Types of Chromosome Mutations

Chromosome mutations can be grouped into three basic categories: chromosome rearrangements, aneuploids, and polyploids. Chromosome rearrangements alter the structure of chromosomes; for example, a piece of a chromosome might be duplicated, deleted, or inverted. In aneuploidy, the *number* of chromosomes is altered: one or more individual chromosomes are added or deleted. In polyploidy, one or more complete *sets* of chromosomes are added. Some organisms (such as yeast) possess a single chromosome set ($1n$) for most of their life cycles and are referred to as haploid, whereas others possess two chromosome sets and are referred to as diploid ($2n$). A polyploid is any organism that has more than two sets of chromosomes ($3n$, $4n$, $5n$, or more).

Chromosome Rearrangements

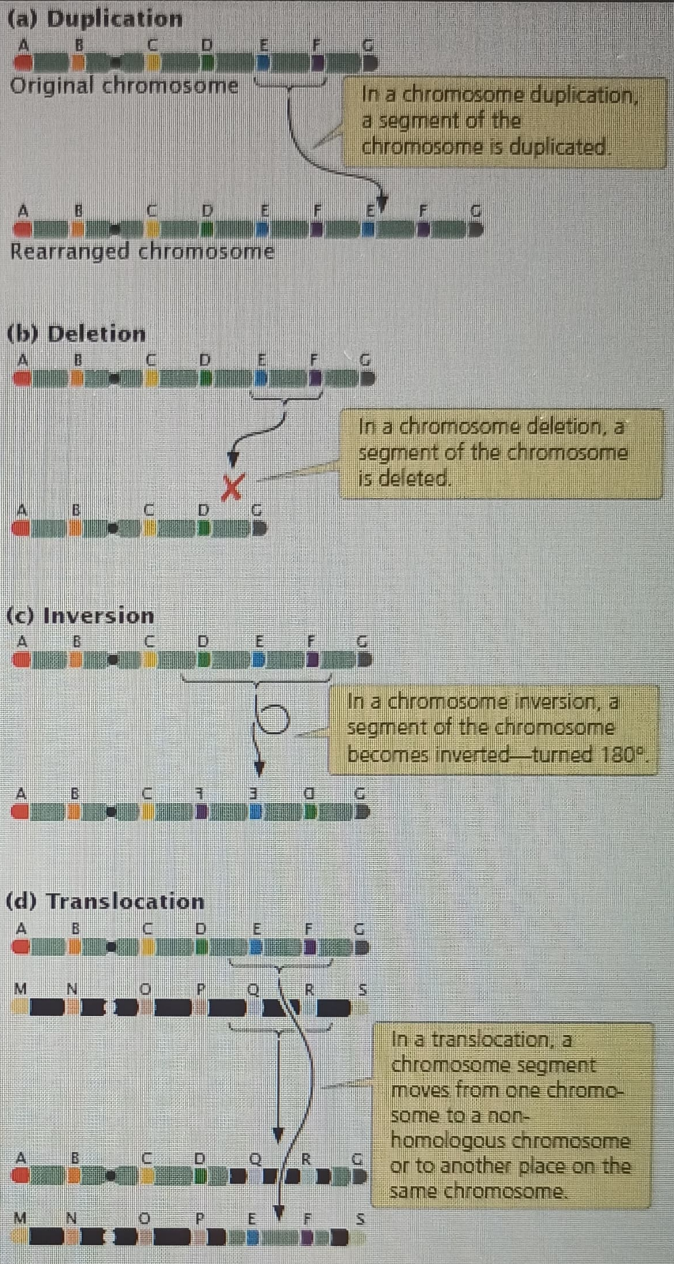
Chromosome rearrangements are mutations that change the structure of individual chromosomes. The four basic types of rearrangements are duplications, deletions, inversions, and translocations (FIGURE 9.5).

Duplications

A **chromosome duplication** is a mutation in which part of the chromosome has been doubled (see Figure 9.5a). Consider a chromosome with segments AB•CDEFG, in which • represents the centromere. A duplication might include the EF segments, giving rise to a chromosome with segments AB•CDEFEFG. This type of duplication, in which the duplicated region is immediately adjacent to the original segment, is called a **tandem duplication.** If the duplicated segment is located some distance from the original segment, either on the same chromosome or on a different one, this type is called a **displaced duplication.** An example of a displaced duplication would be AB•CDEFGEF. A duplication either can be in the same orientation as that of the original sequence, as in the two preceding examples, or can be inverted: AB•CDEFFEG. When the duplication is inverted, it is called a **reverse duplication.**

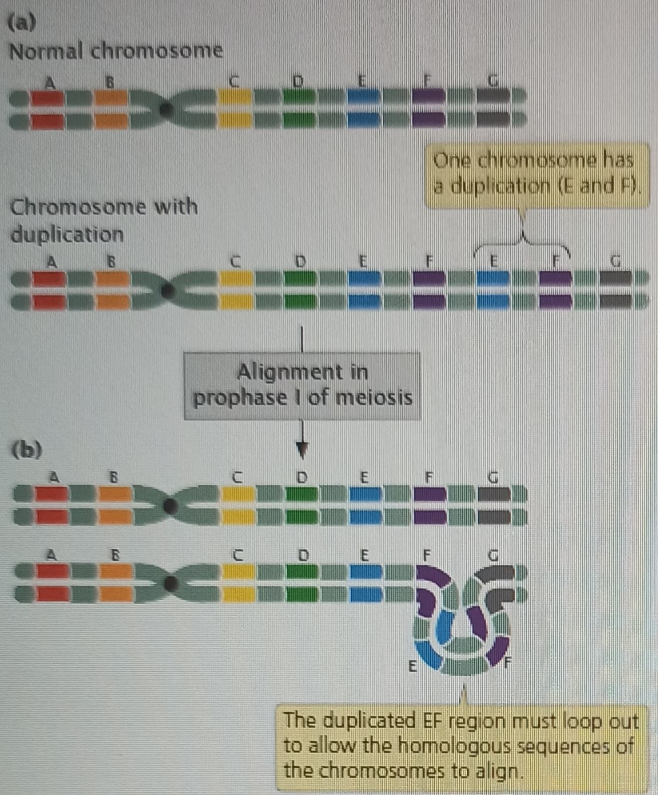
An individual homozygous for a duplication carries the duplication (the mutated sequence) on both homologous chromosomes, and an individual heterozygous for a duplication has one unmutated chromosome and one chromosome with the duplication. In the heterozygotes (FIGURE 9.6a), problems arise in chromosome pairing at prophase I of meiosis, because the two chromosomes are not homologous throughout their length. The pairing and synapsis of homologous regions require that one or both chromosomes loop and twist so that these regions are able to line up (FIGURE 9.6b). The appearance of this characteristic loop structure in meiosis is one way to detect duplications.

Duplications may have major effects on the phenotype. Among *Drosophila melanogaster,* for example, a fly having a *Bar* mutation has a reduced number of facets in the eye, making the eye smaller and bar shaped instead of oval

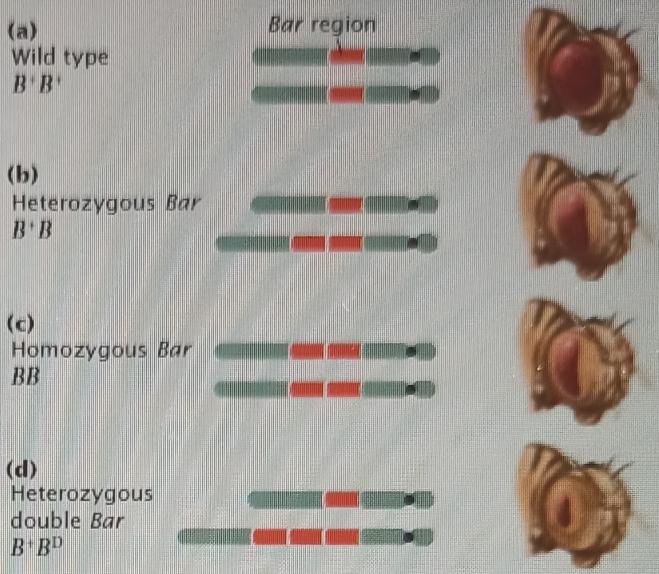


9.5 The four basic types of chromosome rearrangements are duplication, deletion, inversion, and translocation.

(FIGURE 9.7). The *Bar* mutation results from a small duplication on the X chromosome, which is inherited as an incompletely dominant, X-linked trait: heterozygous female flies have somewhat smaller eyes (the number of facets is reduced; see Figure 9.7b), whereas, in homozygous female and hemizygous male flies, the number of facets is greatly reduced (see Figure 9.7c). Occasionally, a fly carries three copies of the *Bar* duplication on its X chromosome; for flies carrying such mutations, which are termed *double Bar,* the number of facets is extremely reduced (see Figure 9.7d). The *Bar* mutation arises from unequal crossing over, a duplication-generating process (FIGURE 9.8; see also Figure 17.15).



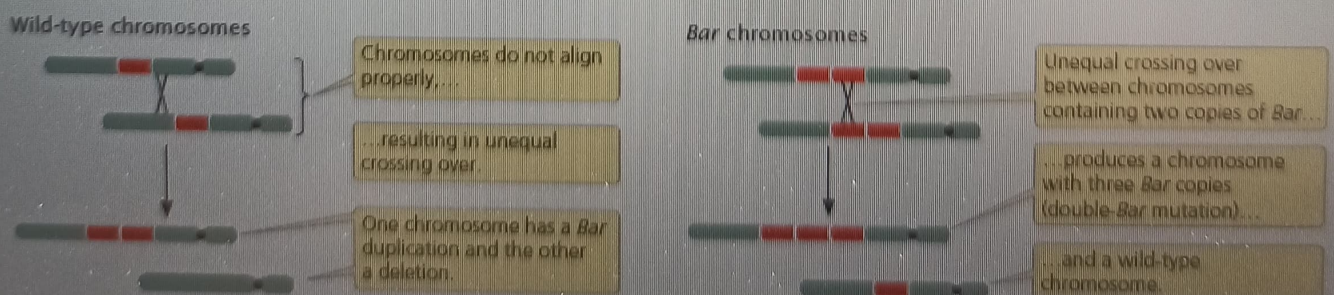
9.6 In an individual heterozygous for a duplication, the duplicated chromosome loops out during pairing in prophase I.



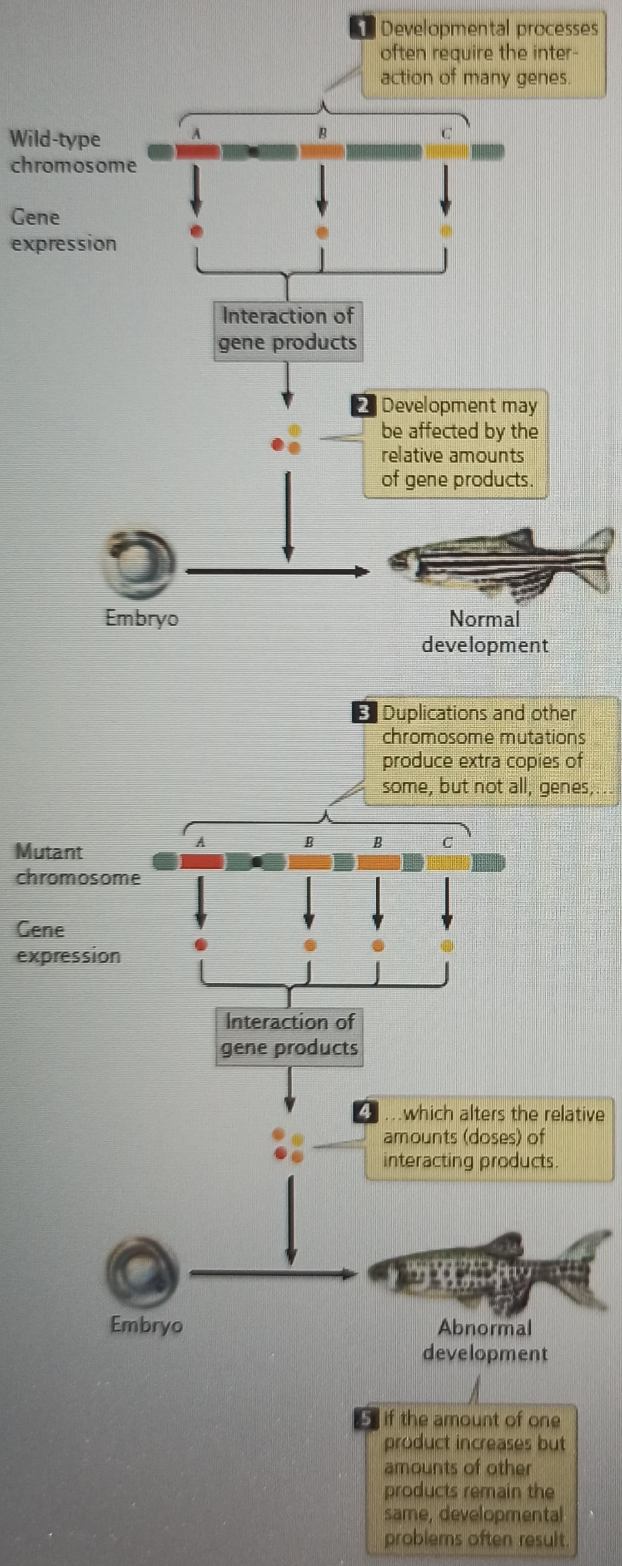
9.7 The Bar phenotype in *Drosophila melanogaster* results from an X-linked duplication. (a) Wild-type fruit flies have normal-size eyes. (b) Flies heterozygous and (c) homozygous for the *Bar* mutation have smaller, bar-shaped eyes. (d) Flies with double *Bar* have three copies of the duplication and much smaller bar-shaped eyes.

How does a chromosome duplication alter the phenotype? After all, gene sequences are not altered by duplications, and no genetic information is missing; the only change is the presence of additional copies of normal sequences. The answer to this question is not well understood, but the effects are most likely due to imbalances in the amounts of gene products (abnormal gene dosage). The amount of a particular protein synthesized by a cell is often directly related to the number of copies of its corresponding gene: an individual organism with three functional copies of a gene often produces 1.5 times as much of the protein encoded by that gene as that produced by an individual with two copies.

Because developmental processes often require the interaction of many proteins, they may critically depend on the relative amounts of the proteins. If the amount of one protein increases while the amounts of others remain constant, problems can result (FIGURE 9.9). Although duplications can have severe consequences when the precise balance of a gene product is critical to cell function, duplications have arisen frequently throughout the evolution of many eukaryotic organisms and are a source of new genes that may provide novel functions. For example, humans have a series of genes that code for different globin chains, some of which function as an oxygen carrier during adult stages and others that function during embryonic and fetal development. All of these globin genes arose from an original ancestral gene that underwent a series of duplications. Human phenotypes associated with some duplications are summarized in Table 9.1.



9.8 Unequal crossing over produces *Bar* and double-*Bar* mutations.



9.9 Unbalanced gene dosage leads to developmental abnormalities.

A chromosome duplication is a mutation that doubles part of a chromosome. In individuals heterozygous for a chromosome duplication, the duplicated region of the chromosome loops out when homologous chromosomes pair in prophase I of meiosis. Duplications often have major effects on the phenotype, possibly by altering gene dosage.

Deletions

A second type of chromosome rearrangement is a **chromosome deletion,** the loss of a chromosome segment (*see* Figure 9.5b). A chromosome with segments AB•CDEFG that undergoes a deletion of segment EF would generate the mutated chromosome AB•CDG.

A large deletion can be easily detected because the chromosome is noticeably shortened. In individuals heterozygous for deletions, the normal chromosome must loop out during the pairing of homologs in prophase I of meiosis (FIGURE 9.10) to allow the homologous regions of the two chromosomes to align and undergo synapsis. This looping out generates a structure that looks very much like that seen for individuals heterozygous for duplications.

The phenotypic consequences of a deletion depend on which genes are located in the deleted region. If the deletion includes the centromere, the chromosome will not segregate in meiosis or mitosis and will usually be lost. Many deletions are lethal in the homozygous state because all copies of any essential genes located in the deleted region are missing. Even individuals heterozygous for a deletion may have multiple defects for three reasons.

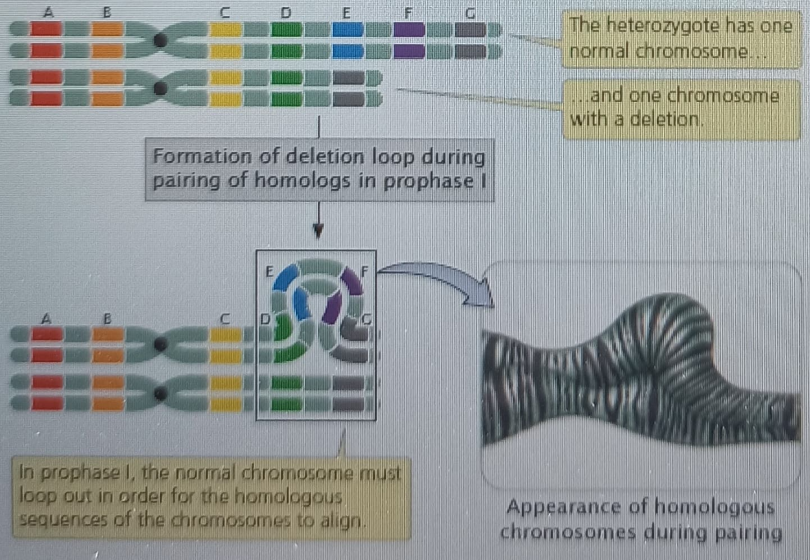
First, the heterozygous condition may produce imbalances in the amounts of gene products, similar to the imbalances produced by extra gene copies. Second, recessive mutations on the homologous chromosome lacking the deletion may be expressed when the wild-type allele has been deleted (and is no longer present to mask the recessive allele's expression). The expression of a recessive mutation is referred to as **pseudodominance,** and it is an indication that one of the homologous chromosomes has a deletion. Third, some genes must be present in two copies for normal function. When a single copy of a gene is not sufficient to produce a wild-type phenotype, it is said to be a **haploinsufficient gene.** Loss-of-function mutations in haploinsufficient genes are dominant. *Notch* is a series of X-linked wing mutations in *Drosophila* that often result from chromosome deletions. *Notch* deletions behave as dominant mutations: when heterozygous for the *Notch* deletion, a fly has wings that are notched at the tips and along the edges (FIGURE 9.11). The *Notch* locus is therefore haploinsufficient. Females that are homozygous for a *Notch* deletion (or males that are hemizygous) die early in embryonic development. The *Notch* gene codes for a receptor that normally transmits signals received from outside the cell to the cell's interior

Table 9.1 Effects of some human chromosome rearrangements

Type of rearrangement	Chromosome	Disorder	Symptoms
Duplication	4, short arm	—	Small head, short neck, low hairline, growth and mental retardation
Duplication	4, long arm	—	Small head, sloping forehead, hand abnormalities
Duplication	7, long arm	—	Delayed development, asymmetry of the head, fuzzy scalp, small nose, low-set ears
Duplication	9, short arm	—	Characteristic face, variable mental retardation, high and broad forehead, hand abnormalities
Deletion	5, short arm	*Cri-du-chat* syndrome	Small head, distinctive cry, widely spaced eyes, round face, mental retardation
Deletion	4, short arm	Wolf-Hirschhorn syndrome	Small head with high forehead, wide nose, cleft lip and palate, severe mental retardation
Deletion	4, long arm	—	Small head, from mild to moderate mental retardation, cleft lip and palate, hand and foot abnormalities
Deletion	15, long arm	Prader-Willi syndrome	Feeding difficulty at early age, but becoming obese after 1 year of age, from mild to moderate mental retardation
Deletion	18, short arm	—	Round face, large low-set ears, from mild to moderate mental retardation
Deletion	18, long arm	—	Distinctive mouth shape, small hands, small head, mental retardation

and is important in fly development. The deletion acts as a recessive lethal because loss of all copies of the *Notch* gene prevents normal development.

In humans, a deletion on the short arm of chromosome 5 is responsible for *cri-du-chat* syndrome. The name (French for "cry of the cat") derives from the peculiar, catlike cry of infants with this syndrome. A child who is heterozygous for this deletion has a small head, widely spaced eyes, and a round face and is mentally retarded. Deletion of part of the short arm of chromosome 4 results in another human disorder—Wolf-Hirschhorn syndrome, which is characterized by seizures and by severe mental and growth retardation.



9.10 In an individual heterozygous for a deletion, the normal chromosome loops out during chromosome pairing in prophase I.

9.11 **The Notch phenotype is produced by a chromosome deletion that includes the *Notch* gene.** (Top) Normal wing veination. (Bottom) Wing veination produced by *Notch* mutation. (Spyros Artavanis-Tsakonas, Kenji Matsuno, and Mark E. Fortini.)

CONCEPTS

A chromosomal deletion is a mutation in which a part of a chromosome is lost. In individuals heterozygous for a deletion, the normal chromosome loops out during prophase I of meiosis. Deletions cause recessive genes on the homologous chromosome to be expressed and may cause imbalances in gene products.

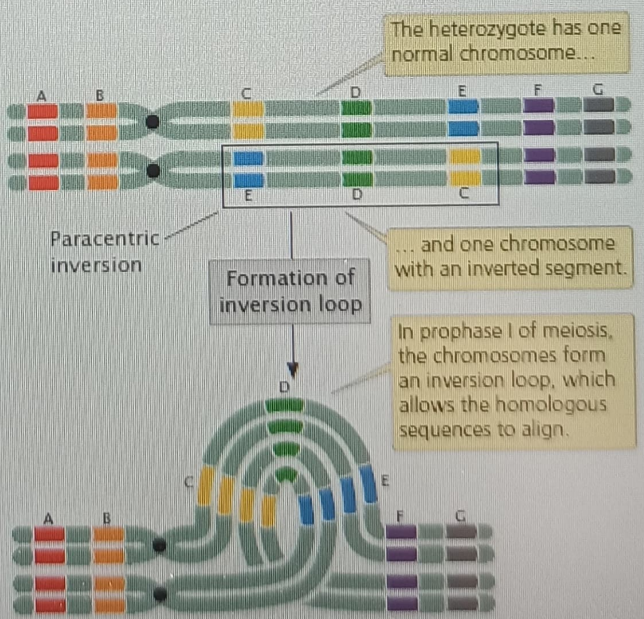
Inversions

A third type of chromosome rearrangement is a **chromosome inversion,** in which a chromosome segment is inverted—turned 180 degrees (see Figure 9.5c). If a chromosome originally had segments AB•CDEFG, then chromosome AB•CFEDG represents an inversion that includes segments DEF. For an inversion to take place, the chromosome must break in two places. Inversions that do not include the centromere, such as AB•CFEDG, are termed **paracentric inversions** (*para* meaning "next to"), whereas inversions that include the centromere, such as ADC•BEFG, are termed **pericentric inversions** (*peri* meaning "around").

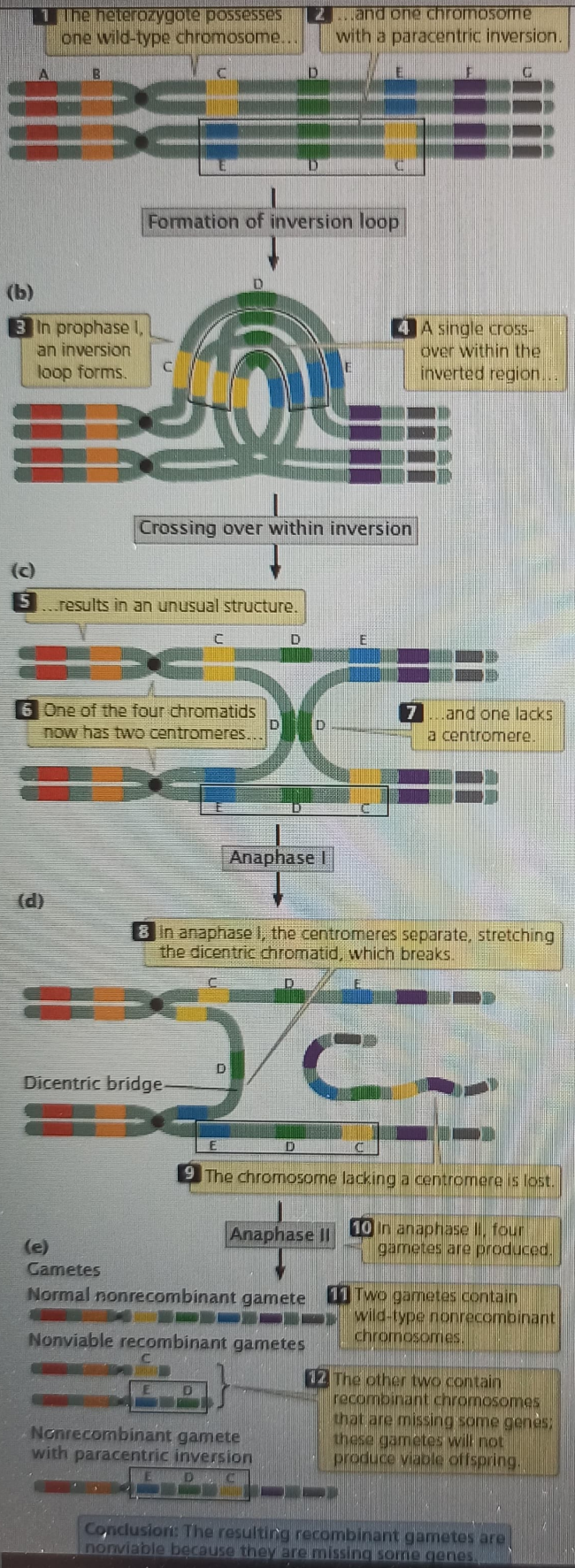
Individual organisms with inversions have neither lost nor gained any genetic material; just the gene order has been altered. Nevertheless, these mutations often have pronounced phenotypic effects. An inversion may break a gene into two parts, with one part moving to a new location and destroying the function of that gene. Even when the chromosome breaks are between genes, phenotypic effects may arise from the inverted gene order in an inversion. Many genes are regulated in a position-dependent manner; if their positions are altered by an inversion, they may be expressed at inappropriate times or in inappropriate tissues. This outcome is referred to as a **position effect.**

When an individual is homozygous for a particular inversion, no special problems arise in meiosis, and the two homologous chromosomes can pair and separate normally. When an individual is heterozygous for an inversion, however, the gene order of the two homologs differs, and the homologous sequences can align and pair only if the two chromosomes form an inversion loop (FIGURE 9.12). The presence of an inversion loop in meiosis indicates that an inversion is present.

Individuals heterozygous for inversions also exhibit reduced recombination among genes located in the inverted region. The frequency of crossing over within the inversion is not actually diminished but, when crossing over does take place, the result is a tendency to produce gametes that are not viable and thus no recombinant progeny are observed. Let's see why this occurs.



9.12 **In an individual heterozygous for a paracentric inversion, the chromosomes form an inversion loop during pairing in prophase I.**



9.13 In a heterozygous individual, a single crossover within a paracentric inversion leads to abnormal gametes.

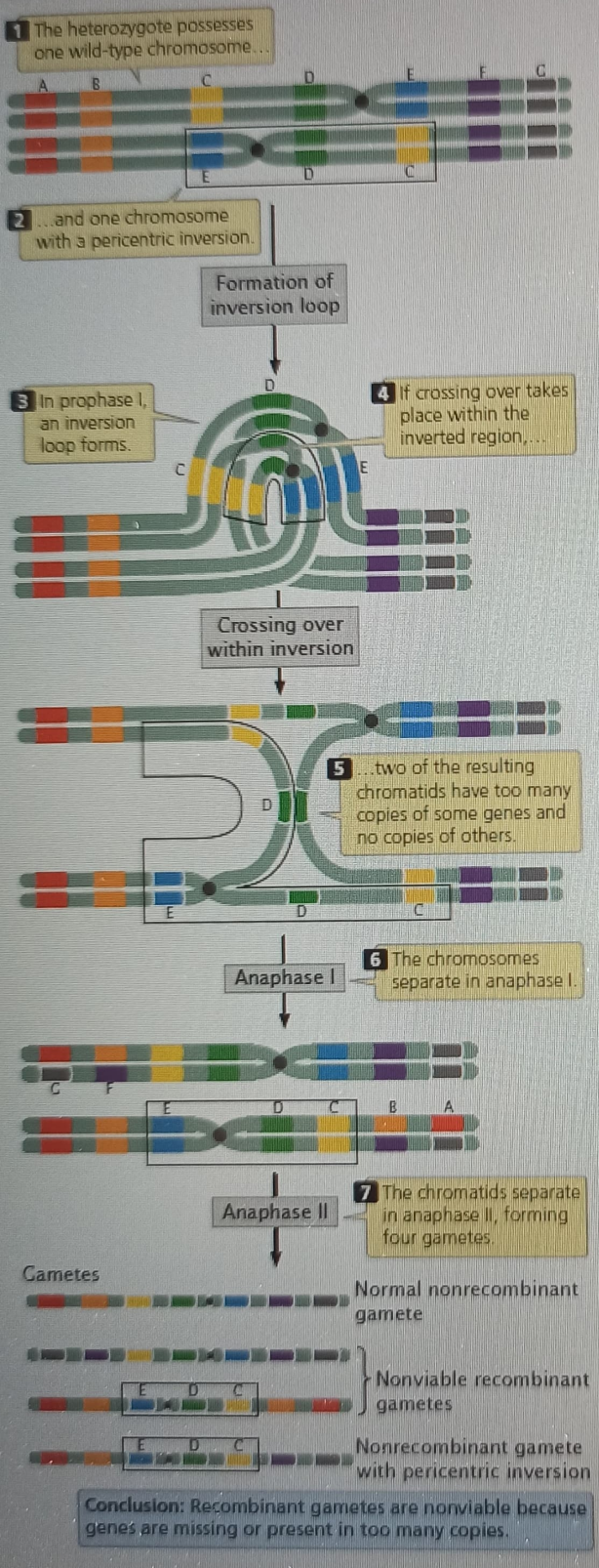
FIGURE 9.13 illustrates the results of crossing over within a paracentric inversion. The individual is heterozygous for an inversion (see Figure 9.13a), with one wild-type, unmutated chromosome (AB•CDEFG) and one inverted chromosome (AB•EDCFG). In prophase I of meiosis, an inversion loop forms, allowing the homologous sequences to pair up (see Figure 9.13b). If a single crossover takes place in the inverted region (between segments C and D in Figure 9.13), an unusual structure results (see Figure 9.13c). The two outer chromatids, which did not participate in crossing over, contain original, nonrecombinant gene sequences. The two inner chromatids, which did cross over, are highly abnormal: each has two copies of some genes and no copies of others. Furthermore, one of the four chromatids now has two centromeres and is said to be a **dicentric chromatid;** the other lacks a centromere and is an **acentric chromatid.**

In anaphase I of meiosis, the centromeres are pulled toward opposite poles and the two homologous chromosomes separate. This stretches the dicentric chromatid across the center of the nucleus, forming a structure called a **dicentric bridge** (see Figure 9.13d). Eventually, the dicentric bridge breaks, as the two centromeres are pulled farther apart. The acentric fragment has no centromere. Spindle fibers do not attach to it, and so this fragment does not segregate into a nucleus in meiosis and is usually lost.

In the second division of meiosis, the chromatids separate and four gametes are produced (see Figure 9.13e). Two of the gametes contain the original, nonrecombinant chromosomes (AB•CDEFG and AB•EDCFG). The other two gametes contain recombinant chromosomes that are missing some genes; these gametes will not produce viable offspring. Thus, no recombinant progeny result when crossing over takes place within a paracentric inversion.

Recombination is also reduced within a pericentric inversion (FIGURE 9.14). No dicentric bridges or acentric fragments are produced, but the recombinant chromosomes have too many copies of some genes and no copies of others; so gametes that receive the recombinant chromosomes cannot produce viable progeny.

Figures 9.13 and 9.14 illustrate the results of single crossovers within inversions. Double crossovers, in which both crossovers are on the same two strands (two-strand, double crossovers), result in functional, recombinant chromosomes. (Try drawing out the results of a double crossover.) Thus, even though the overall rate of recombination is reduced within an inversion, some viable recombinant progeny may still be produced through two-stranded double crossovers.



9.14 In a heterozygous individual, a single crossover within a pericentric inversion leads to abnormal gametes.

Inversion heterozygotes are common in many organisms, including a number of plants, some species of *Drosophila*, mosquitoes, and grasshoppers. Inversions may have played an important role in human evolution: G-banding patterns reveal that several human chromosomes differ from those of chimpanzees by only a pericentric inversion (FIGURE 9.15).

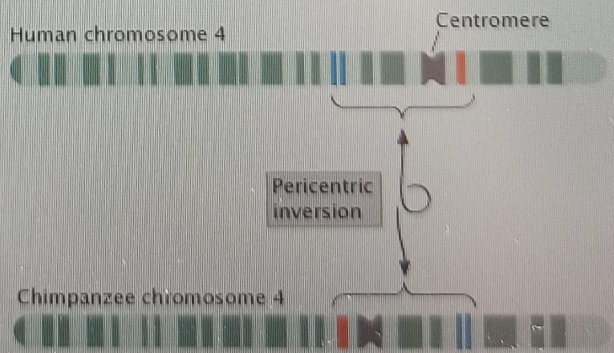
CONCEPTS

In an inversion, a segment of a chromosome is inverted. Inversions cause breaks in some genes and may move others to new locations. In heterozygotes for a chromosome inversion, the homologous chromosomes form loops in prophase I of meiosis. When crossing over takes place within the inverted region, nonviable gametes are usually produced, resulting in a depression in observed recombination frequencies.

Translocations

A **translocation** entails the movement of genetic material between nonhomologous chromosomes (see Figure 9.5d) or within the same chromosome. Translocation should not be confused with crossing over, in which there is an exchange of genetic material between *homologous* chromosomes.

In a **nonreciprocal translocation,** genetic material moves from one chromosome to another without any reciprocal exchange. Consider the following two nonhomologous chromosomes: AB•CDEFG and MN•OPQRS. If chromosome segment EF moves from the first chromosome to the second without any transfer of segments from



9.15 Chromosome 4 differs in humans and chimpanzees in a pericentric inversion.

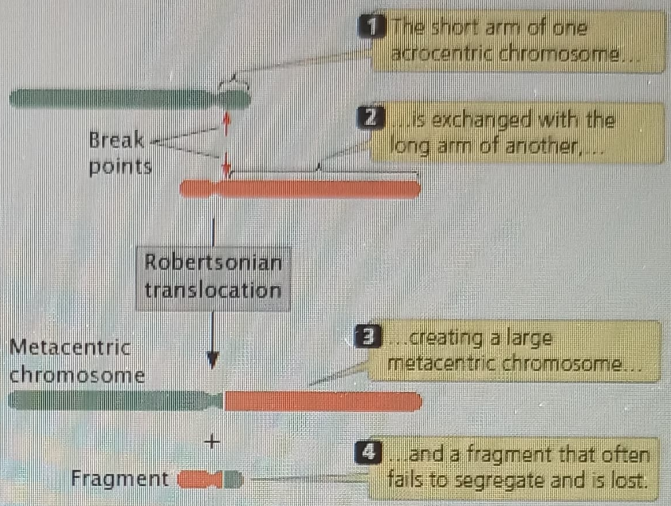
the second chromosome to the first, a nonreciprocal translocation has taken place, producing chromosomes AB•CDG and MN•OPEFQRS. More commonly, there is a two-way exchange of segments between the chromosomes, resulting in a **reciprocal translocation.** A reciprocal translocation between chromosomes AB•CDEFG and MN•OPQRS might give rise to chromosomes AB•CDQRG and MN•OPEFS.

Translocations can affect a phenotype in several ways. First, they may create new linkage relations that affect gene expression (a position effect): genes translocated to new locations may come under the control of different regulatory sequences or other genes that affect their expression—an example is found in Burkitt lymphoma, to be discussed later in this chapter.

Second, the chromosomal breaks that bring about translocations may take place within a gene and disrupt its function. Molecular geneticists have used these types of effects to map human genes. Neurofibromatosis is a genetic disease characterized by numerous fibrous tumors of the skin and nervous tissue; it results from an autosomal dominant mutation. Linkage studies first placed the locus for neurofibromatosis on chromosome 17. Geneticists later identified two patients with neurofibromatosis who possessed a translocation affecting chromosome 17. These patients were assumed to have developed neurofibromatosis because one of the chromosome breaks that occurred in the translocation disrupted a particular gene that causes neurofibromatosis. DNA from the regions around the breaks was sequenced and eventually led to the identification of the gene responsible for neurofibromatosis.

Deletions frequently accompany translocations. In a **Robertsonian translocation,** for example, the long arms of two acrocentric chromosomes become joined to a common centromere through a translocation, generating a metacentric chromosome with two long arms and another chromosome with two very short arms (FIGURE 9.16). The smaller chromosome often fails to segregate, leading to an overall reduction in chromosome number. As we will see, Robertsonian translocations are the cause of some cases of Down syndrome.

The effects of a translocation on chromosome segregation in meiosis depend on the nature of the translocation. Let us consider what happens in an individual heterozygous for a reciprocal translocation. Suppose that the original chromosomes were AB•CDEFG and MN•OPQRS (designated N_1 and N_2, respectively), and a reciprocal translocation takes place, producing chromosomes AB•CDQRS and MN•OPEFG (designated T_1 and T_2, respectively). An individual heterozygous for this translocation would possess one normal copy of each chromosome and one translocated copy (FIGURE 9.17a). Each of these chromosomes contains segments that are homologous to *two* other chromosomes. When the homologous sequences pair in prophase I of meiosis, crosslike



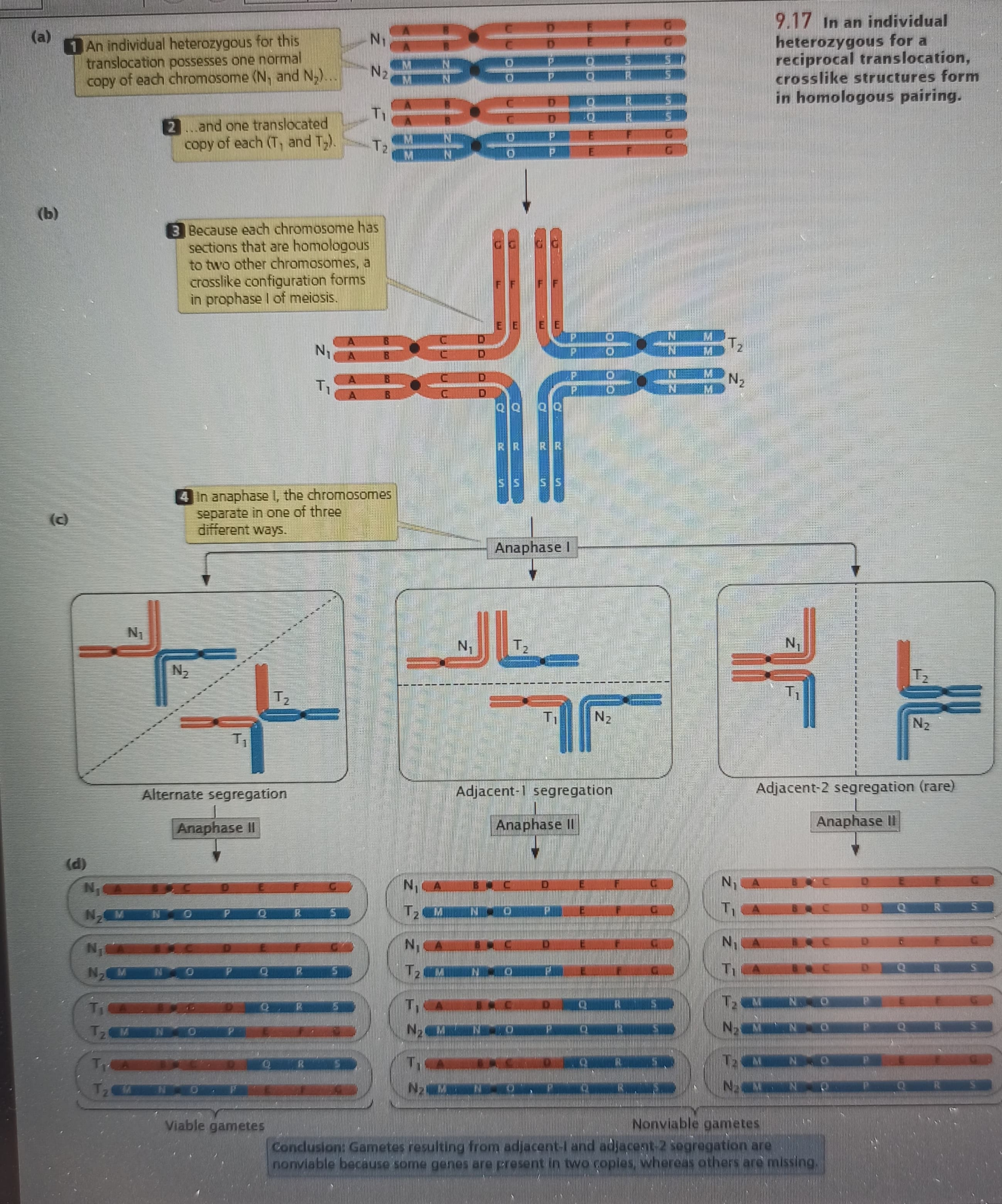
9.16 In a Robertsonian translocation, the short arm of one acrocentric chromosome is exchanged with the long arm of another.

configurations consisting of all four chromosomes (FIGURE 9.17b) form.

Notice that N_1 and T_1 have homologous centromeres (in both chromosomes, the centromere is between segments B and C); similarly, N_2 and T_2 have homologous centromeres (between segments N and O). Normally, homologous centromeres separate and move toward opposite poles in anaphase I of meiosis. With a reciprocal translocation, the chromosomes may segregate in three different ways. In **alternate segregation** (FIGURE 9.17c), N_1 and N_2 move toward one pole and T_1 and T_2 move toward the opposite pole. In **adjacent-1 segregation,** N_1 and T_2 move toward one pole and T_1 and N_2 move toward the other pole. In both alternate and adjacent-1 segregation, homologous centromeres segregate toward opposite poles. **Adjacent-2 segregation,** in which N_1 and T_1 move toward one pole and T_2 and N_2 move toward the other, is rare.

The products of the three segregation patterns are illustrated in FIGURE 9.17d. As you can see, the gametes produced by alternate segregation possess one complete set of the chromosome segments. These gametes are therefore functional and can produce viable progeny. In contrast, gametes produced by adjacent-1 and adjacent-2 segregation are not viable, because some chromosome segments are present in two copies, whereas others are missing. Adjacent-2 segregation is rare, and so most gametes are produced by alternate or adjacent-1 segregation. Therefore, approximately half of the gametes from an individual heterozygous for a reciprocal translocation are expected to be functional.

Translocations can play an important role in the evolution of karyotypes. Chimpanzees, gorillas, and orangutans all have 48 chromosomes, whereas humans have 46. Human chromosome 2 is a large, metacentric chromosome with G-banding patterns that match those found on two different



9.17 In an individual heterozygous for a reciprocal translocation, crosslike structures form in homologous pairing.

1.9.5 Position effect

The change in the phenotypic expression of one or more genes as a result of a change in position in the genome is called *position effect*. Position effect may be exhibited if a gene located in euchromatin is brought near heterochromatin. These effects are either *stable*, as in the Bar eye of *Drosophila* or *variegated*, as with *Drosophila* eye colour.

The white gene controls eye pigment production in *Drosophila*. The locus for white gene is near the tip of the X-chromosome. Wild type flies with a normal white gene (*white*$^+$) have normal pigment production, which gives them red eyes, but if the white gene is mutated and inactivated, the mutant flies (*white*$^-$) make no pigment and have white eyes. In case of *position effect variegation*, the eyes are mottled, with both red and white patches. The white patches represent cells in which *white*$^+$ gene is inactive, whereas red patches represent cells with active *white*$^+$ gene. Inactivation of *white*$^+$ gene in cells of white patches is due to change in the position of *white*$^+$ gene from euchromatin region to adjacent heterochromatin region. This difference in gene expression is an example of position effects because the activity of a gene depends on its position along a chromosome.

There is also a position effect in the *Bar system*. Both a homozygous Bar and a heterozygous double Bar have four copies of the 16A regions. It would therefore be reasonable to expect that both genotypes would produce the same phenotype. However, the homozygous Bar has about 70 facets in each eye, whereas the heterozygote has about 45.

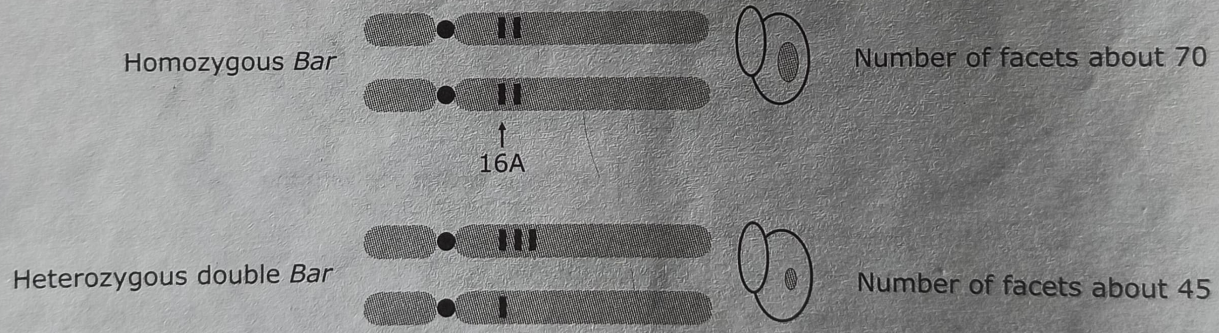
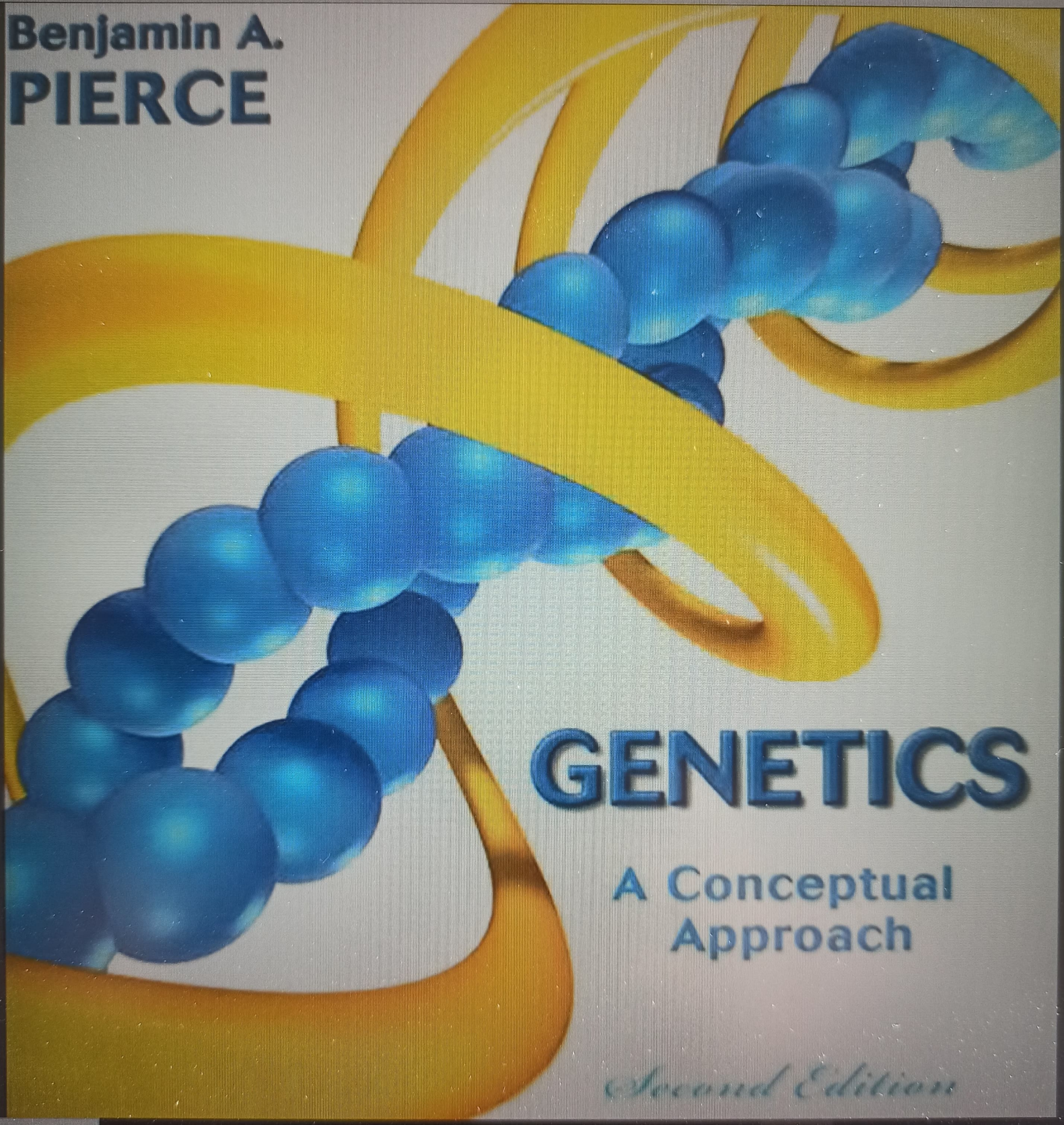


Figure 1.41 Position effect and Bar eye in *Drosophila*. In homozygous Bar females, there are four copies of 16A loci, two on each homolog; these flies have about 70 facets in their reduced eyes. In females heterozygous for double-Bar, there are also four copies of 16A loci, three on the double-Bar chromosome and one on the normal chromosome; even though the number of loci is the same, these flies have smaller eyes, with about 45 facets.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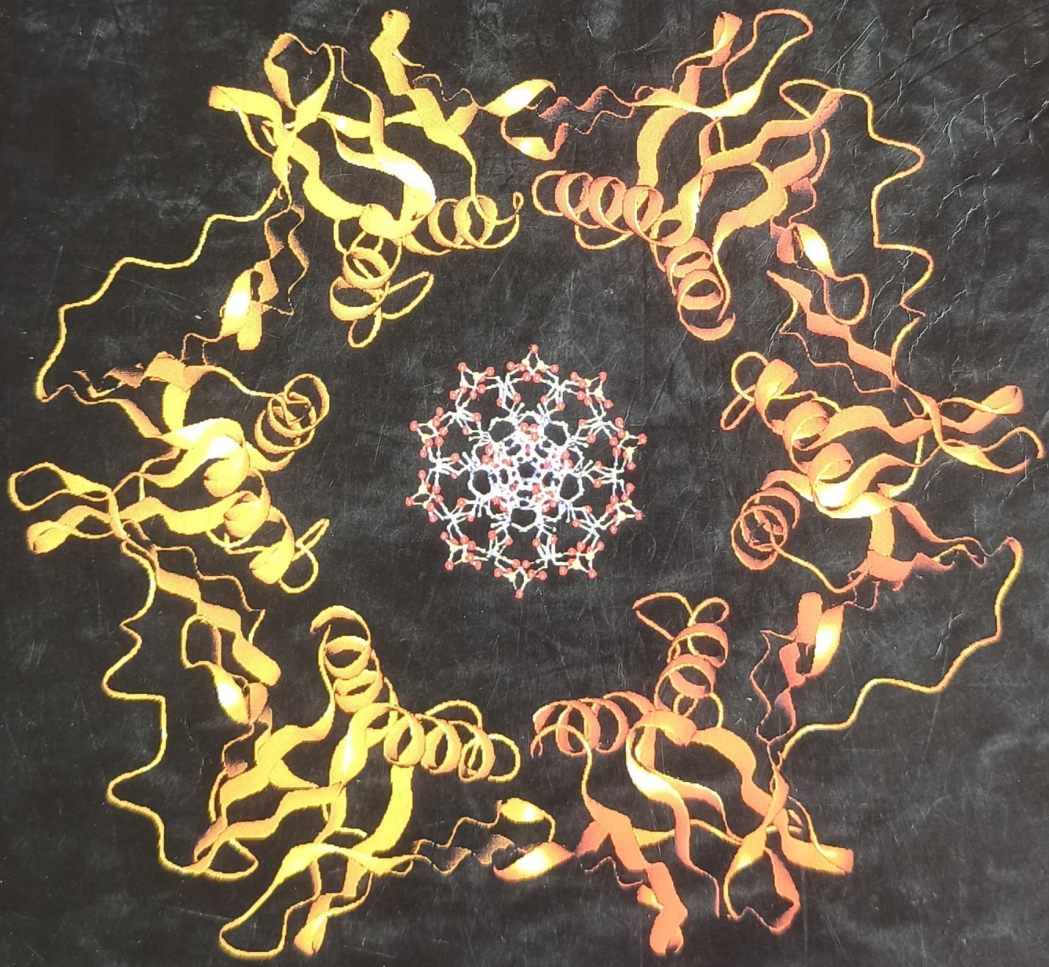

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