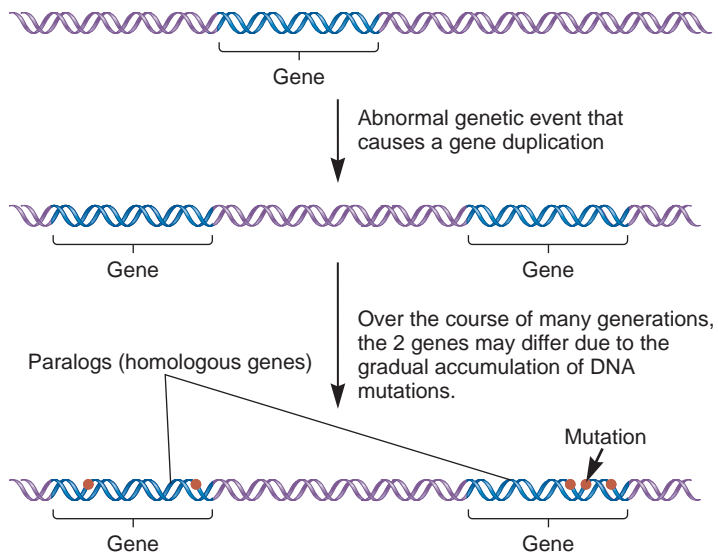


FIGURE 8.6 Gene duplication and the evolution of paralogs. An abnormal crossover event like the one described in Figure 8.5 leads to a gene duplication. Over time, each gene accumulates different mutations.

in **Figure 8.7**, which illustrates the evolution of the globin gene family found in humans. The globin genes encode polypeptides that are subunits of proteins that function in oxygen binding. For example, hemoglobin is a protein found in red blood cells; its function is to carry oxygen throughout the body. The globin gene family is composed of 14 paralogs that were originally derived from a single ancestral globin gene. According to an evolutionary analysis, the ancestral globin gene first duplicated about 500 million years ago and became separate genes encoding myoglobin and the hemoglobin group of genes. The primordial hemoglobin gene duplicated into an α -chain gene and a β -chain gene, which subsequently duplicated to produce several genes located on chromosomes 16 and 11, respectively. Currently, 14 globin genes are found on three different human chromosomes.

Why is it advantageous to have a family of globin genes? Although all globin polypeptides are subunits of proteins that play a role in oxygen binding, the accumulation of different mutations in the various family members has produced globins that are more specialized in their function. For example, myoglobin is better at binding and storing oxygen in muscle cells, and the hemoglobins are better at binding and transporting oxygen via the red blood cells. Also, different globin genes are expressed during different stages of human development. The ϵ - and ζ -globin genes are expressed very early in embryonic life, whereas the α -globin and γ -globin genes are expressed during the second and third trimesters of gestation. Following birth, the α -globin gene remains turned on, but the γ -globin genes are turned off and the β -globin gene is turned on. These differences in the expression of the globin genes reflect the differences in the oxygen transport needs of humans during the embryonic, fetal, and postpartum stages of life.

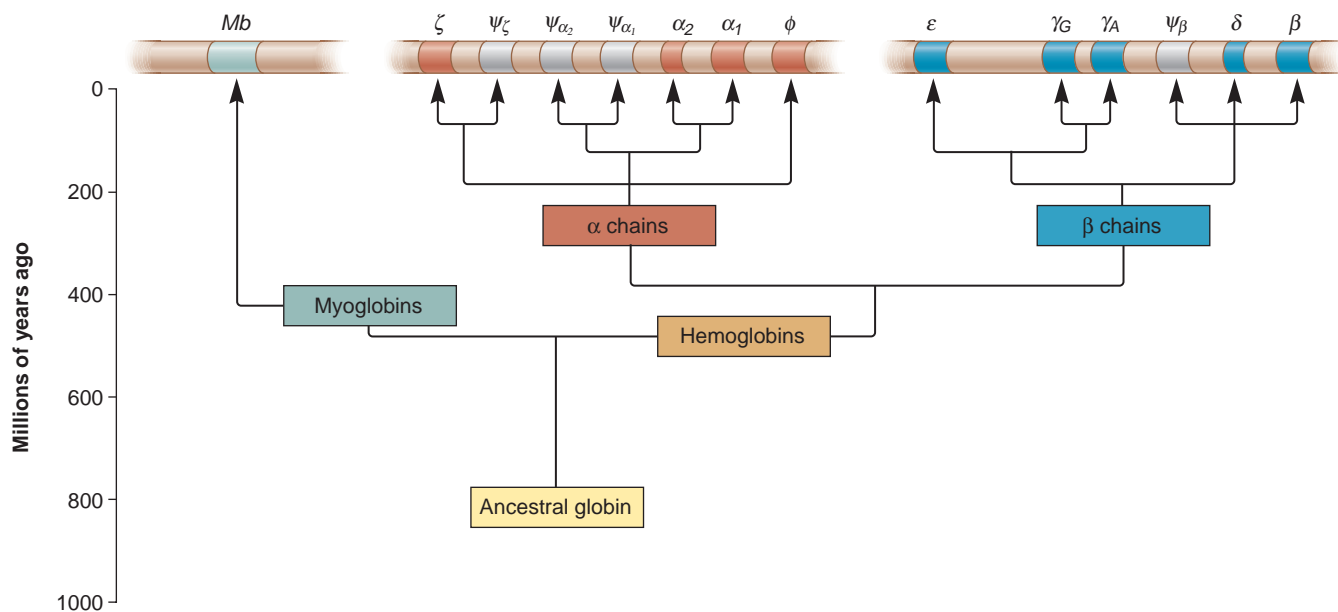


FIGURE 8.7 The evolution of the globin gene family in humans. The globin gene family evolved from a single ancestral globin gene. The first gene duplication produced two genes that accumulated mutations and became the genes encoding myoglobin (on chromosome 22) and the group of hemoglobins. The primordial hemoglobin gene then duplicated to produce several α -chain and β -chain genes, which are found on chromosomes 16 and 11, respectively. The four genes shown in gray are nonfunctional pseudogenes.

Copy Number Variation Is Relatively Common Among Members of the Same Species

The term **copy number variation (CNV)** refers to a type of structural variation in which a segment of DNA, which is 1000 bp or more in length, exhibits copy number differences among members of the same species. One possibility is that some members of a species may carry a chromosome that is missing a particular gene or part of a gene. Alternatively, a CNV may involve a duplication. For example, some members of a diploid species may have one copy of gene *A* on both homologs of a chromosome, and thereby have two copies of the gene (Figure 8.8). By comparison, other members of the same species might have one copy of gene *A* on a particular chromosome and two copies on its homolog for a total of three copies. The homolog with two copies of gene *A* is said to have undergone a **segmental duplication**.

In the past 10 years, researchers have discovered that copy number variation is relatively common in animal and plant species. Though the analysis of structural variation is a relatively new area of investigation, researchers estimate that between 1% and 10% of a genome may show CNV within a typical species of animal or plant.

Most CNV is inherited and has happened in the past, but it may also be caused by new mutations. A variety of mechanisms may bring about copy number variation. One common cause is nonallelic homologous recombination, which was described earlier in Figure 8.5. This type of event can produce a chromosome with a duplication or deletion, and thereby alter the copy number of genes. Researchers also speculate that the proliferation of transposable elements, which are described in Chapter 17, may increase the copy number of DNA segments. A third mechanism that underlies CNV may involve errors in DNA replication, which is described in Chapter 11.

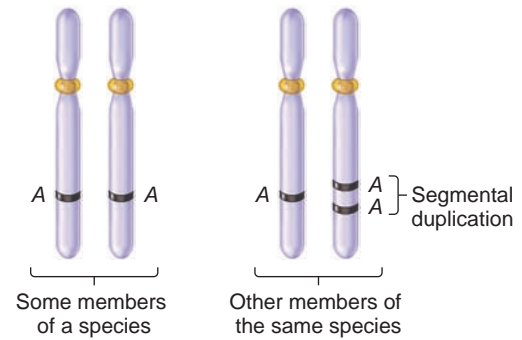


FIGURE 8.8 An example of copy number variation. On the left, some individuals have two copies of gene *A*, whereas other individuals, shown on the right, have three copies.

What are the phenotypic consequences of CNV? In many cases, CNV has no obvious phenotypic consequences. However, recent medical research is revealing that some CNV is associated with specific human diseases. For example, particular types of CNV are associated with schizophrenia, autism, and certain forms of learning disabilities. In addition, CNV may affect susceptibility to infectious diseases. An example is the human *CCL3* gene that encodes a chemokine protein, which is involved in immunity. In human populations, the copy number of this gene varies from 1 to 6. In people infected with HIV (human immunodeficiency virus), copy number variation of *CCL3* may affect the progression of AIDS (acquired immune deficiency syndrome). Individuals with a higher copy number of *CCL3* produce more chemokine protein and often show a slower advancement of AIDS. Finally, another reason why researchers are interested in copy number variation is its relationship to cancer, which is described next.

EXPERIMENT 8A

Comparative Genomic Hybridization Is Used to Detect Chromosome Deletions and Duplications

As we have seen, chromosome deletions and duplications may influence the phenotypes of individuals who inherit them. One very important reason why researchers have become interested in these types of chromosomal changes is related to cancer. As discussed in Chapter 22, chromosomal deletions and duplications have been associated with many types of human cancers. Though such changes may be detectable by traditional chromosomal staining and karyotyping methods, small deletions and duplications may be difficult to detect in this manner. Fortunately, researchers have been able to develop more sensitive methods for identifying changes in chromosome structure.

In 1992, Anne Kallioniemi, Daniel Pinkel, and colleagues devised a method called **comparative genomic hybridization (CGH)**. This technique is largely used to determine if cancer cells have changes in chromosome structure, such as deletions or duplications. To begin this procedure, DNA is isolated from a test sample, which in this case was a sample of breast cancer cells, and also from a normal reference sample (Figure 8.9). The DNA from

the breast cancer cells was used as a template to make green fluorescent DNA, and the DNA from normal cells was used to make red fluorescent DNA. These green or red DNA molecules averaged 800 bp in length and were made from sites that were scattered all along each chromosome. The green and red DNA molecules were then denatured by heat treatment. Equal amounts of the two fluorescently labeled DNA samples were mixed together and applied to normal metaphase chromosomes in which the DNA had also been denatured. Because the fluorescently labeled DNA fragments and the metaphase chromosomes had both been denatured, the fluorescently labeled DNA strands can bind to complementary regions on the metaphase chromosomes. This process is called **hybridization** because the DNA from one sample (a green or red DNA strand) forms a double-stranded region with a DNA strand from another sample (an unlabeled metaphase chromosome). Following hybridization, the metaphase chromosomes were visualized using a fluorescence microscope, and the images were analyzed by a computer that can determine the relative intensities of green and red fluorescence. What are the expected results? If a chromosomal region in the breast cancer cells and the normal cells are present in the same amount, the

ratio between green and red fluorescence should be 1. If a chromosomal region is deleted in the breast cancer cell line, the ratio will be less than 1, or if a region is duplicated, it will be greater than 1.

THE GOAL

Deletions or duplications in cancer cells can be detected by comparing the ability of fluorescently labeled DNA from cancer cells and normal cells to bind (hybridize) to normal metaphase chromosomes.

ACHIEVING THE GOAL — FIGURE 8.9 The use of comparative genomic hybridization to detect deletions and duplications in cancer cells.

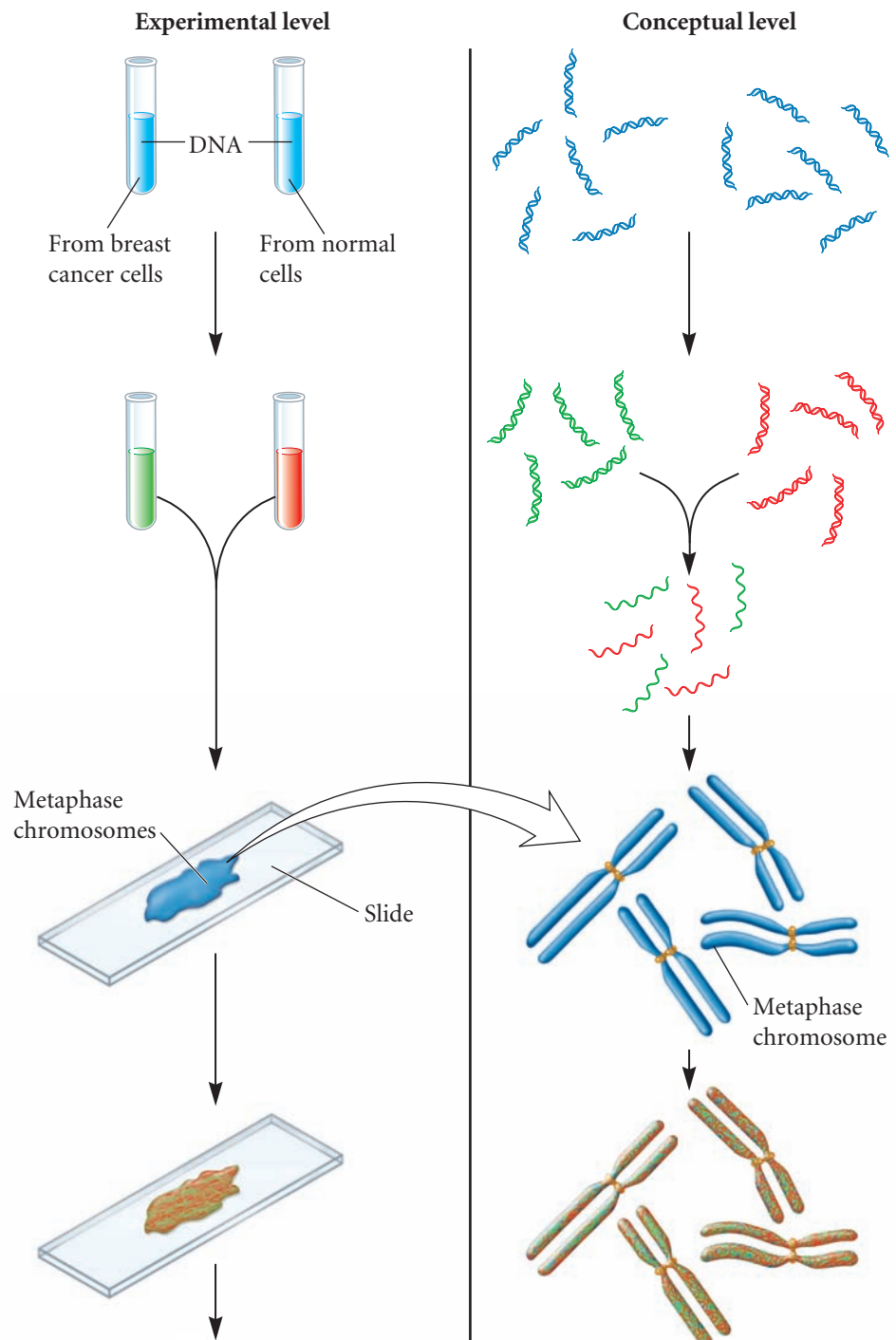
Starting materials: Breast cancer cells and normal cells.

1. Isolate DNA from human breast cancer cells and normal cells. This involved breaking open the cells and isolating the DNA by chromatography. (See Appendix for description of chromatography.)

2. Label the breast cancer DNA with a green fluorescent molecule and the normal DNA with a red fluorescent molecule. This was done by using the DNA from step 1 as a template, and incorporating fluorescently labeled nucleotides into newly made DNA strands.

3. The DNA strands were then denatured by heat treatment. Mix together equal amounts of fluorescently labeled DNA and add it to a preparation of metaphase chromosomes from white blood cells. The procedure for preparing metaphase chromosomes is described in Figure 3.2. The metaphase chromosomes were also denatured.

4. Allow the fluorescently labeled DNA to hybridize to the metaphase chromosomes.

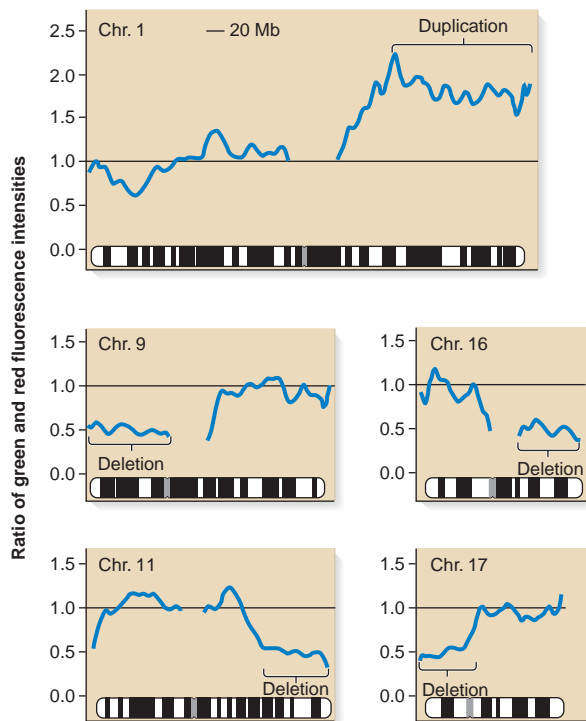


5. Visualize the chromosomes with a fluorescence microscope. Analyze the amount of green and red fluorescence along each chromosome with a computer.



Deletions in the chromosomes of cancer cells show a green to red ratio of less than 1, whereas chromosome duplications show a ratio greater than 1.

THE DATA



Note: Unlabeled repetitive DNA was also included in this experiment to decrease the level of nonspecific, background labeling. This repetitive DNA also prevents labeling near the centromere. As seen in the data, regions in the chromosomes where the curves are missing are due to the presence of highly repetitive sequences near the centromere. Data from A. Kallioniemi, O. P. Kallioniemi, D. Sudar, et al. (1992) Comparative genomic hybridization for molecular cytogenetic analysis of solid tumors. *Science* 258, 818–821.

INTERPRETING THE DATA

The data of Figure 8.9 show the ratio of green (cancer DNA) to red (normal DNA) fluorescence along five different metaphase chromosomes. Chromosome 1 shows a large duplication, as indicated by the ratio of 2. One interpretation of this observation is that both copies of chromosome 1 carry a duplication. In comparison, chromosomes 9, 11, 16, and 17 have regions with a value of 0.5. This value indicates that one of the two chromosomes of these four types in the cancer cells carries a deletion, but the other chromosome does not. (A value of 0 would indicate both copies of a chromosome had deleted the same region.) Overall, these results illustrate how this technique can be used to map chromosomal duplications and deletions in cancer cells.

This method is named comparative genomic hybridization because a comparison is made between the ability of two DNA samples (cancer versus normal cells) to hybridize to an entire genome. In this case, the entire genome is in the form of metaphase chromosomes. As discussed in Chapter 20, the fluorescently labeled DNAs can be hybridized to a DNA microarray instead of metaphase chromosomes. This newer method, called array comparative genomic hybridization (aCGH), is gaining widespread use in the analysis of cancer cells.

A self-help quiz involving this experiment can be found at www.mhhe.com/brookergenetics4e.

Inversions Often Occur Without Phenotypic Consequences

We now turn our attention to inversions, changes in chromosome structure that involve a rearrangement in the genetic material. A chromosome with an inversion contains a segment that has been flipped to the opposite direction. Geneticists classify inversions according to the location of the centromere. If the centromere lies within the inverted region of the chromosome, the inverted region is known as a **pericentric inversion** (Figure 8.10b). Alternatively, if the centromere is found outside the inverted region, the inverted region is called a **paracentric inversion** (Figure 8.10c).

When a chromosome contains an inversion, the total amount of genetic material remains the same as in a normal chromosome. Therefore, the great majority of inversions do not have any phenotypic consequences. In rare cases, however, an inversion can alter the phenotype of an individual. Whether or not this occurs is related to the boundaries of the inverted segment. When an inversion occurs, the chromosome is broken in two places, and the center piece flips around to produce the inversion. If either breakpoint occurs within a vital gene, the function of the gene is expected to be disrupted, possibly producing a phenotypic effect. For example, some people with hemophilia (type A)

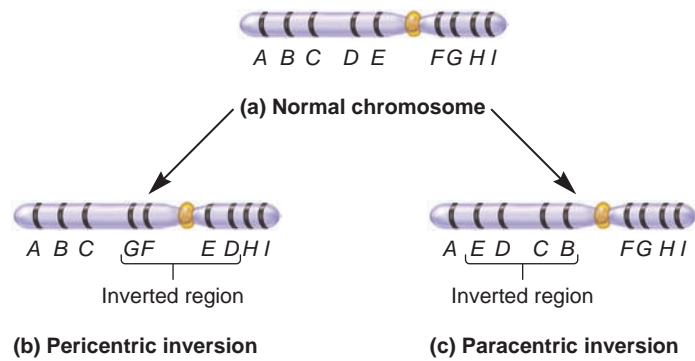


FIGURE 8.10 Types of inversions. (a) Depicts a normal chromosome with the genes ordered from A through I. A pericentric inversion (b) includes the centromere, whereas a paracentric inversion (c) does not.

have inherited an X-linked inversion in which the breakpoint has inactivated the gene for factor VIII—a blood-clotting protein. In other cases, an inversion (or translocation) may reposition a gene on a chromosome in a way that alters its normal level of expression. This is a type of **position effect**—a change in phenotype that occurs when the position of a gene changes from one chromosomal site to a different location. This topic is also discussed in Chapter 16 (see Figures 16.2 and 16.3).

Because inversions seem like an unusual genetic phenomenon, it is perhaps surprising that they are found in human populations in significant numbers. About 2% of the human population carries inversions that are detectable with a light microscope. In most cases, such individuals are phenotypically normal and live their lives without knowing they carry an inversion. In a few cases, however, an individual with an inversion chromosome may produce offspring with phenotypic abnormalities. This event may prompt a physician to request a microscopic examination of the individual's chromosomes. In this way, phenotypically normal individuals may discover they have a chromosome with an inversion. Next, we will examine how an individual carrying an inversion may produce offspring with phenotypic abnormalities.

Inversion Heterozygotes May Produce Abnormal Chromosomes Due to Crossing Over

An individual carrying one copy of a normal chromosome and one copy of an inverted chromosome is known as an **inversion heterozygote**. Such an individual, though possibly phenotypically normal, may have a high probability of producing haploid cells that are abnormal in their total genetic content.

The underlying cause of gamete abnormality is the phenomenon of crossing over within the inverted region. During meiosis I, pairs of homologous sister chromatids synapse with each other. **Figure 8.11** illustrates how this occurs in an inversion heterozygote. For the normal chromosome and inversion chromosome to synapse properly, an **inversion loop** must form to permit the homologous genes on both chromosomes to align next to each other despite the inverted sequence. If a crossover occurs within the inversion loop, highly abnormal chromosomes

are produced. A crossover is more likely to occur in this region if the inversion is large. Therefore, individuals carrying large inversions are more likely to produce abnormal gametes.

The consequences of this type of crossover depend on whether the inversion is pericentric or paracentric. **Figure 8.11a** describes a crossover in the inversion loop when one of the homologs has a pericentric inversion in which the centromere lies within the inverted region of the chromosome. This event consists of a single crossover that involves only two of the four sister chromatids. Following the completion of meiosis, this single crossover yields two abnormal chromosomes. Both of these abnormal chromosomes have a segment that is deleted and a different segment that is duplicated. In this example, one of the abnormal chromosomes is missing genes H and I and has an extra copy of genes A, B, and C. The other abnormal chromosome has the opposite situation; it is missing genes A, B, and C and has an extra copy of genes H and I. These abnormal chromosomes may result in gametes that are inviable. Alternatively, if these abnormal chromosomes are passed to offspring, they are likely to produce phenotypic abnormalities, depending on the amount and nature of the duplicated and deleted genetic material. A large deletion is likely to be lethal.

Figure 8.11b shows the outcome of a crossover involving a paracentric inversion in which the centromere lies outside the inverted region. This single crossover event produces a very strange outcome. One chromosome, called a **dicentric** chromosome, contains two centromeres. The region of the chromosome connecting the two centromeres is a **dicentric bridge**. The crossover also produces a piece of chromosome without any centromere—an **acentric fragment**, which is lost and degraded in subsequent cell divisions. The dicentric chromosome is a temporary condition. If the two centromeres try to move toward opposite poles during anaphase, the dicentric bridge will be forced to break at some random location. Therefore, the net result of this crossover is to produce one normal chromosome, one chromosome with an inversion, and two chromosomes that contain deletions. These two chromosomes with deletions result from the breakage of the dicentric chromosome. They are missing the genes that were located on the acentric fragment.

Translocations Involve Exchanges Between Different Chromosomes

Another type of chromosomal rearrangement is a translocation in which a piece from one chromosome is attached to another chromosome. Eukaryotic chromosomes have telomeres, which tend to prevent translocations from occurring. As described in Chapters 10 and 11, **telomeres**—specialized repeated sequences of DNA—are found at the ends of normal chromosomes. Telomeres allow cells to identify where a chromosome ends and prevent the attachment of chromosomal DNA to the natural ends of a chromosome.

If cells are exposed to agents that cause chromosomes to break, the broken ends lack telomeres and are said to be reactive—a reactive end readily binds to another reactive end. If a single chromosome break occurs, DNA repair enzymes will usually recognize the two reactive ends and join them back together;

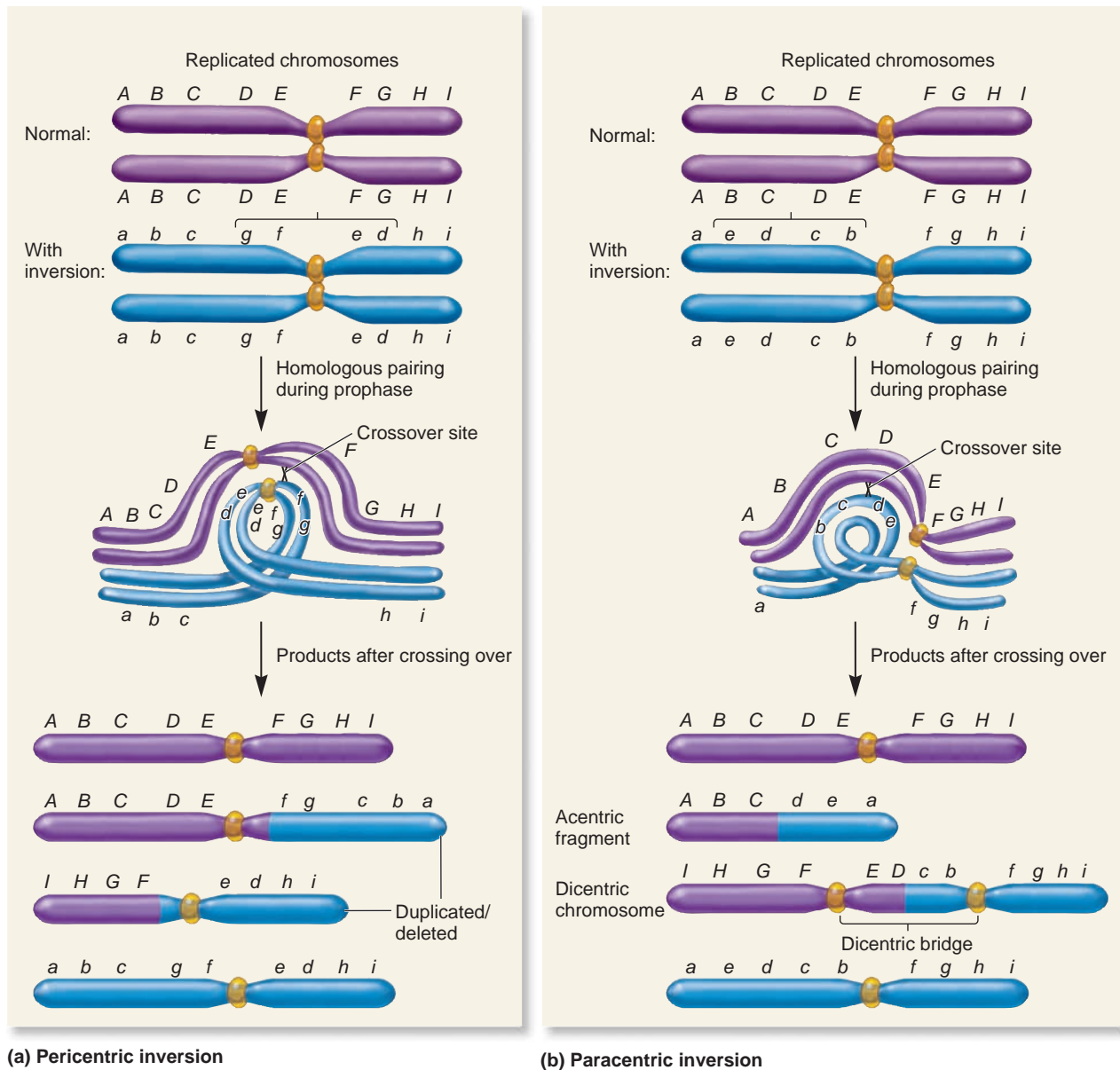


FIGURE 8.11 The consequences of crossing over in the inversion loop. (a) Crossover within a pericentric inversion. (b) Crossover within a paracentric inversion.

the chromosome is repaired properly. However, if multiple chromosomes are broken, the reactive ends may be joined incorrectly to produce abnormal chromosomes (Figure 8.12a). This is one mechanism that causes reciprocal translocations to occur.

A second mechanism that can cause a translocation is an abnormal crossover. As shown in Figure 8.12b, a reciprocal translocation can be produced when two nonhomologous chromosomes cross over. This type of rare aberrant event results in a rearrangement of the genetic material, though not a change in the total amount of genetic material.

The reciprocal translocations we have considered thus far are also called **balanced translocations** because the total amount of genetic material is not altered. Like inversions, balanced translocations usually occur without any phenotypic consequences because the individual has a normal amount of genetic

material. In a few cases, balanced translocations can result in position effects similar to those that can occur in inversions. In addition, carriers of a reciprocal translocation are at risk of having offspring with an **unbalanced translocation**, in which significant portions of genetic material are duplicated and/or deleted. Unbalanced translocations are generally associated with phenotypic abnormalities or even lethality.

Let's consider how a person with a balanced translocation may produce gametes and offspring with an unbalanced translocation. An inherited human syndrome known as familial Down syndrome provides an example. A person with a normal phenotype may have one copy of chromosome 14, one copy of chromosome 21, and one copy of a chromosome that is a fusion between chromosome 14 and 21 (Figure 8.13a). The individual has a normal phenotype because the total amount of genetic material is present

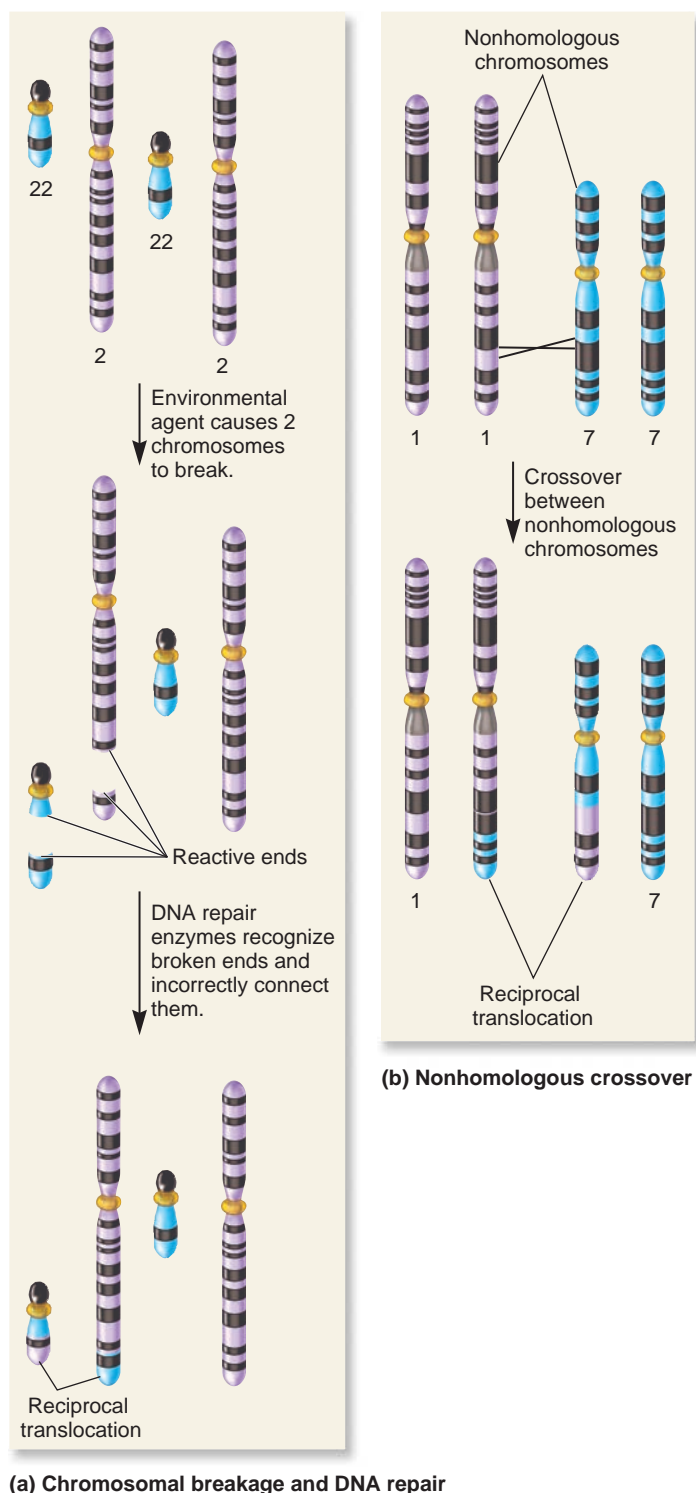


FIGURE 8.12 Two mechanisms that cause a reciprocal translocation. (a) When two different chromosomes break, the reactive ends are recognized by DNA repair enzymes, which attempt to reattach them. If two different chromosomes are broken at the same time, the incorrect ends may become attached to each other. (b) A nonhomologous crossover has occurred between chromosome 1 and chromosome 7. This crossover yields two chromosomes that carry translocations.

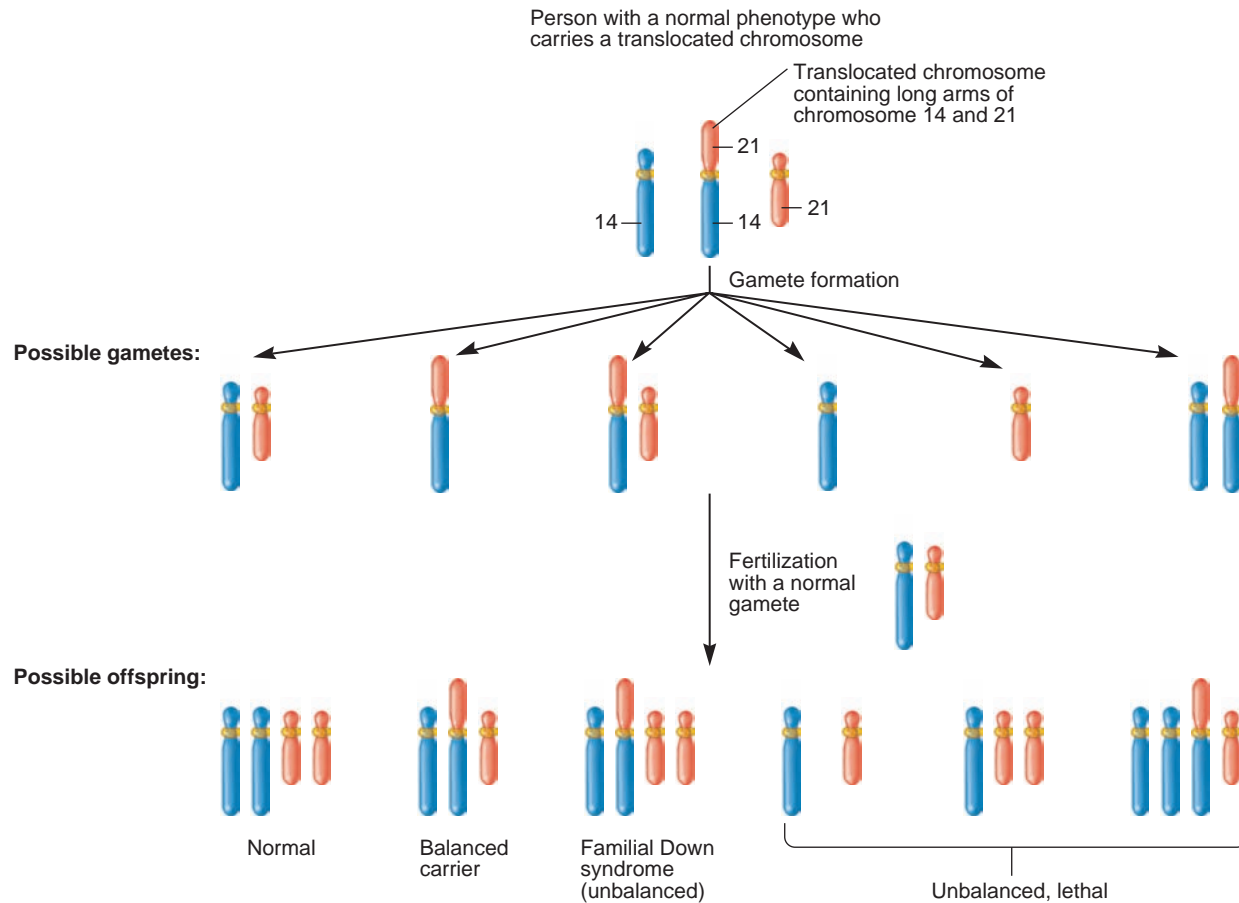
(with the exception of the short arms of these chromosomes that do not carry vital genetic material). During meiosis, these three types of chromosomes replicate and segregate from each other. However, because the three chromosomes cannot segregate evenly, six possible types of gametes may be produced. One gamete is normal, and one is a balanced carrier of a translocated chromosome. The four gametes to the right, however, are unbalanced, either containing too much or too little material from chromosome 14 or 21. The unbalanced gametes may be inviable, or they could combine with a normal gamete. The three offspring on the right will not survive. In comparison, the unbalanced gamete that carries chromosome 21 and the fused chromosome results in an offspring with familial Down syndrome (also see karyotype in **Figure 8.13b**). Such an offspring has three copies of the genes that are found on the long arm of chromosome 21. **Figure 8.13c** shows a person with this disorder. She has characteristics similar to those of an individual who has the more prevalent form of Down syndrome, which is due to three entire copies of chromosome 21. We will examine this common form of Down syndrome later in this chapter.

The abnormal chromosome that occurs in familial Down syndrome is an example of a **Robertsonian translocation**, named after William Robertson, who first described this type of fusion in grasshoppers. This type of translocation arises from breaks near the centromeres of two nonhomologous acrocentric chromosomes. In the example shown in **Figure 8.13**, the long arms of chromosomes 14 and 21 had fused, creating one large single chromosome; the two short arms are lost. This type of translocation between two nonhomologous acrocentric chromosomes is the most common type of chromosome rearrangement in humans, occurring at a frequency of approximately one in 900 live births. In humans, Robertsonian translocations involve only the acrocentric chromosomes 13, 14, 15, 21, and 22.

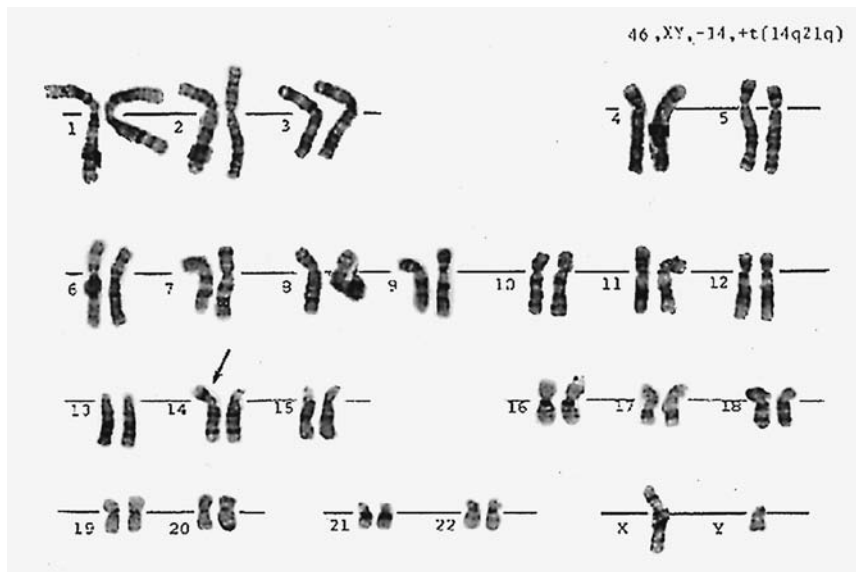
Individuals with Reciprocal Translocations May Produce Abnormal Gametes Due to the Segregation of Chromosomes

As we have seen, individuals who carry balanced translocations have a greater risk of producing gametes with unbalanced combinations of chromosomes. Whether or not this occurs depends on the segregation pattern during meiosis I (**Figure 8.14**). In this example, the parent carries a reciprocal translocation and is likely to be phenotypically normal. During meiosis, the homologous chromosomes attempt to synapse with each other. Because of the translocations, the pairing of homologous regions leads to the formation of an unusual structure that contains four pairs of sister chromatids (i.e., eight chromatids), termed a **translocation cross**.

To understand the segregation of translocated chromosomes, pay close attention to the centromeres, which are numbered in **Figure 8.14**. For these translocated chromosomes, the expected segregation pattern is governed by the centromeres. Each haploid gamete should receive one centromere located on chromosome 1 and one centromere located on chromosome 2. This can occur in two ways. One possibility is alternate segregation. As shown in



(a) Possible transmission patterns



(b) Karyotype of a male with familial Down syndrome



(c) Child with Down syndrome

FIGURE 8.13 Transmission of familial Down syndrome. (a) Potential transmission of familial Down syndrome. The individual with the chromosome composition shown at the top of this figure may produce a gamete carrying chromosome 21 and a fused chromosome containing the long arms of chromosomes 14 and 21. Such a gamete can give rise to an offspring with familial Down syndrome. (b) The karyotype of an individual with familial Down syndrome. This karyotype shows that the long arm of chromosome 21 has been translocated to chromosome 14 (see arrow). In addition, the individual also carries two normal copies of chromosome 21. (c) An individual with this disorder.

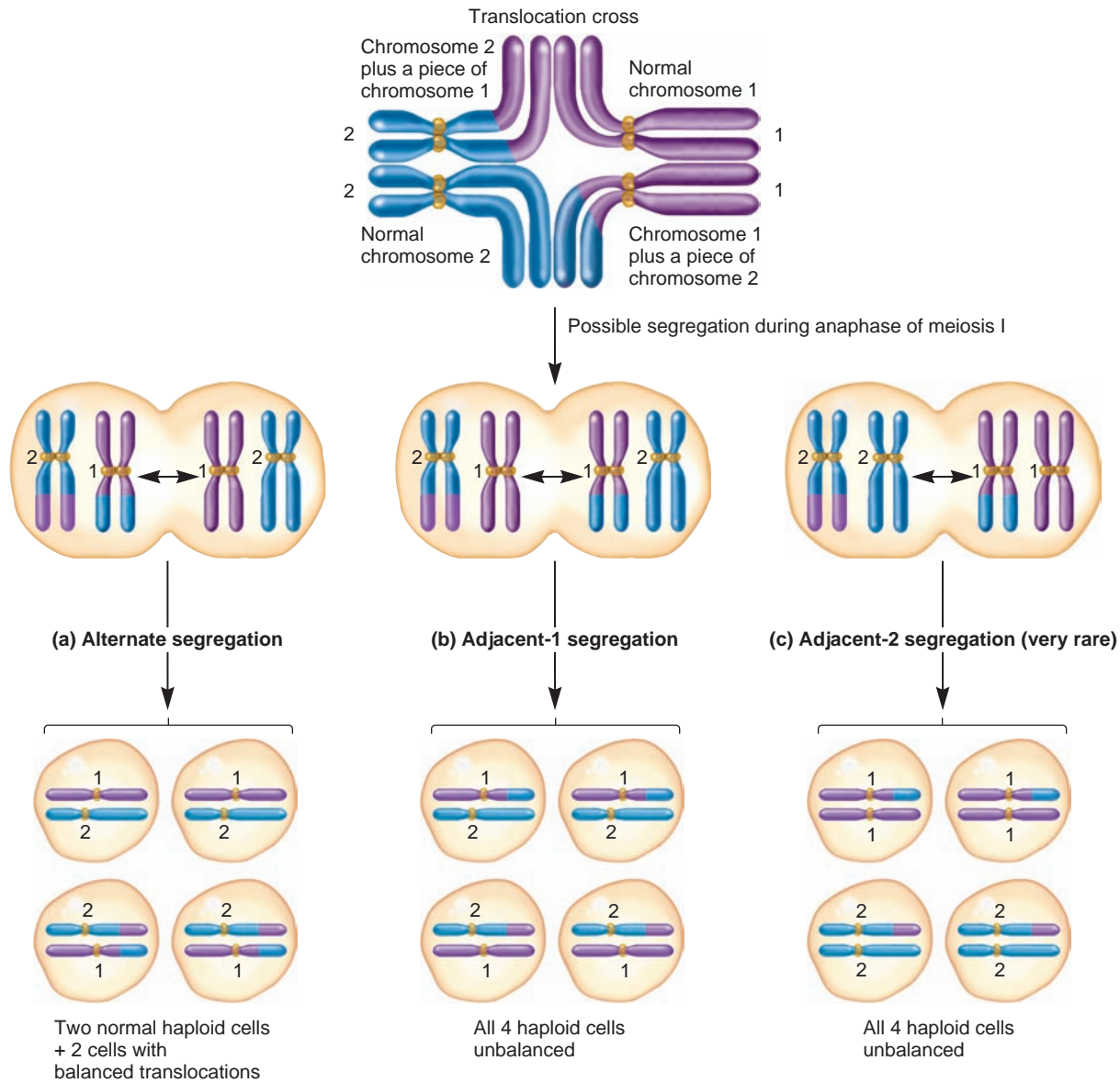


FIGURE 8.14 Meiotic segregation of a reciprocal translocation. Follow the numbered centromeres through each process. (a) Alternate segregation gives rise to balanced haploid cells, whereas (b) adjacent-1 and (c) adjacent-2 produce haploid cells with an unbalanced amount of genetic material.

Figure 8.14a, this occurs when the chromosomes diagonal to each other within the translocation cross sort into the same cell. One daughter cell receives two normal chromosomes, and the other cell gets two translocated chromosomes. Following meiosis II, four haploid cells are produced: two have normal chromosomes, and two have reciprocal (balanced) translocations.

Another possible segregation pattern is called adjacent-1 segregation (Figure 8.14b). This occurs when adjacent chromosomes (one of each type of centromere) segregate into the same cell. Following anaphase of meiosis I, each daughter cell receives one normal chromosome and one translocated chromosome. After meiosis II is completed, four haploid cells are produced, all of which are genetically unbalanced because part of one chromosome has been deleted and part of another has been duplicated. If these haploid cells give rise to gametes that unite with a

normal gamete, the zygote is expected to be abnormal genetically and possibly phenotypically.

On very rare occasions, adjacent-2 segregation can occur (Figure 8.14c). In this case, the centromeres do not segregate as they should. One daughter cell has received both copies of the centromere on chromosome 1; the other, both copies of the centromere on chromosome 2. This rare segregation pattern also yields four abnormal haploid cells that contain an unbalanced combination of chromosomes.

Alternate and adjacent-1 segregation patterns are the likely outcomes when an individual carries a reciprocal translocation. Depending on the sizes of the translocated segments, both types may be equally likely to occur. In many cases, the haploid cells from adjacent-1 segregation are not viable, thereby lowering the fertility of the parent. This condition is called **semisterility**.

8.2 VARIATION IN CHROMOSOME NUMBER

As we saw in Section 8.1, chromosome structure can be altered in a variety of ways. Likewise, the total number of chromosomes can vary. Eukaryotic species typically contain several chromosomes that are inherited as one or more sets. Variations in chromosome number can be categorized in two ways: variation in the number of sets of chromosomes and variation in the number of particular chromosomes within a set.

Organisms that are **euploid** have a chromosome number that is an exact multiple of a chromosome set. In *Drosophila melanogaster*, for example, a normal individual has 8 chromosomes. The species is diploid, having two sets of 4 chromosomes each (Figure 8.15a). A normal fruit fly is euploid because 8 chromosomes divided by 4 chromosomes per set equals two exact sets. On rare occasions, an abnormal fruit fly can be produced with 12 chromosomes, containing three sets of 4 chromosomes each. This alteration in euploidy produces a **triploid** fruit fly with 12 chromosomes. Such a fly is also euploid because it has exactly three sets of chromosomes. Organisms with three or more sets of chromosomes are also called **polyploid** (Figure 8.15b). Geneticists use the letter n to represent a set of chromosomes. A diploid organism is referred to as $2n$, a triploid organism as $3n$, a **tetraploid** organism as $4n$, and so on.

A second way in which chromosome number can vary is by **aneuploidy**. Such variation involves an alteration in the number of particular chromosomes, so the total number of chromosomes is not an exact multiple of a set. For example, an abnormal fruit fly could contain nine chromosomes instead of eight because it has three copies of chromosome 2 instead of the normal two copies (Figure 8.15c). Such an animal is said to have trisomy 2 or to be **trisomic**. Instead of being perfectly diploid ($2n$), a trisomic animal is $2n + 1$. By comparison, a fruit fly could be lacking a single chromosome, such as chromosome 1, and contain a total of seven chromosomes ($2n - 1$). This animal is **monosomic** and is described as having monosomy 1.

In this section, we will begin by considering several examples of aneuploidy. This is generally regarded as an abnormal condition that usually has a negative effect on phenotype. We will then examine euploid variation that occurs occasionally in animals and quite frequently in plants, and consider how it affects phenotypic variation.

Aneuploidy Causes an Imbalance in Gene Expression That Is Often Detrimental to the Phenotype of the Individual

The phenotype of every eukaryotic species is influenced by thousands of different genes. In humans, for example, a single set of chromosomes contains approximately 20,000 to 25,000 different

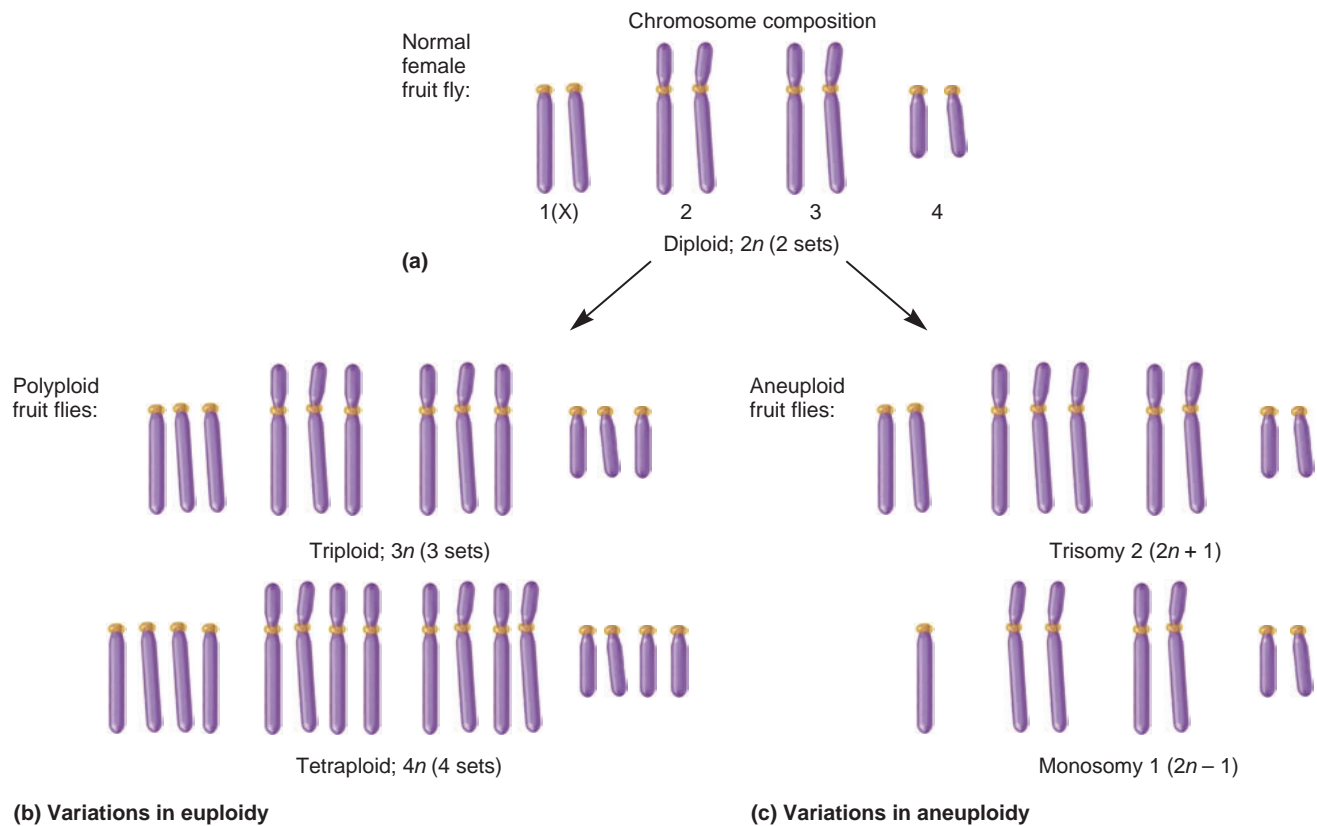


FIGURE 8.15 Types of variation in chromosome number. (a) Depicts the normal diploid number of chromosomes in *Drosophila*. (b) Examples of polyploidy. (c) Examples of aneuploidy.

genes. To produce a phenotypically normal individual, intricate coordination has to occur in the expression of thousands of genes. In the case of humans and other diploid species, evolution has resulted in a developmental process that works correctly when somatic cells have two copies of each chromosome. In other words, when a human is diploid, the balance of gene expression among many different genes usually produces a person with a normal phenotype.

Aneuploidy commonly causes an abnormal phenotype. To understand why, let's consider the relationship between gene expression and chromosome number in a species that has three pairs of chromosomes (Figure 8.16). The level of gene expression is influenced by the number of genes per cell. Compared with a diploid cell, if a gene is carried on a chromosome that is present

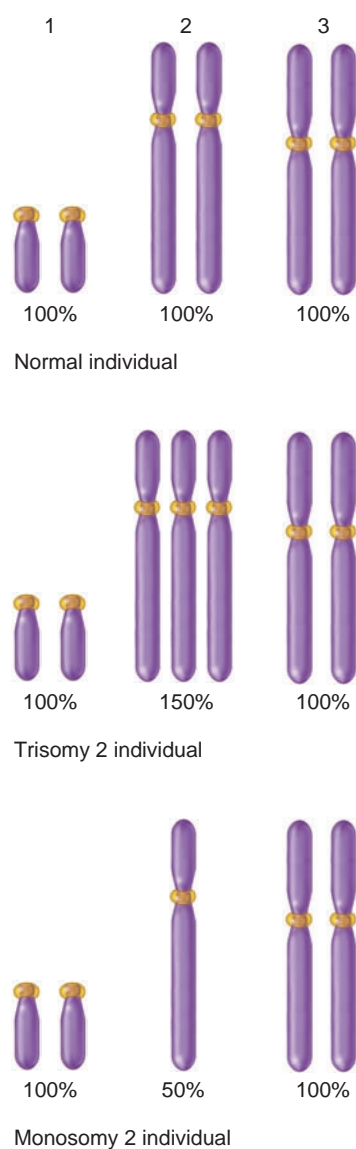


FIGURE 8.16 Imbalance of gene products in trisomic and monosomic individuals. Aneuploidy of chromosome 2 (i.e., trisomy and monosomy) leads to an imbalance in the amount of gene products from chromosome 2 compared with the amounts from chromosomes 1 and 3.

in three copies instead of two, more of the gene product is typically made. For example, a gene present in three copies instead of two may produce 150% of the gene product, though that number may vary due to effects of gene regulation. Alternatively, if only one copy of that gene is present due to a missing chromosome, less of the gene product is usually made, perhaps only 50%. Therefore, in trisomic and monosomic individuals, an imbalance occurs between the level of gene expression on the chromosomes found in pairs versus the one type that is not.

At first glance, the difference in gene expression between euploid and aneuploid individuals may not seem terribly dramatic. Keep in mind, however, that a eukaryotic chromosome carries hundreds or even thousands of different genes. Therefore, when an organism is trisomic or monosomic, many gene products occur in excessive or deficient amounts. This imbalance among many genes appears to underlie the abnormal phenotypic effects that aneuploidy frequently causes. In most cases, these effects are detrimental and produce an individual that is less likely to survive than a euploid individual.

Aneuploidy in Humans Causes Abnormal Phenotypes

A key reason why geneticists are so interested in aneuploidy is its relationship to certain inherited disorders in humans. Even though most people are born with a normal number of chromosomes (i.e., 46), alterations in chromosome number occur fairly frequently during gamete formation. About 5% to 10% of all fertilized human eggs result in an embryo with an abnormality in chromosome number! In most cases, these abnormal embryos do not develop properly and result in a spontaneous abortion very early in pregnancy. Approximately 50% of all spontaneous abortions are due to alterations in chromosome number.

In some cases, an abnormality in chromosome number produces an offspring that survives to birth or longer. Several human disorders involve abnormalities in chromosome number. The most common are trisomies of chromosomes 13, 18, or 21, and abnormalities in the number of the sex chromosomes (Table 8.1). Most of the known trisomies involve chromosomes that are relatively small—chromosome 13, 18, or 21—and carry fewer genes compared to larger chromosomes. Trisomies of the other human autosomes and monosomies of all autosomes are presumed to produce a lethal phenotype, and many have been found in spontaneously aborted embryos and fetuses. For example, all possible human trisomies have been found in spontaneously aborted embryos except trisomy 1. It is believed that trisomy 1 is lethal at such an early stage that it prevents the successful implantation of the embryo. Variation in the number of X chromosomes, unlike that of other large chromosomes, is often nonlethal. The survival of trisomy X individuals may be explained by X inactivation, which is described in Chapter 5. In an individual with more than one X chromosome, all additional X chromosomes are converted to Barr bodies in the somatic cells of adult tissues. In an individual with trisomy X, for example, two out of three X chromosomes are converted to inactive Barr bodies. Unlike the level of expression for autosomal genes, the normal level

TABLE 8.1

Aneuploid Conditions in Humans

Condition	Frequency	Syndrome	Characteristics
Autosomal			
Trisomy 13	1/15,000	Patau	Mental and physical deficiencies, wide variety of defects in organs, large triangular nose, early death
Trisomy 18	1/6000	Edward	Mental and physical deficiencies, facial abnormalities, extreme muscle tone, early death
Trisomy 21	1/800	Down	Mental deficiencies, abnormal pattern of palm creases, slanted eyes, flattened face, short stature
Sex Chromosomal			
XXY	1/1000 (males)	Klinefelter	Sexual immaturity (no sperm), breast swelling
YY	1/1000 (males)	Jacobs	Tall and thin
XXX	1/1500 (females)	Triple X	Tall and thin, menstrual irregularity
X0	1/5000 (females)	Turner	Short stature, webbed neck, sexually undeveloped

of expression for X-linked genes is from a single X chromosome. In other words, the correct level of mammalian gene expression results from two copies of each autosomal gene and one copy of each X-linked gene. This explains how the expression of X-linked genes in males (XY) can be maintained at the same levels as in females (XX). It may also explain why trisomy X is not a lethal condition. The phenotypic effects noted in Table 8.1 involving sex chromosomal abnormalities may be due to the expression of X-linked genes prior to embryonic X inactivation or to the expression of genes on the inactivated X chromosome. As described in Chapter 5, pseudoautosomal genes and some other genes on the inactivated X chromosome are expressed in humans. Having one or three copies of the sex chromosomes results in an under- or overexpression of these X-linked genes, respectively.

Human abnormalities in chromosome number are influenced by the age of the parents. Older parents are more likely to produce children with abnormalities in chromosome number. Down syndrome provides an example. The common form of this disorder is caused by the inheritance of three copies of chromosome 21. The incidence of Down syndrome rises with the age of either parent. In males, however, the rise occurs relatively late in life, usually past the age when most men have children. By comparison, the likelihood of having a child with Down syndrome rises dramatically during a woman's reproductive age (Figure 8.17). This syndrome was first described by the English physician John Langdon Down in 1866. The association between maternal age and Down syndrome was later discovered by L. S. Penrose in 1933, even before the chromosomal basis for the disorder was

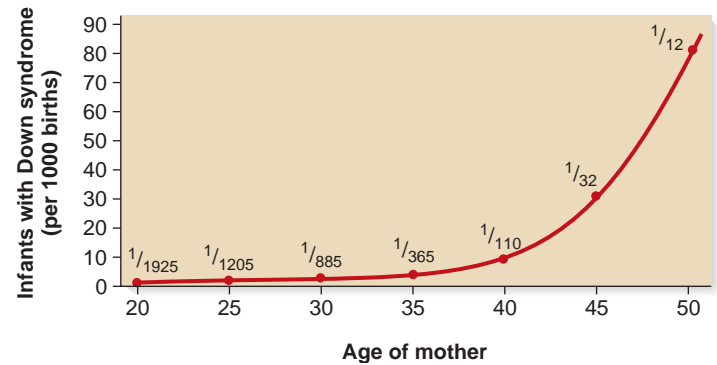


FIGURE 8.17 The incidence of Down syndrome births according to the age of the mother. The y-axis shows the number of infants born with Down syndrome per 1000 live births, and the x-axis plots the age of the mother at the time of birth. The data points indicate the fraction of live offspring born with Down syndrome.

identified by the French scientist Jérôme Lejeune in 1959. Down syndrome is most commonly caused by **nondisjunction**, which means that the chromosomes do not segregate properly. (Nondisjunction is discussed later in this chapter.) In this case, nondisjunction of chromosome 21 most commonly occurs during meiosis I in the oocyte.

Different hypotheses have been proposed to explain the relationship between maternal age and Down syndrome. One popular idea suggests that it may be due to the age of the oocytes. Human primary oocytes are produced within the ovary of the female fetus prior to birth and are arrested at prophase of meiosis I and remain in this stage until the time of ovulation. Therefore, as a woman ages, her primary oocytes have been in prophase I for a progressively longer period of time. This added length of time may contribute to an increased frequency of nondisjunction. About 5% of the time, Down syndrome is due to an extra paternal chromosome. Prenatal tests can determine if a fetus has Down syndrome and some other genetic abnormalities. The topic of genetic testing is discussed in Chapter 22.

Variations in Euploidy Occur Naturally in a Few Animal Species

We now turn our attention to changes in the number of sets of chromosomes, referred to as variations in euploidy. Most species of animals are diploid. In some cases, changes in euploidy are not well tolerated. For example, polyploidy in mammals is generally a lethal condition. However, many examples of naturally occurring variations in euploidy occur. In **haplodiploid** species, which include many species of bees, wasps, and ants, one of the sexes is haploid, usually the male, and the other is diploid. For example, male bees, which are called drones, contain a single set of chromosomes. They are produced from unfertilized eggs. By comparison, female bees are produced from fertilized eggs and are diploid.

Many examples of vertebrate polyploid animals have been discovered. Interestingly, on several occasions, animals that are

morphologically very similar can be found as a diploid species as well as a separate polyploid species. This situation occurs among certain amphibians and reptiles. **Figure 8.18** shows photographs of a diploid and a tetraploid ($4n$) frog. As you can see, they look indistinguishable from each other. Their difference can be revealed only by an examination of the chromosome number in the somatic cells of the animals and by mating calls—*H. chrysoscelis* has a faster trill rate than *H. versicolor*.

Variations in Euploidy Can Occur in Certain Tissues Within an Animal

Thus far, we have considered variations in chromosome number that occur at fertilization, so all somatic cells of an individual contain this variation. In many animals, certain tissues of the body display normal variations in the number of sets of chromosomes. Diploid animals sometimes produce tissues that are polyploid. For example, the cells of the human liver can vary to a great degree in their ploidy. Liver cells contain nuclei that can be triploid, tetraploid, and even octaploid ($8n$). The occurrence of polyploid tissues or cells in organisms that are otherwise diploid is known as **endopolyploidy**. What is the biological significance of endopolyploidy? One possibility is that the increase in chromosome number in certain cells may enhance their ability to produce specific gene products that are needed in great abundance.

An unusual example of natural variation in the ploidy of somatic cells occurs in *Drosophila* and some other insects. Within certain tissues, such as the salivary glands, the chromosomes undergo repeated rounds of chromosome replication without cellular division. For example, in the salivary gland cells of *Drosophila*, the pairs of chromosomes double approximately nine times ($2^9 = 512$). **Figure 8.19a** illustrates how repeated rounds of chromosomal replication produce a bundle of chromosomes that lie together in a parallel fashion. This bundle, termed a **polytene chromosome**, was first observed by E. G. Balbiani in 1881. Later, in the 1930s, Theophilus Painter and colleagues recognized that the size and morphology of polytene chromosomes provided geneticists with unique opportunities to study chromosome structure and gene organization.

Figure 8.19b shows a micrograph of a polytene chromosome. The structure of polytene chromosomes is different from other forms of endopolyploidy because the replicated chromosomes remain attached to each other. Prior to the formation of polytene chromosomes, *Drosophila* cells contain eight chromosomes (two sets of four chromosomes each; see Figure 8.15a). In the salivary gland cells, the homologous chromosomes synapse with each other and replicate to form a polytene structure. During this process, the four types of chromosomes aggregate to form a single structure with several polytene arms. The central point where the chromosomes aggregate is known as the **chromocenter**. Each of the four types of chromosome is attached to the chromocenter near its centromere. The X and Y and chromosome 4 are telocentric, and chromosomes 2 and 3 are metacentric. Therefore, chromosomes 2 and 3 have two arms that radiate from the chromocenter, whereas the X and Y and chromosome 4 have a single arm projecting from the chromocenter (**Figure 8.19c**).



(a) *Hyla chrysoscelis*



(b) *Hyla versicolor*

FIGURE 8.18 Differences in euploidy in two closely related frog species. The frog in (a) is diploid, whereas the frog in (b) is tetraploid.

Genes → Traits Though similar in appearance, these two species differ in their number of chromosome sets. At the level of gene expression, this observation suggests that the number of copies of each gene (two versus four) does not critically affect the phenotype of these two species.

Variations in Euploidy Are Common in Plants

We now turn our attention to variations of euploidy that occur in plants. Compared with animals, plants more commonly exhibit polyploidy. Among ferns and flowering plants, at least 30% to 35% of species are polyploid. Polyploidy is also important in agriculture. Many of the fruits and grains we eat are produced from polyploid plants. For example, the species of wheat that we use to make bread, *Triticum aestivum*, is a hexaploid ($6n$) that arose from the union of diploid genomes from three closely related species (**Figure 8.20a**). Different species of strawberries are diploid, tetraploid, hexaploid, and even octaploid!

In many instances, polyploid strains of plants display outstanding agricultural characteristics. They are often larger in size

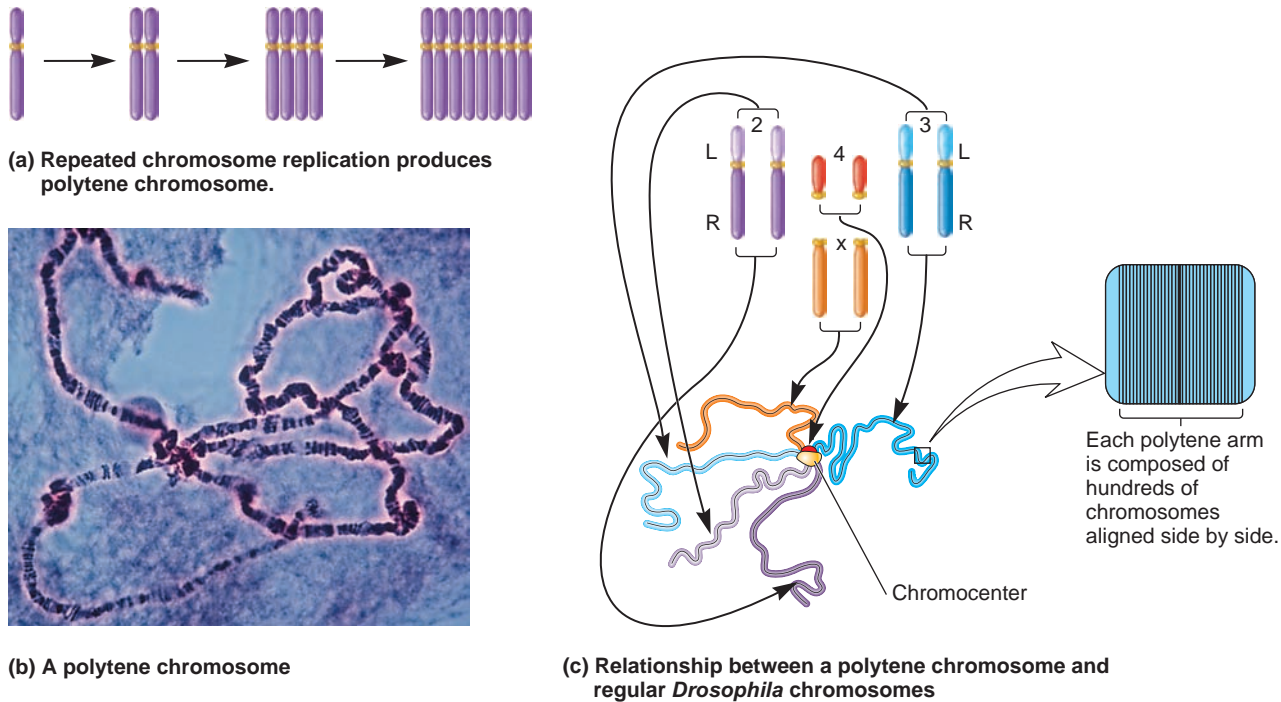


FIGURE 8.19 **Polytene chromosomes in *Drosophila*.** (a) A schematic illustration of the formation of polytene chromosomes. Several rounds of repeated replication without cellular division result in a bundle of sister chromatids that lie side by side. Both homologs also lie parallel to each other. This replication does not occur in highly condensed, heterochromatic DNA near the centromere. (b) A photograph of a polytene chromosome. (c) This drawing shows the relationship between the four pairs of chromosomes and the formation of a polytene chromosome in the salivary gland. The heterochromatic regions of the chromosomes aggregate at the chromocenter, and the arms of the chromosomes project outward. In chromosomes with two arms, the short arm is labeled L and the long arm is labeled R.



(a) Cultivated wheat, a hexaploid species



Tetraploid



Diploid

(b) A comparison of diploid and tetraploid petunias

FIGURE 8.20 **Examples of polyploid plants.** (a) Cultivated wheat, *Triticum aestivum*, is a hexaploid. It was derived from three different diploid species of grasses that originally were found in the Middle East and were cultivated by ancient farmers in that region. (b) Differences in euploidy may exist in two closely related petunia species. The larger flower at the left is tetraploid, whereas the smaller one at the right is diploid.

Genes → Traits An increase in chromosome number from diploid to tetraploid or hexaploid affects the phenotype of the individual. In the case of many plant species, a polyploid individual is larger and more robust than its diploid counterpart. This suggests that having additional copies of each gene is somewhat better than having two copies of each gene. This phenomenon in plants is rather different from the situation in animals. Tetraploidy in animals may have little effect (as in Figure 8.18b), but it is also common for polyploidy in animals to be detrimental.

and more robust. These traits are clearly advantageous in the production of food. In addition, polyploid plants tend to exhibit a greater adaptability, which allows them to withstand harsher environmental conditions. Also, polyploid ornamental plants often produce larger flowers than their diploid counterparts (**Figure 8.20b**).

Polyloid plants having an odd number of chromosome sets, such as triploids ($3n$) or pentaploids ($5n$), usually cannot reproduce. Why are they sterile? The sterility arises because they produce highly aneuploid gametes. During prophase of meiosis I, homologous pairs of sister chromatids form bivalents. However, organisms with an odd number of chromosomes, such as three, display an unequal separation of homologous chromosomes during anaphase of meiosis I (**Figure 8.21**). An odd number cannot be divided equally between two daughter cells. For each type of chromosome, a daughter cell randomly gets one or two copies. For example, one daughter cell might receive one copy of chromosome 1, two copies of chromosome 2, two copies of chromosome 3, one copy of chromosome 4, and so forth. For a triploid species containing many different chromosomes in a set, meiosis is very unlikely to produce a daughter cell that is euploid. If we assume that a daughter cell receives either one copy or two copies of each kind of chromosome, the probability that meiosis will produce a cell that is perfectly haploid or diploid is $(1/2)^{n-1}$, where n is the number of chromosomes in a set. As an example, in a triploid organism containing 20 chromosomes per set, the probability of producing a haploid or diploid cell is 0.000001907, or 1 in 524,288. Thus, meiosis is almost certain to produce cells that contain one copy of some chromosomes and two copies of the others. This high probability of aneuploidy underlies the reason for triploid sterility.

Though sterility is generally a detrimental trait, it can be desirable agriculturally because it may result in a seedless fruit.

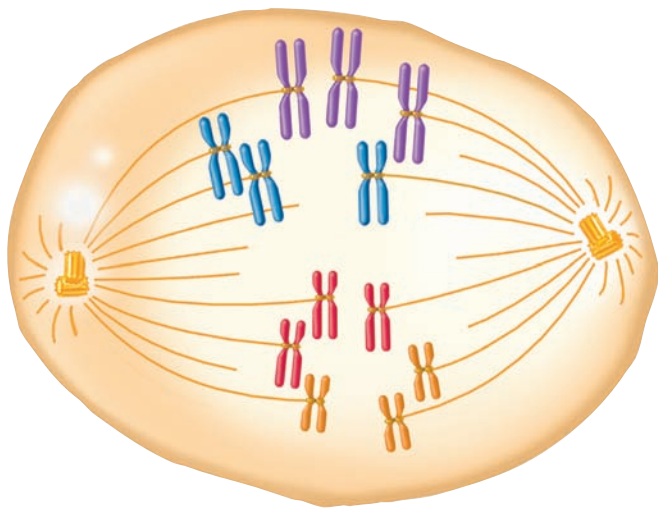


FIGURE 8.21 Schematic representation of anaphase of meiosis I in a triploid organism containing three sets of four chromosomes. In this example, the homologous chromosomes (three each) do not evenly separate during anaphase. Each cell receives one copy of some chromosomes and two copies of other chromosomes. This produces aneuploid gametes.

For example, domestic bananas and seedless watermelons are triploid varieties. The domestic banana was originally derived from a seed-producing diploid species and has been asexually propagated by humans via cuttings. The small black spots in the center of a domestic banana are degenerate seeds. In the case of flowers, the seedless phenotype can also be beneficial. Seed producers such as Burpee have developed triploid varieties of flowering plants such as marigolds. Because the triploid marigolds are sterile and unable to set seed, more of their energy goes into flower production. According to Burpee, “They bloom and bloom, unweakened by seed bearing.”

8.3 NATURAL AND EXPERIMENTAL WAYS TO PRODUCE VARIATIONS IN CHROMOSOME NUMBER

As we have seen, variations in chromosome number are fairly widespread and usually have a significant effect on the phenotypes of plants and animals. For these reasons, researchers have wanted to understand the cellular mechanisms that cause variations in chromosome number. In some cases, a change in chromosome number is the result of nondisjunction. The term nondisjunction refers to an event in which the chromosomes do not segregate properly. As we will see, it may be caused by an improper separation of homologous pairs in a bivalent in meiosis or a failure of the centromeres to disconnect during mitosis.

Meiotic nondisjunction can produce haploid cells that have too many or too few chromosomes. If such a cell gives rise to a gamete that fuses with a normal gamete during fertilization, the resulting offspring will have an abnormal chromosome number in all of its cells. An abnormal nondisjunction event also may occur after fertilization in one of the somatic cells of the body. This second mechanism is known as **mitotic nondisjunction**. When this occurs during embryonic stages of development, it may lead to a patch of tissue in the organism that has an altered chromosome number. A third common way in which the chromosome number of an organism can vary is by interspecies crosses. An **allopolyploid** organism contains sets of chromosomes from two or more different species. This term refers to the occurrence of chromosome sets (ploidy) from the genomes of different (allo) species.

In this section, we will examine these three mechanisms in greater detail. Also, in the past few decades, researchers have devised several methods for manipulating chromosome number in experimentally and agriculturally important species. We will conclude this section by exploring how the experimental manipulation of chromosome number has had an important impact on genetic research and agriculture.

Meiotic Nondisjunction Can Produce Aneuploidy or Polyploidy

Nondisjunction during meiosis can occur during anaphase of meiosis I or meiosis II. If it happens during meiosis I, an entire

bivalent migrates to one pole (**Figure 8.22a**). Following the completion of meiosis, the four resulting haploid cells produced from this event are abnormal. If nondisjunction occurs during anaphase of meiosis II (**Figure 8.22b**), the net result is two abnormal and two normal haploid cells. If a gamete that is missing a chromosome is viable and participates in fertilization, the resulting offspring is monosomic for the missing chromosomes. Alternatively, if a gamete carrying an extra chromosome unites with a normal gamete, the offspring will be trisomic.

In rare cases, all of the chromosomes can undergo nondisjunction and migrate to one of the daughter cells. The net result of **complete nondisjunction** is a diploid cell and a cell without any chromosomes. The cell without chromosomes is nonviable, but the diploid cell might participate in fertilization with a normal haploid gamete to produce a triploid individual. Therefore, complete nondisjunction can produce individuals that are polyploid.

Mitotic Nondisjunction or Chromosome Loss Can Produce a Patch of Tissue with an Altered Chromosome Number

Abnormalities in chromosome number occasionally occur after fertilization takes place. In this case, the abnormal event happens during mitosis rather than meiosis. One possibility is that the sister chromatids separate improperly, so one daughter cell has three

copies of a chromosome, whereas the other daughter cell has only one (**Figure 8.23a**). Alternatively, the sister chromatids could separate during anaphase of mitosis, but one of the chromosomes could be improperly attached to the spindle, so it does not migrate to a pole (**Figure 8.23b**). A chromosome will be degraded if it is left outside the nucleus when the nuclear membrane re-forms. In this case, one of the daughter cells has two copies of that chromosome, whereas the other has only one.

When genetic abnormalities occur after fertilization, the organism contains a subset of cells that are genetically different from those of the rest of the organism. This condition is referred to as **mosaicism**. The size and location of the mosaic region depend on the timing and location of the original abnormal event. If a genetic alteration happens very early in the embryonic development of an organism, the abnormal cell will be the precursor for a large section of the organism. In the most extreme case, an abnormality can take place at the first mitotic division. As a bizarre example, consider a fertilized *Drosophila* egg that is XX. One of the X chromosomes may be lost during the first mitotic division, producing one daughter cell that is XX and one that is XO. Flies that are XX develop into females, and XO flies develop into males. Therefore, in this example, one-half of the organism becomes female and one-half becomes male! This peculiar and rare individual is referred to as a **bilateral gynandromorph** (**Figure 8.24**).

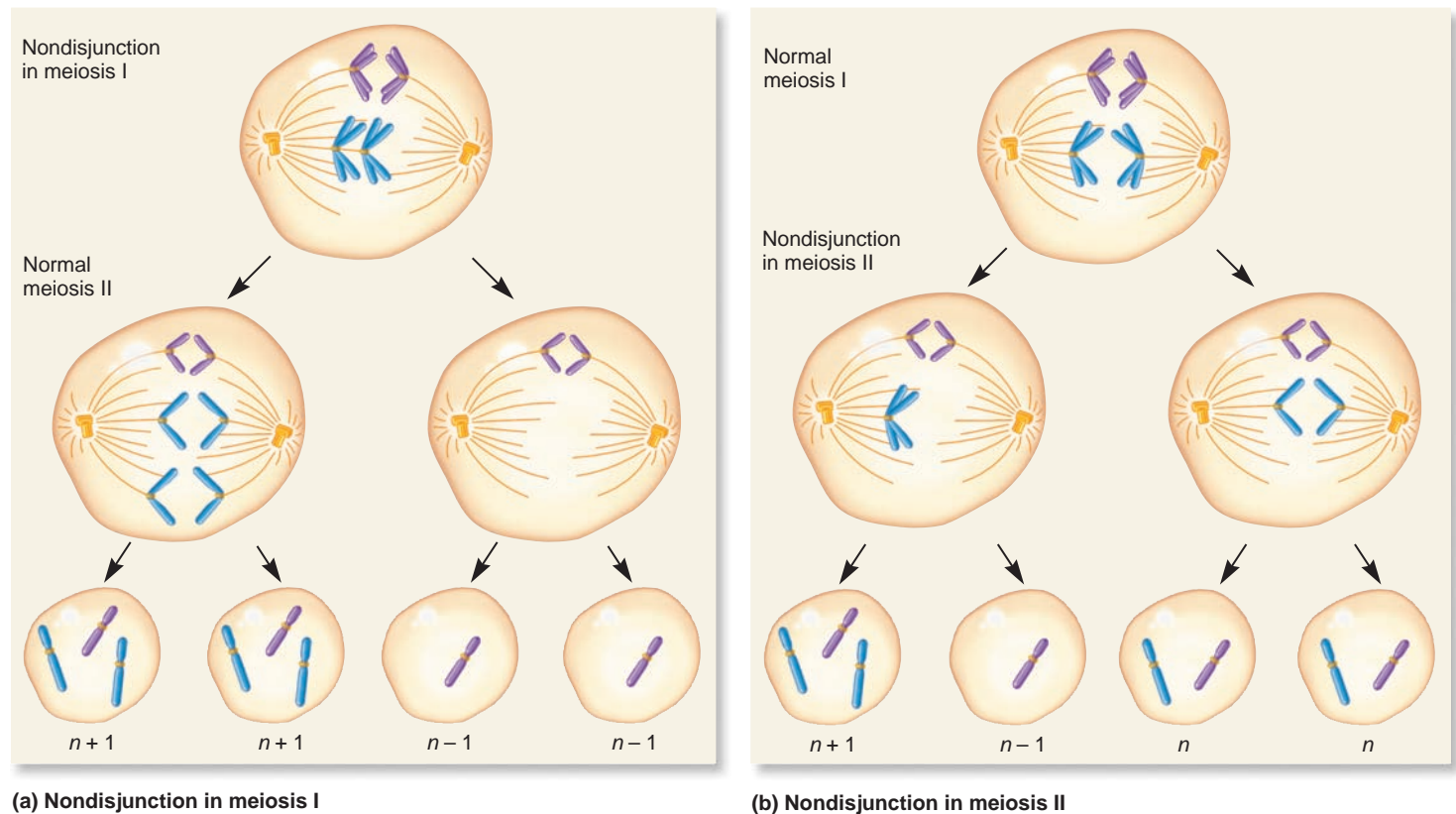
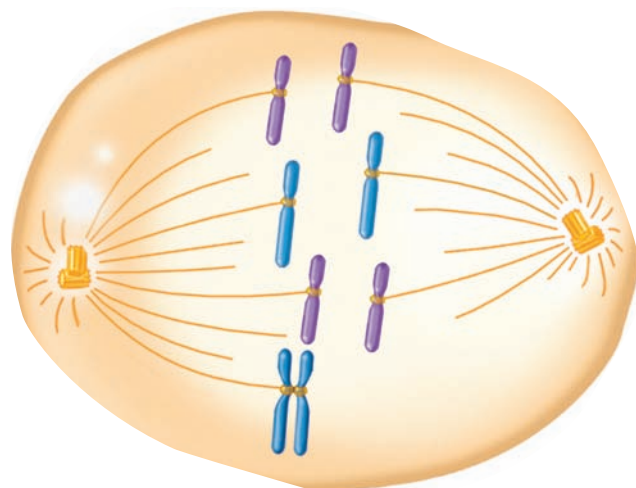
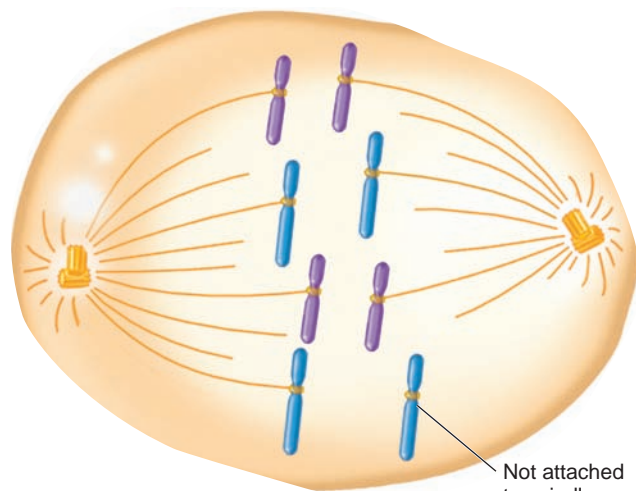


FIGURE 8.22 Nondisjunction during meiosis I and II. The chromosomes shown in purple are behaving properly during meiosis I and II, so each cell receives one copy of this chromosome. The chromosomes shown in blue are not disjoining correctly. In (a), nondisjunction occurred in meiosis I, so the resulting four cells receive either two copies of the blue chromosome or zero copies. In (b), nondisjunction occurred during meiosis II, so one cell has two blue chromosomes and another cell has zero. The remaining two cells are normal.



(a) Mitotic nondisjunction



(b) Chromosome loss

FIGURE 8.23 Nondisjunction and chromosome loss during mitosis in somatic cells. (a) Mitotic nondisjunction produces a trisomic and a monosomic daughter cell. (b) Chromosome loss produces a normal and a monosomic daughter cell.

FIGURE 8.24 A bilateral gynandromorph of *Drosophila melanogaster*.

Genes → Traits In *Drosophila*, the ratio between genes on the X chromosome and genes on the autosomes determines sex. This fly began as an XX female. One X chromosome carried the recessive white-eye and miniature wing alleles; the other X chromosome carried the wild-type alleles. The X chromosome carrying the wild-type alleles was lost from one of the cells during the first mitotic division, producing one XX cell and one XO cell. The XX cell became the precursor for the left side of the fly, which developed as female. The XO cell became the precursor for the other side of the fly, which developed as male with a white eye and a miniature wing.



Changes in Euploidy Can Occur by Autopolyploidy, Allopolyploidy, and Allopolyploidy

Different mechanisms account for changes in the number of chromosome sets among natural populations of plants and animals (Figure 8.25). As previously mentioned, complete nondisjunction, due to a general defect in the spindle apparatus, can produce an individual with one or more extra sets of chromosomes. This individual is known as an **autopolyploid** (Figure 8.25a). The prefix auto- (meaning self) and term polyploid (meaning many sets of chromosomes) refer to an increase in the number of chromosome sets within a single species.

A much more common mechanism for change in chromosome number, called **allopolyploidy**, is a result of interspecies crosses (Figure 8.25b). An allopolyploid that has one set of chromosomes from two different species is called an **allohexaploid**. This event is most likely to occur between species that are close evolutionary relatives. For example, closely related species of grasses may interbreed to produce allohexaploids. As shown in Figure 8.25c, an **allopolyploid** contains two (or more) sets of chromosomes from two (or more) species. In this case, the **allohexaploid** contains two complete sets of chromosomes from two different species, for a total of four sets. In nature, allohexaploids usually arise from allohexaploids. This can occur when a somatic cell in an allohexaploid undergoes complete nondisjunction to create an allohexaploid cell. In plants, such a cell can continue to grow and produce a section of the plant that is allohexaploid. If this part of the plant produced seeds by self-pollination, the seeds would give rise to allohexaploid offspring. Cultivated wheat (refer back to Figure 8.20a) is a plant in which two species must have interbred to create an allohexaploid, and then a third species interbred with the allohexaploid to create an allohexaploid.

Allohexaploids Are Often Sterile, but Allohexaploids Are More Likely to Be Fertile

Geneticists are interested in the production of allohexaploids and allopolyploids as ways to generate interspecies hybrids with desirable traits. For example, if one species of grass can withstand hot temperatures and a closely related species is adapted to survive cold winters, a plant breeder may attempt to produce an interspecies hybrid that combines both qualities—good growth in the heat and survival through the winter. Such an allohexaploid may be desirable in climates with both hot summers and cold winters.

An important determinant of success in producing a fertile allohexaploid is the degree of similarity of the different species' chromosomes. In two very closely related species, the number and types of chromosomes might be very similar. Figure 8.26 shows a karyotype of an interspecies hybrid between the roan antelope (*Hippotragus equinus*) and the sable antelope (*Hippotragus niger*). As seen here, these two closely related species have the same number of chromosomes. The sizes and banding patterns of the chromosomes show that they correspond to one another. For example, chromosome 1 from both species is fairly large, has very similar banding patterns, and carries many of the same genes. Evolutionarily related chromosomes from two different species are called **homeologous** chromosomes (not to be confused with

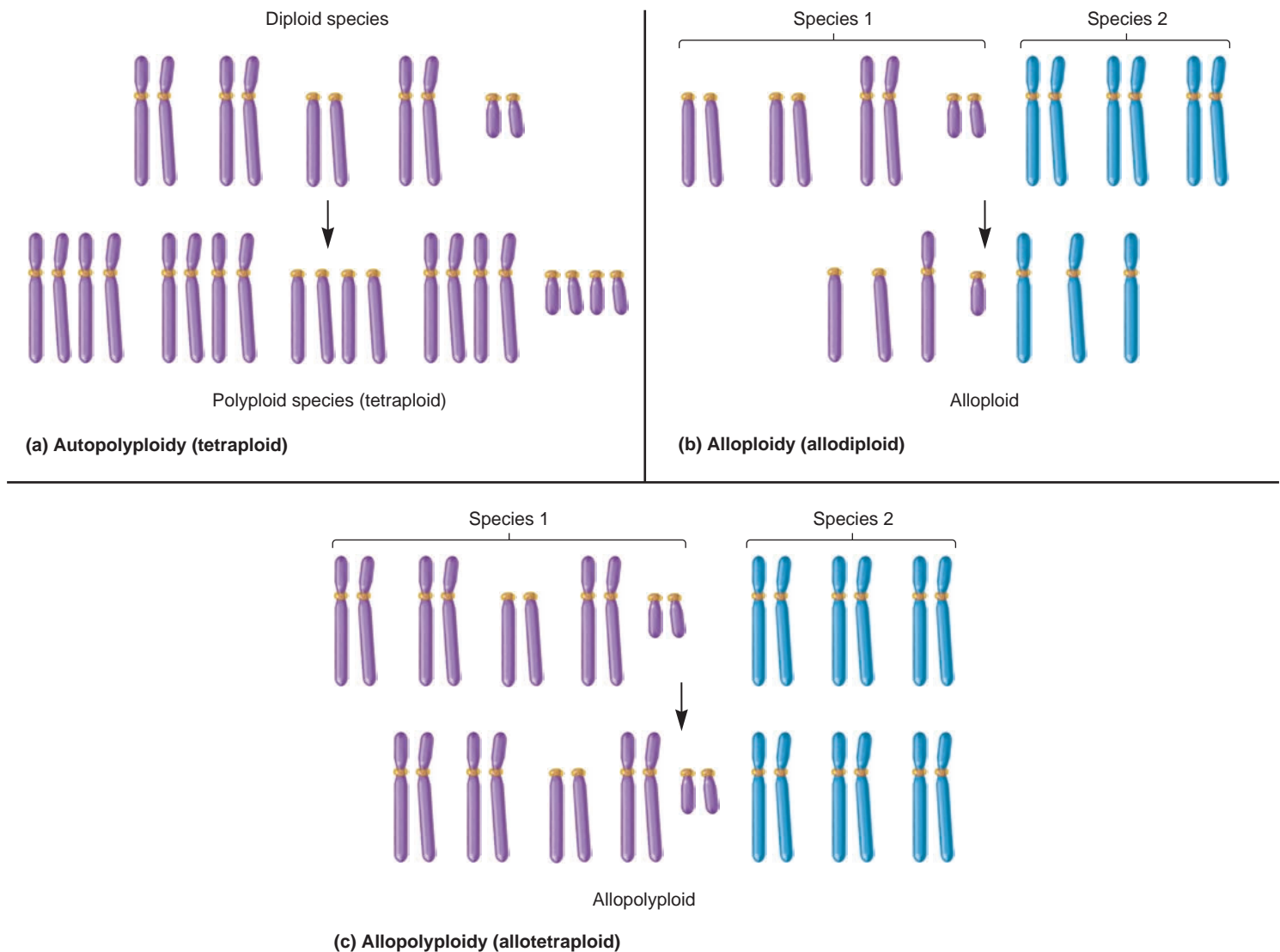


FIGURE 8.25 A comparison of autopolyploidy, allopolyploidy, and allopolyploidy.

homologous). This allodiploid is fertile because the homeologous chromosomes can properly synapse during meiosis to produce haploid gametes.

The critical relationship between chromosome pairing and fertility was first recognized by the Russian cytogeneticist Georgi Karpechenko in 1928. He crossed a radish (*Raphanus*) and a cabbage (*Brassica*), both of which are diploid and contain 18 chromosomes. Each of these organisms produces haploid cells containing 9 chromosomes. Therefore, the allodiploid produced from this interspecies cross contains 18 chromosomes. However, because the radish and cabbage are not closely related species, the nine *Raphanus* chromosomes are distinctly different from the nine *Brassica* chromosomes. During meiosis I, the radish and cabbage chromosomes cannot synapse with each other. This prevents the proper chromosome pairing and results in a high degree of aneuploidy (Figure 8.27a). Therefore, the radish/cabbage hybrid is sterile.

Among his strains of sterile allopolyploids, Karpechenko discovered that on rare occasions a plant produced a viable seed.

When such seeds were planted and subjected to karyotyping, the plants were found to be allotetraploids with two sets of chromosomes from each of the two species. In the example shown in Figure 8.27b, the radish/cabbage allotetraploid contains 36 chromosomes instead of 18. The homologous chromosomes from each of the two species can synapse properly. When anaphase of meiosis I occurs, the pairs of synapsed chromosomes can disjoin equally to produce cells with 18 chromosomes each (a haploid set from the radish plus a haploid set from the cabbage). These cells can give rise to gametes with 18 chromosomes that can combine with each other to produce an allotetraploid containing 36 chromosomes. In this way, the allotetraploid is a fertile organism. Karpechenko's goal was to create a "vegetable for the masses" that would combine the nutritious roots of a radish with the flavorful leaves of a cabbage. Unfortunately, however, the allotetraploid had the leaves of the radish and the roots of the cabbage! Nevertheless, Karpechenko's scientific contribution was still important because he showed that it is possible to artificially produce a new self-perpetuating species of plant by creating an allotetraploid.

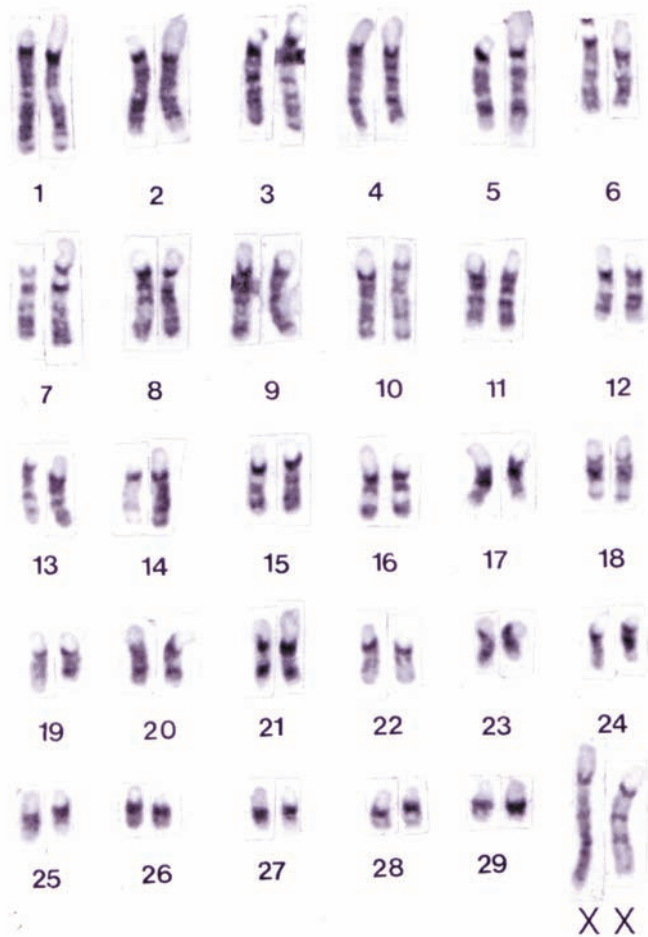
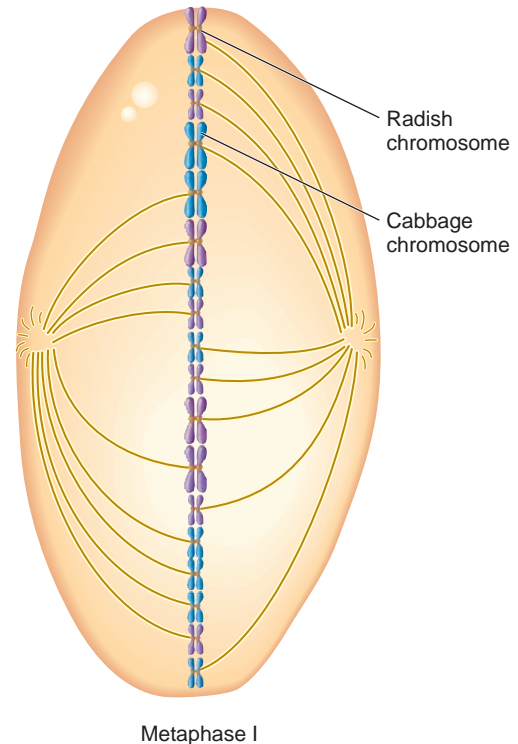


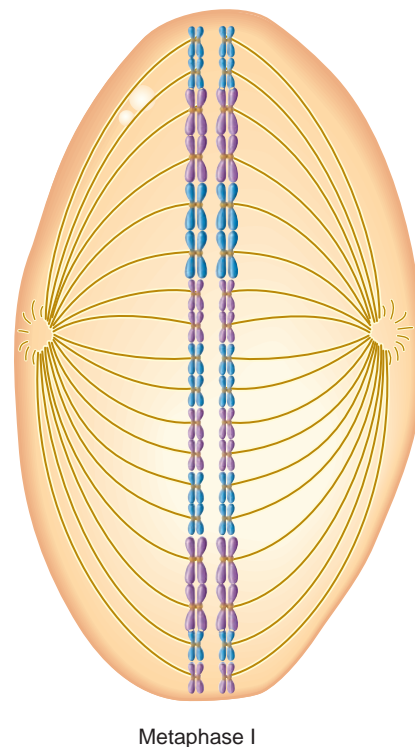
FIGURE 8.26 The karyotype of a hybrid animal produced from two closely related antelope species. In each chromosome pair in this karyotype, one chromosome was inherited from the roan antelope (*Hippotragus equinus*) and the other from the sable antelope (*Hippotragus niger*). When it is possible to distinguish the chromosomes from the two species, the roan chromosomes are shown on the left side of each pair.

Modern plant breeders employ several different strategies to produce allotetraploids. One method is to start with two different tetraploid species. Because tetraploid plants make diploid gametes, the hybrid from this cross contains a diploid set from each species. Alternatively, if an allodiploid containing one set of chromosomes from each species already exists, a second approach is to create an allotetraploid by using agents that alter chromosome number. We will explore such experimental treatments next.

FIGURE 8.27 A comparison of metaphase I of meiosis in an allodiploid and an allotetraploid. The purple chromosomes are from the radish (*Raphanus*), and the blue are from the cabbage (*Brassica*). (a) In the allodiploid, the radish and cabbage chromosomes have not synapsed and are randomly aligned during metaphase. (b) In the allotetraploid, the homologous radish and homologous cabbage chromosomes are properly aligned along the metaphase plate.



(a) Allodiploid with a monoploid set from each species



(b) Allotetraploid with a diploid set from each species

Experimental Treatments Can Promote Polyploidy

Because polyploid and allopolyploid plants often exhibit desirable traits, the development of polyploids is of considerable interest among plant breeders. Experimental studies on the ability of environmental agents to promote polyploidy began in the early 1900s. Since that time, various agents have been shown to promote nondisjunction and thereby lead to polyploidy. These include abrupt temperature changes during the initial stages of seedling growth and the treatment of plants with chemical agents that interfere with the formation of the spindle apparatus.

The drug colchicine is commonly used to promote polyploidy. Once inside the cell, colchicine binds to tubulin (a protein found in the spindle apparatus) and thereby interferes with normal chromosome segregation during mitosis or meiosis. In 1937, Alfred Blakeslee and Amos Avery applied colchicine to plant tissue and, at high doses, were able to cause complete mitotic nondisjunction and produce polyploidy in plant cells. Colchicine can be applied to seeds, young embryos, or rapidly growing regions of a plant (Figure 8.28). This application may produce aneuploidy, which is usually an undesirable outcome, but it often produces polyploid cells, which may grow faster than the surrounding diploid tissue. In a diploid plant, colchicine may cause complete mitotic nondisjunction, yielding tetraploid ($4n$) cells. As the tetraploid cells continue to divide, they generate a portion of the plant that is often morphologically distinguishable from the remainder. For example, a tetraploid stem may have a larger diameter and produce larger leaves and flowers.

Because individual plants can be propagated asexually from pieces of plant tissue (i.e., cuttings), the polyploid portion of the plant can be removed, treated with the proper growth hormones, and grown as a separate plant. Alternatively, the tetraploid region of a plant may have flowers that produce seeds by self-pollination. For many plant species, a tetraploid flower produces diploid pollen and eggs, which can combine to produce tetraploid offspring. In this way, the use of colchicine provides a straightforward method of producing polyploid strains of plants.

Cell Fusion Techniques Can Be Used to Make Hybrid Plants

Thus far, we have examined several mechanisms that produce variations in chromosome number. Some of these processes occur naturally and have figured prominently in speciation and evolution. In addition, agricultural geneticists can administer treatments such as colchicine to promote nondisjunction and thereby obtain useful strains of organisms. More recently, researchers have developed cellular approaches to produce hybrids with altered chromosomal composition. As described here, these cellular approaches have important applications in research and agriculture.

In the technique known as **cell fusion**, individual cells are mixed together and made to fuse. In agriculture, cell fusion can create new strains of plants. An advantage of this approach is that researchers can artificially “cross” two species that cannot interbreed naturally. As an example, Figure 8.29 illustrates the

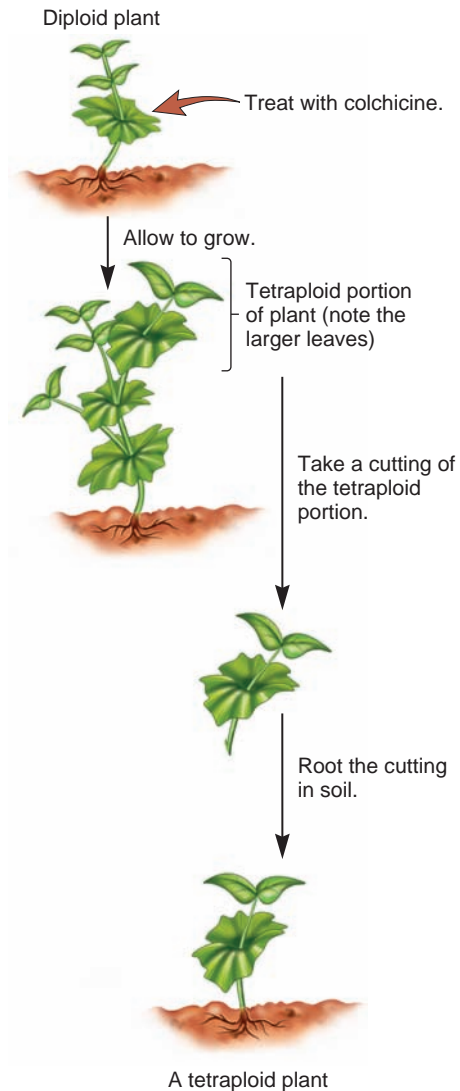


FIGURE 8.28 Use of colchicine to promote polyploidy in plants. Colchicine interferes with the mitotic spindle apparatus and promotes nondisjunction. If complete nondisjunction occurs in a diploid cell, a daughter cell will be formed that is tetraploid. Such a tetraploid cell may continue to divide and produce a segment of the plant with more robust characteristics. This segment may be cut from the rest of the plant and rooted. In this way, a tetraploid plant can be propagated.

use of cell fusion to produce a hybrid grass. The parent cells were derived from tall fescue grass (*Festuca arundinacea*) and Italian ryegrass (*Lolium multiflorum*). Prior to fusion, the cells from these two species were treated with agents that gently digest the cell wall without rupturing the plasma membrane. A plant cell without a cell wall is called a **protoplast**. The protoplasts were mixed together and treated with agents that promote cellular fusion. Immediately after this takes place, a cell containing two separate nuclei is formed. This cell, known as a **heterokaryon**, spontaneously goes through a nuclear fusion process to produce a **hybrid cell** with a single nucleus. After nuclear fusion, the hybrid cells can be grown on laboratory media and eventually regenerate an entire plant. The allotetraploid shown in

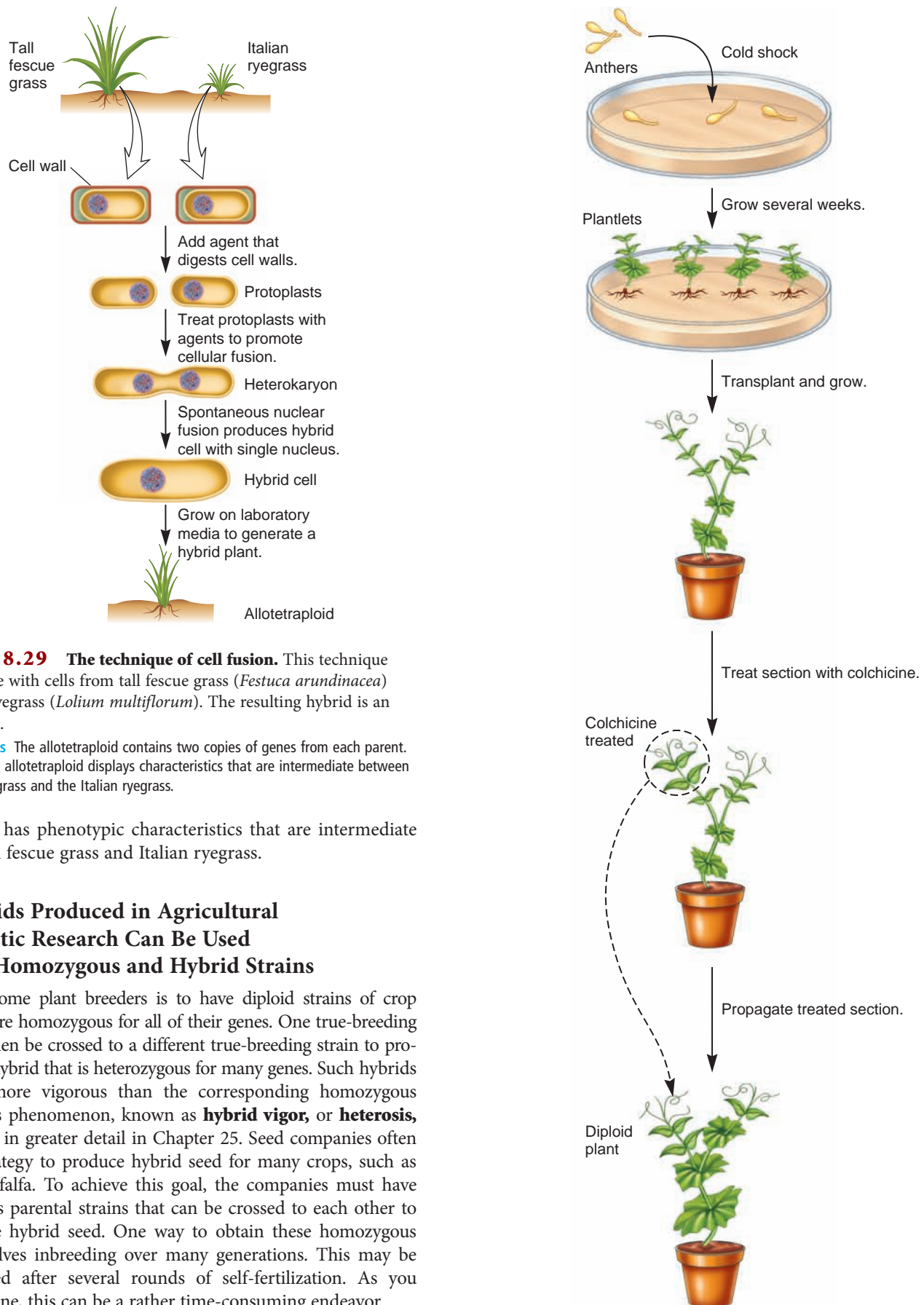


FIGURE 8.29 The technique of cell fusion. This technique is shown here with cells from tall fescue grass (*Festuca arundinacea*) and Italian ryegrass (*Lolium multiflorum*). The resulting hybrid is an allotetraploid.

Genes → Traits The allotetraploid contains two copies of genes from each parent. In this case, the allotetraploid displays characteristics that are intermediate between the tall fescue grass and the Italian ryegrass.

Figure 8.29 has phenotypic characteristics that are intermediate between tall fescue grass and Italian ryegrass.

Monoploids Produced in Agricultural and Genetic Research Can Be Used to Make Homozygous and Hybrid Strains

A goal of some plant breeders is to have diploid strains of crop plants that are homozygous for all of their genes. One true-breeding strain can then be crossed to a different true-breeding strain to produce an F_1 hybrid that is heterozygous for many genes. Such hybrids are often more vigorous than the corresponding homozygous strains. This phenomenon, known as **hybrid vigor**, or **heterosis**, is described in greater detail in Chapter 25. Seed companies often use this strategy to produce hybrid seed for many crops, such as corn and alfalfa. To achieve this goal, the companies must have homozygous parental strains that can be crossed to each other to produce the hybrid seed. One way to obtain these homozygous strains involves inbreeding over many generations. This may be accomplished after several rounds of self-fertilization. As you might imagine, this can be a rather time-consuming endeavor.

FIGURE 8.30 The experimental production of monoploids with anther culture. In the technique of anther culture, the anthers are collected, and the haploid pollen within them is induced to begin development by a cold shock treatment. After several weeks, monoploid plantlets emerge, and these can be grown on an agar medium. Eventually, the plantlets can be transferred to small pots. After the plantlets have grown to a reasonable size, a section of the monoploid plantlet can be treated with colchicine to convert it to diploid tissue. A cutting from this diploid section can then be used to generate a diploid plant.

As an alternative, the production of **monoploids**—organisms that have a single set of chromosomes in their somatic cells—can be used as part of an experimental strategy to develop homozygous diploid strains of plants. Monoploids have been used to improve agricultural crops such as wheat, rice, corn, barley, and potato. In 1964, Sipra Guha-Mukherjee and Satish Maheshwari developed a method to produce monoploid plants directly from pollen grains. **Figure 8.30** describes the experimental technique called **anther culture**, which has been extensively used to produce diploid strains of crop plants that are homozygous for all of their genes. The method involves alternation between monoploid and diploid generations. The parental plant is diploid but not homozygous for all of its genes. The anthers from this diploid plant are collected, and the haploid pollen grains are induced to

begin development by a cold shock—an abrupt exposure to cold temperature. After several weeks, monoploid plantlets emerge, which can then be grown on agar media in a laboratory. However, due to the presence of deleterious alleles that are recessive, many of the pollen grains may fail to produce viable plantlets. Therefore, anther culture has been described as a “monoploid sieve” that weeds out individuals that carry deleterious recessive alleles.

Eventually, plantlets that are healthy can be transferred to small pots. After the plants grow to a reasonable size, a section of the monoploid plant can be treated with colchicine to convert it to diploid tissue. A cutting from this diploid section can then be used to generate a separate plant. This diploid plant is homozygous for all of its genes because it was produced by the chromosomal doubling of a monoploid strain.

In certain animal species, monoploids can be produced by experimental treatments that induce the eggs to begin development without fertilization by sperm. This process is known as **parthenogenesis**. In many cases, however, the haploid zygote develops only for a short time before it dies. Nevertheless, a short phase of development can be useful to research scientists. For example, the zebrafish (*Danio rerio*), a common aquarium fish, has gained popularity among researchers interested in vertebrate development. The haploid egg can be induced to begin development by exposure to sperm rendered biologically inactive by UV irradiation.

KEY TERMS

Page 189. genetic variation, allelic variation, cytogeneticist

Page 191. metacentric, submetacentric, acrocentric, telocentric, karyotype, G banding, deletion, deficiency, duplication, inversion, translocation, simple translocation, reciprocal translocation

Page 192. terminal deletion, interstitial deletion

Page 193. repetitive sequences, nonallelic homologous recombination, gene duplication, gene family

Page 194. homologous, paralogs

Page 195. copy number variation (CNV), segmental duplication, comparative genomic hybridization (CGH), hybridization

Page 197. pericentric inversion, paracentric inversion

Page 198. position effect, inversion heterozygote, inversion loop, dicentric, dicentric bridge, acentric fragment, telomeres

Page 199. balanced translocations, unbalanced translocation

Page 200. Robertsonian translocation, translocation cross

Page 202. semisterility

Page 203. euploid, triploid, polyploid, tetraploid, aneuploidy, trisomic, monosomic

Page 205. nondisjunction, haplodiploid

Page 206. endopolyploidy, polytene chromosome, chromocenter

Page 208. meiotic nondisjunction, mitotic nondisjunction, allopolyploid

Page 209. complete nondisjunction, mosaicism, bilateral gynandromorph

Page 210. autopolyploid, allopolyploidy, allodiploid, allopolyploid, allotetraploid, homeologous

Page 213. cell fusion, protoplast, heterokaryon, hybrid cell

Page 214. hybrid vigor, heterosis

Page 215. monoploids, anther culture, parthenogenesis

Page 217. pseudodominance

CHAPTER SUMMARY

8.1 Variation in Chromosome Structure

- Among different species, natural variation exists with regard to chromosome structure and number. Three features of chromosomes that aid in their identification are centromere location, size, and banding patterns (see Figure 8.1).
- Variations in chromosome structure include deletions, duplications, inversions, and translocations (see Figure 8.2).
- Chromosome breaks can create terminal and interstitial deletions. Some deletions are associated with human genetic disorders such as cri-du-chat syndrome (see Figures 8.3, 8.4).
- Nonallelic homologous recombination can create gene duplications and deletions. Over time, gene duplications can lead to the formation of gene families, such as the globin gene family (see Figures 8.5–8.7).
- Copy number variation (CNV) is fairly common within a species. In humans, CNV is associated with certain diseases (see Figure 8.8).
- Comparative genomic hybridization is one technique for detecting chromosome deletions and duplications. It is widely used in the analysis of cancer cells (see Figure 8.9).
- Inversions can be pericentric or paracentric. In an inversion heterozygote, crossing over can create deletions and duplications in the resulting chromosomes (see Figures 8.10, 8.11).
- Two mechanisms that may produce translocations are chromosome breakage and subsequent repair and nonhomologous crossing over (see Figure 8.12).
- Familial Down syndrome is due to a translocation between chromosome 14 and 21 (see Figure 8.13).
- Due to the formation of a translocation cross, individuals that carry a balanced translocation may have a high probability of producing unbalanced gametes (see Figure 8.14).

8.2 Variation in Chromosome Number

- Chromosome number variation may involve changes in the number of sets (euploidy) or changes in the number of

particular chromosomes within a set (aneuploidy) (see Figure 8.15).

- Aneuploidy is often detrimental due to an imbalance in gene expression. Down syndrome, an example of an aneuploidy in humans, increases in frequency with maternal age (see Figures 8.16, 8.17, Table 8.1).
- Among animals, variation in euploidy is relatively rare, though it does occur. Some tissues within an animal may exhibit polyploidy. An example is the polytene chromosomes found in salivary cells of *Drosophila* (see Figures 8.18, 8.19).
- Polyploidy in plants is relatively common and has found many advantages in agriculture. Triploid plants are usually seedless because they cannot segregate their chromosomes evenly during meiosis (see Figures 8.20, 8.21).

8.3 Natural and Experimental Ways to Produce Variations in Chromosome Number

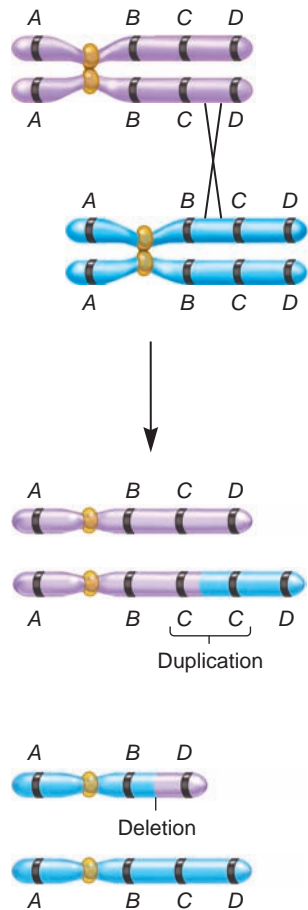
- Meiotic nondisjunction, mitotic nondisjunction, and chromosome loss can result in changes in chromosome number (see Figures 8.22–8.24).
- Autopolyploidy is an increase in the number of sets within a single species. Interspecies matings result in allopolyploids. Allopolyploids with multiple sets of chromosomes from each species are allopolyploids (see Figures 8.25, 8.26).
- The chromosomes from allodiploids may not be able to pair up during meiosis, but the homologs in an allotetraploid can. For this reason, allotetraploids are usually fertile (see Figure 8.27).
- The drug colchicine promotes nondisjunction and can be used to make polyploid plants (see Figure 8.28).
- Cell fusion can be used to make allotetraploids (see Figure 8.29).
- Anther culture creates monoploid plants, which later can be made diploid via colchicine treatment (see Figure 8.30).

PROBLEM SETS & INSIGHTS

Solved Problems

- S1. Describe how a gene family is produced. Discuss the common and unique features of the family members in the globin gene family.

Answer: A gene family is produced when a single gene is copied one or more times by a gene duplication event. This duplication may occur by an abnormal (misaligned) crossover, which produces a chromosome with a deletion and another chromosome with a gene duplication.

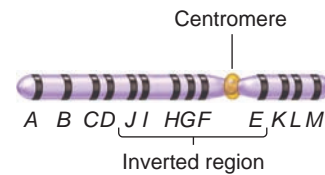


Over time, this type of duplication may occur several times to produce many copies of a particular gene. In addition, translocations may move the duplicated genes to other chromosomes, so the members of the gene family may be dispersed among several different chromosomes. Eventually, each member of a gene family will accumulate mutations, which may subtly alter their function.

All members of the globin gene family bind oxygen. Myoglobin tends to bind it more tightly; therefore, it is good at storing oxygen. Hemoglobin binds it more loosely, so it can transport oxygen throughout the body (via red blood cells) and release it to the tissues that need oxygen. The polypeptides that form hemoglobins are predominantly expressed in red blood cells, whereas myoglobin genes are expressed in many different cell types. The expression pattern of the globin genes changes during different stages of development. The ϵ - and ζ -globin genes are expressed in the early embryo. They are turned off near the end of the first trimester, and then the γ -globin genes exhibit their maximal expression during the second and third trimesters of gestation. Following birth, the γ -globin genes are silenced, and the β -globin gene is expressed for the rest of a person's life. These differences in the expression of the globin genes reflect the differences in the oxygen transport needs of humans during the different stages of life. Overall,

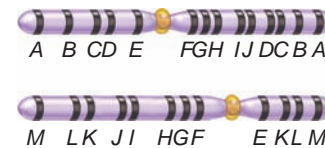
the evolution of gene families has resulted in gene products that are better suited to a particular tissue or stage of development. This has allowed a better “fine-tuning” of human traits.

S2. An inversion heterozygote has the following inverted chromosome:



What is the result if a crossover occurs between genes F and G on one inversion and one normal chromosome?

Answer: The resulting product is four chromosomes. One chromosome is normal, one is an inversion chromosome, and two chromosomes have duplications and deletions. The two duplicated or deficient chromosomes are shown here:



S3. In humans, the number of chromosomes per set equals 23. Even though the following conditions are lethal, what would be the total number of chromosomes for the following individuals?

- Trisomy 22
- Monosomy 11
- Triploid individual

Answer:

- 47 (the diploid number, 46, plus 1)
 - 45 (the diploid number, 46, minus 1)
 - 69 (3 times 23)
- S4. A diploid species with 44 chromosomes (i.e., 22/set) is crossed to another diploid species with 38 chromosomes (i.e., 19/set). How many chromosomes are produced in an allodiploid or allotetraploid from this cross? Would you expect the offspring to be sterile or fertile?

Answer: An allodiploid would have $22 + 19 = 41$ chromosomes. This individual would likely be sterile, because not all of the chromosomes would have homeologous partners to pair with during meiosis. This yields aneuploidy, which usually causes sterility. An allotetraploid would have $44 + 38 = 82$ chromosomes. Because each chromosome would have a homologous partner, the allotetraploid would likely be fertile.

S5. **Pseudodominance** occurs when a single copy of a recessive allele is phenotypically expressed because the second copy of the gene has been deleted from the homologous chromosome; the individual is hemizygous for the recessive allele. As an example, we can consider the notch phenotype in *Drosophila*, which is an X-linked trait. Fruit

flies with this condition have wings with a notched appearance at their edges. Female flies that are heterozygous for this mutation have notched wings; homozygous females and hemizygous males are unable to survive. The notched phenotype is due to a defect in a single gene called *Notch* (*N*). Geneticists studying fruit flies with this phenotype have discovered that one X chromosome of some of the mutant flies has a small deletion that includes the *Notch* gene as well as a few genes on either side of it. The mutation causing this phenotype in other flies is confined within the *Notch* gene itself. A genetic analysis can distinguish between notched fruit flies carrying a deletion versus those that carry a single-gene mutation. This is possible because the *Notch* gene happens to be located next to the red/white eye color gene on the X chromosome. How would you distinguish between a notched phenotype due to a deletion that included the *Notch* gene and the adjacent eye color gene versus a notch phenotype due to a small mutation only within the *Notch* gene itself?

Answer: To determine if the *Notch* mutation is due to a deletion, red-eyed females with the notched phenotype can be crossed to white-eyed males. Only the daughters with notched wings need to be analyzed. If they have red eyes, this means the *Notch* mutation has not deleted the red-eye allele from the X chromosome. Alternatively, if they have white eyes, this indicates the red-eye allele has been deleted from the X chromosome that carries the *Notch* mutation. In this case, the white-eye allele is expressed because it is present in a single copy in a female fly with two X chromosomes. This phenomenon is pseudodominance.

S6. Albert Blakeslee began using the Jimson weed (*Datura stramonium*) as an experimental organism to teach his students the laws of Mendelian inheritance. Although this plant has not gained widespread use in genetic studies, Blakeslee's work provided a

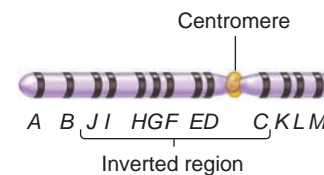
convincing demonstration that changes in chromosome number affect the phenotype of organisms. Blakeslee's assistant, B. T. Avery, identified a Jimson weed mutant that he called "globe" because the capsule is more rounded than normal. In genetic crosses, he found that the globe mutant had a peculiar pattern of inheritance. The globe trait was passed to about 25% of the offspring when the globe plants were allowed to self-fertilize. Unexpectedly, about 25% of the offspring also had the globe phenotype when globe plants were pollinated by a normal plant. In contrast, when pollen from a globe plant was used to pollinate a normal plant, less than 2% of the offspring had the globe phenotype. This non-Mendelian pattern of inheritance caused Blakeslee and his colleagues to investigate the nature of this trait further. We now know the globe phenotype is due to trisomy 11. Can you explain this unusual pattern of inheritance knowing it is due to trisomy 11?

Answer: This unusual pattern of inheritance of these aneuploid strains can be explained by the viability of euploid versus aneuploid gametes or gametophytes. An individual that is trisomic has a 50% chance of producing an egg or sperm that will inherit an extra chromosome and a 50% chance that a gamete will be normal. Blakeslee's results indicate that when a pollen grain inherited an extra copy of chromosome 11, it was almost always nonviable and unable to produce an aneuploid offspring. However, a significant percentage of aneuploid eggs were viable, so some (25%) of the offspring were aneuploid. Because an aneuploid plant should produce a 1:1 ratio between euploid and aneuploid eggs, the observation that only 25% of the offspring were aneuploid also indicates that about half of the female gametophytes or aneuploid eggs from such gametophytes were also nonviable. Overall, these results provide compelling evidence that imbalances in chromosome number can alter reproductive viability and also cause significant phenotypic consequences.

Conceptual Questions

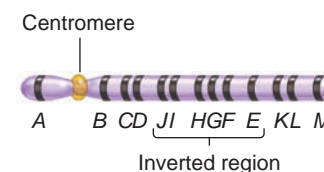
- C1. Which changes in chromosome structure cause a change in the total amount of genetic material, and which do not?
- C2. Explain why small deletions and duplications are less likely to have a detrimental effect on an individual's phenotype than large ones. If a small deletion within a single chromosome happens to have a phenotypic effect, what would you conclude about the genes in this region?
- C3. How does a chromosomal duplication occur?
- C4. What is a gene family? How are gene families produced over time? With regard to gene function, what is the biological significance of a gene family?
- C5. Following a gene duplication, two genes will accumulate different mutations, causing them to have slightly different sequences. In Figure 8.7, which pair of genes would you expect to have more similar sequences, α_1 and α_2 or ψ_{α_1} and α_2 ? Explain your answer.
- C6. Two chromosomes have the following order of genes:
 Normal: *A B C* centromere *D E F G H I*
 Abnormal: *A B G F E D* centromere *C H I*
 Does the abnormal chromosome have a pericentric or paracentric inversion? Draw a sketch showing how these two chromosomes would pair during prophase of meiosis I.

- C7. An inversion heterozygote has the following inverted chromosome:



What would be the products if a crossover occurred between genes *H* and *I* on one inverted and one normal chromosome?

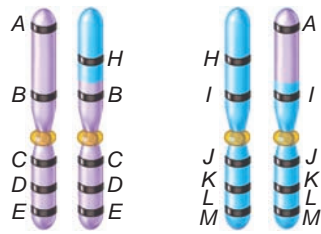
- C8. An inversion heterozygote has the following inverted chromosome:



What would be the products if a crossover occurred between genes *H* and *I* on one inverted and one normal chromosome?

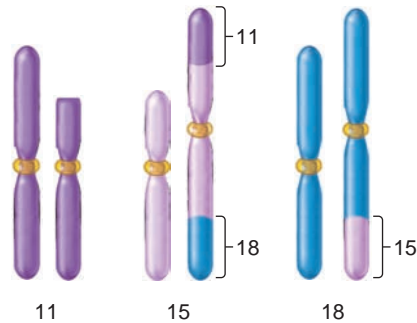
- C9. Explain why inversions and reciprocal translocations do not usually cause a phenotypic effect. In a few cases, however, they do. Explain how.

C10. An individual has the following reciprocal translocation:



What would be the outcome of alternate and adjacent-1 segregation?

C11. A phenotypically normal individual has the following combinations of abnormal chromosomes:



The normal chromosomes are shown on the left of each pair. Suggest a series of events (breaks, translocations, crossovers, etc.) that may have produced this combination of chromosomes.

C12. Two phenotypically normal parents produce a phenotypically abnormal child in which chromosome 5 is missing part of its long arm but has a piece of chromosome 7 attached to it. The child also has one normal copy of chromosome 5 and two normal copies of chromosome 7. With regard to chromosomes 5 and 7, what do you think are the chromosomal compositions of the parents?

C13. In the segregation of centromeres, why is adjacent-2 segregation less frequent than alternate or adjacent-1 segregation?

C14. Which of the following types of chromosomal changes would you expect to have phenotypic consequences? Explain your choices.

- A. Pericentric inversion
- B. Reciprocal translocation
- C. Deletion
- D. Unbalanced translocation

C15. Explain why a translocation cross occurs during metaphase of meiosis I when a cell contains a reciprocal translocation.

C16. A phenotypically abnormal individual has a phenotypically normal father with an inversion on one copy of chromosome 7 and a normal mother without any changes in chromosome structure. The order of genes along chromosome 7 in the father is as follows:

R T D M centromere *P U X Z C* (normal chromosome 7)

R T D U P centromere *M X Z C* (inverted chromosome 7)

The phenotypically abnormal offspring has a chromosome 7 with the following order of genes:

R T D M centromere *P U D T R*

With a sketch, explain how this chromosome was formed. In your answer, explain where the crossover occurred (i.e., between which two genes).

- C17. A diploid fruit fly has eight chromosomes. How many total chromosomes would be found in the following flies?
- A. Tetraploid
 - B. Trisomy 2
 - C. Monosomy 3
 - D. $3n$
 - E. $4n + 1$
- C18. A person is born with one X chromosome, zero Y chromosomes, trisomy 21, and two copies of the other chromosomes. How many chromosomes does this person have altogether? Explain whether this person is euploid or aneuploid.
- C19. Two phenotypically unaffected parents produce two children with familial Down syndrome. With regard to chromosomes 14 and 21, what are the chromosomal compositions of the parents?
- C20. Aneuploidy is typically detrimental, whereas polyploidy is sometimes beneficial, particularly in plants. Discuss why you think this is the case.
- C21. Explain how aneuploidy, deletions, and duplications cause genetic imbalances. Why do you think that deletions and monosomies are more detrimental than duplications and trisomies?
- C22. Female fruit flies homozygous for the X-linked white-eye allele are crossed to males with red eyes. On very rare occasions, an offspring is a male with red eyes. Assuming these rare offspring are not due to a new mutation in one of the mother's X chromosomes that converted the white-eye allele into a red-eye allele, explain how this red-eyed male arose.
- C23. A cytogeneticist has collected tissue samples from members of the same butterfly species. Some of the butterflies were located in Canada, and others were found in Mexico. Upon karyotyping, the cytogeneticist discovered that chromosome 5 of the Canadian butterflies had a large inversion compared with the Mexican butterflies. The Canadian butterflies were inversion homozygotes, whereas the Mexican butterflies had two normal copies of chromosome 5.
- A. Explain whether a mating between the Canadian and Mexican butterflies would produce phenotypically normal offspring.
 - B. Explain whether the offspring of a cross between Canadian and Mexican butterflies would be fertile.
- C24. Why do you think that human trisomies 13, 18, and 21 can survive but the other trisomies are lethal? Even though X chromosomes are large, aneuploidies of this chromosome are also tolerated. Explain why.
- C25. A zookeeper has collected a male and female lizard that look like they belong to the same species. They mate with each other and produce phenotypically normal offspring. However, the offspring are sterile. Suggest one or more explanations for their sterility.
- C26. What is endopolyploidy? What is its biological significance?
- C27. What is mosaicism? How is it produced?

- C28. Explain how polytene chromosomes of *Drosophila melanogaster* are produced and how they form a six-armed structure.
- C29. Describe some of the advantages of polyploid plants. What are the consequences of having an odd number of chromosome sets?
- C30. While conducting field studies on a chain of islands, you decide to karyotype two phenotypically identical groups of turtles, which are found on different islands. The turtles on one island have 24 chromosomes, but those on another island have 48 chromosomes. How would you explain this observation? How do you think the turtles with 48 chromosomes came into being? If you mated the two types of turtles together, would you expect their offspring to be phenotypically normal? Would you expect them to be fertile? Explain.
- C31. A diploid fruit fly has eight chromosomes. Which of the following terms should not be used to describe a fruit fly with four sets of chromosomes?
- Polyploid
 - Aneuploid
 - Euploid
 - Tetraploid
 - $4n$
- C32. Which of the following terms should not be used to describe a human with three copies of chromosome 12?
- Polyploid
 - Triploid
 - Aneuploid
 - Euploid
 - $2n + 1$
 - Trisomy 12
- C33. The kidney bean, *Phaseolus vulgaris*, is a diploid species containing a total of 22 chromosomes in somatic cells. How many possible types of trisomic individuals could be produced in this species?
- C34. The karyotype of a young girl who is affected with familial Down syndrome revealed a total of 46 chromosomes. Her older brother, however, who is phenotypically unaffected, actually had 45 chromosomes. Explain how this could happen. What would you expect to be the chromosomal number in the parents of these two children?
- C35. A triploid plant has 18 chromosomes (i.e., 6 chromosomes per set). If we assume a gamete has an equal probability of receiving one or two copies of each of the six types of chromosome, what are the odds of this plant producing a monoploid or a diploid gamete? What are the odds of producing an aneuploid gamete? If the plant is allowed to self-fertilize, what are the odds of producing a euploid offspring?
- C36. Describe three naturally occurring ways that the chromosome number can change.
- C37. Meiotic nondisjunction is much more likely than mitotic nondisjunction. Based on this observation, would you conclude that meiotic nondisjunction is usually due to nondisjunction during meiosis I or meiosis II? Explain your reasoning.
- C38. A woman who is heterozygous, *Bb*, has brown eyes. *B* (brown) is a dominant allele, and *b* (blue) is recessive. In one of her eyes, however, there is a patch of blue color. Give three different explanations for how this might have occurred.
- C39. What is an allodiploid? What factor determines the fertility of an allodiploid? Why are allotetraploids more likely to be fertile?
- C40. What are homeologous chromosomes?
- C41. Meiotic nondisjunction usually occurs during meiosis I. What is not separating properly: bivalents or sister chromatids? What is not separating properly during mitotic nondisjunction?
- C42. Table 8.1 shows that Turner syndrome occurs when an individual inherits one X chromosome but lacks a second sex chromosome. Can Turner syndrome be due to nondisjunction during oogenesis, spermatogenesis, or both? If a phenotypically normal couple has a color-blind child (due to a recessive X-linked allele) with Turner syndrome, did nondisjunction occur during oogenesis or spermatogenesis in this child's parents? Explain your answer.
- C43. Male honeybees, which are monoploid, produce sperm by meiosis. Explain what unusual event (compared to other animals) must occur during spermatogenesis in honeybees to produce sperm? Does this unusual event occur during meiosis I or meiosis II?

Experimental Questions

- E1. What is the main goal of comparative genome hybridization? Explain how the ratio of green to red fluorescence provides information regarding chromosome structure.
- E2. Let's suppose a researcher conducted comparative genomic hybridization (see Figure 8.9) and accidentally added twice as much (red) DNA from normal cells. What green to red ratio would you expect in a region from a chromosome from a cancer cell that carried a duplication on both chromosomal copies? What ratio would be observed for a region that was deleted on just one of the chromosomes from cancer cells?
- E3. With regard to the analysis of chromosome structure, explain the experimental advantage that polytene chromosomes offer. Discuss why changes in chromosome structure are more easily detected in polytene chromosomes than in ordinary (nonpolytene) chromosomes.
- E4. Describe how colchicine can be used to alter chromosome number.
- E5. Describe the steps you would take to produce a tetraploid plant that is homozygous for all of its genes.
- E6. In agriculture, what is the primary purpose of anther culture?
- E7. What are some experimental advantages of cell fusion techniques as opposed to interbreeding approaches?
- E8. It is an exciting time to be a plant breeder because so many options are available for the development of new types of agriculturally useful plants. Let's suppose you wish to develop a seedless tomato that could grow in a very hot climate and is resistant to a viral pathogen that commonly infects tomato plants. At your disposal, you have a seed-bearing tomato strain that is heat-resistant and produces great-tasting tomatoes. You also have a wild strain of tomato plants (which have lousy-tasting tomatoes) that is resistant

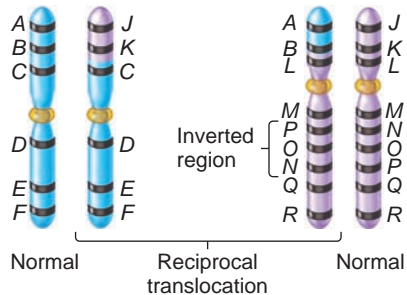
to the viral pathogen. Suggest a series of steps you might follow to produce a great-tasting, seedless tomato that is resistant to heat and the viral pathogen.

- E9. What is a G band? Discuss how G bands are useful in the analysis of chromosome structure.
- E10. A female fruit fly contains one normal X chromosome and one X chromosome with a deletion. The deletion is in the middle of the X chromosome and is about 10% of the entire length of the X chromosome. If you stained and observed the chromosomes of this female fly in salivary gland cells, draw a picture of the polytene arm of the X chromosome. Explain your drawing.
- E11. Describe two different experimental strategies to create an allotetraploid from two different diploid species of plants.

- E12. In the procedure of anther culture (see Figure 8.30), an experimenter may begin with a diploid plant and then cold shock the pollen to get them to grow as haploid plantlets. In some cases, the pollen may come from a phenotypically vigorous plant that is heterozygous for many genes. Even so, many of the haploid plantlets appear rather weak and nonvigorous. In fact, many of them fail to grow at all. In contrast, some of the plantlets are fairly healthy. Explain why some plantlets would be weak, but others are quite healthy.

Questions for Student Discussion/Collaboration

1. A chromosome involved in a reciprocal translocation also has an inversion. In addition, the cell contains two normal chromosomes.



Make a drawing that shows how these chromosomes will pair during metaphase of meiosis I.

2. Besides the ones mentioned in this textbook, look for other examples of variations in euploidy. Perhaps you might look in more advanced textbooks concerning population genetics, ecology, or the like. Discuss the phenotypic consequences of these changes.
3. Cell biology textbooks often discuss cellular proteins encoded by genes that are members of a gene family. Examples of such proteins include myosins and glucose transporters. Look through a cell biology textbook and identify some proteins encoded by members of gene families. Discuss the importance of gene families at the cellular level.
4. Discuss how variation in chromosome number has been useful in agriculture.

Note: All answers appear at the website for this textbook; the answers to even-numbered questions are in the back of the textbook.

www.mhhe.com/brookergenetics4e

Visit the website for practice tests, answer keys, and other learning aids for this chapter. Enhance your understanding of genetics with our interactive exercises, quizzes, animations, and much more.