

# 8

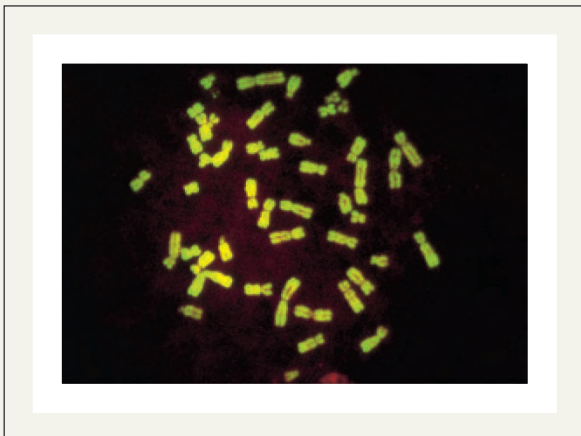
## CYTOGENETICS

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1. To observe the nature and consequences of chromosomal breakage and reunion 178
2. To observe the nature and consequences of variation in chromosome numbers in human and nonhuman organisms 190

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Chromosomes of an individual with trisomy 21, Down syndrome. (© Dr. Ram Verma /Phototake, NYC.)

Our understanding of the chromosomal theory of genetics grew primarily through mapping loci, using techniques that require alternative allelic forms, or mutations, of these loci. Changes in the genetic material also occur at a much coarser level—the level of **cytogenetics**, which is a level visible under the light microscope. The word *cytogenetics* combines the words *cytology* and *genetics*; cytology is the study of cells. Cytogenetics is thus defined as the study of cells from the perspective of genetics. In practice, it is the study of changes in the gross structure and number of chromosomes in cells. In this chapter, we investigate how these alterations happen and what their consequences are to the organism.

## VARIATION IN CHROMOSOMAL STRUCTURE



In general, chromosomes can break due to ionizing radiation, physical stress, or chemical compounds. When a break occurs in the chromosome before DNA replication, during the S phase of the cell cycle (see fig. 3.6), the break itself is replicated. After the S phase, any breaks that occur affect single chromatids.

Every break in a chromatid produces two ends. These ends have been described as “sticky,” meaning simply that enzymatic processes of the cell tend to reunite them. Broken ends do not attach to the undamaged terminal ends of other chromosomes. (Normal chromosomal ends are capped with structures called *telomeres*—see chapter 15.) If broken ends are not brought together, they can remain broken. But, if broken chromatid ends are brought into apposition, they may rejoin in any of several ways. First, the two broken ends of a single chromatid can reunite. Second, the broken end of one chromatid can fuse with the broken end of another chromatid, resulting in an exchange of chromosomal material and a new combination of alleles. Multiple breaks can lead to a variety of alternative recombinations. These chromosomal aberrations have major genetic, evolutionary, and medical consequences. The types of breaks and reunions discussed in this chapter can be summarized as follows:

- I. Noncentromeric breaks
  - A. Single breaks
    1. Restitution
    2. Deletion
    3. Dicentric bridge
  - B. Two breaks (same chromosome)
    1. Deletion
    2. Inversion
  - C. Two breaks (nonhomologous chromosomes)

- II. Centromeric breaks
  - A. Fission
  - B. Fusion

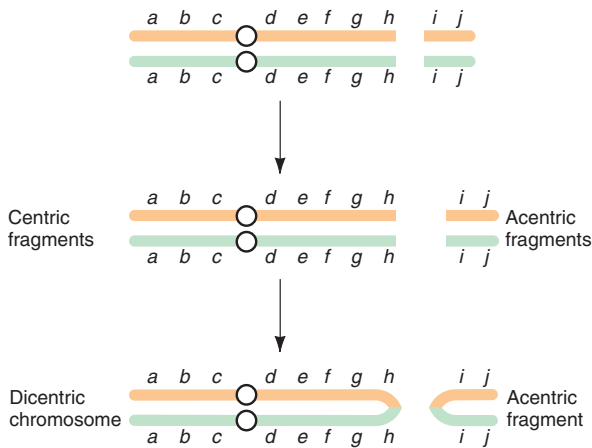
### Single Breaks

If a chromosome breaks, the broken ends may rejoin. When the broken ends of a single chromatid rejoin (in a process called restitution), there is no consequence to the break. If they do not rejoin, the result is an **acentric fragment**, without a centromere, and a **centric fragment**, with a centromere. The centric fragment migrates normally during the division process because it has a centromere. The acentric fragment, however, is soon lost. It is subsequently excluded from the nuclei formed and eventually degrades. In other words, the viable, centric part of the chromosome has suffered a deletion. After mitosis, the daughter cell that receives the **deletion chromosome** may show several effects.

Pseudodominance is one possible effect. (This term was used in chapter 5 when we described alleles located on the X chromosome. With only one copy of the locus present, a recessive allele in males shows itself in the phenotype as if it were dominant—hence the term *pseudodominance*.) The normal chromosome homologous to the deletion chromosome has loci in the region, and recessive alleles show pseudodominance. A second possible effect is that, depending on the length of the deleted segment and the specific loci lost, the imbalance the deletion chromosome creates in the daughter cell may be lethal. If the deletion occurs before or during meiosis, it may be observed under the microscope. We discuss this event later in the chapter.

A single break can have yet another effect. Occasionally, the two centric fragments of a single chromosome may join, forming a two-centromere, or **dicentric chromosome** and leaving the two acentric fragments to join or, alternatively, remain as two fragments (fig. 8.1). The acentric fragments are lost, as mentioned before. Because the centromeres are on sister chromatids, the dicentric fragment is pulled to opposite ends of a mitotic cell forming a bridge there; or, if meiosis is occurring, the dicentric fragment is pulled apart during the second meiotic division. The ultimate fate of this bridge is breakage as the spindle fibers pull the centromeres to opposite poles (or possibly exclusion from a new nucleus if the bridge is not broken).

The dicentric chromosome does not necessarily break in the middle, and subsequent processes exacerbate the imbalance created by an off-center break: duplications occur on one strand, whereas more deletions occur on the other (fig. 8.2). In addition, the “sticky” ends produced on both fragments increase the likelihood of repeating this **breakage-fusion-bridge cycle** in each generation. The great imbalances resulting from the duplications and deletions usually cause the cell line to die within several generations.

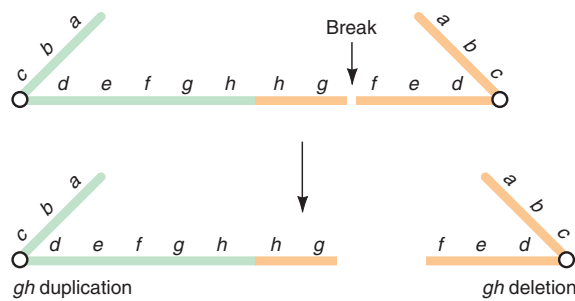


**Figure 8.1** Chromosomal break with subsequent reunion to form a dicentric chromosome and an acentric fragment.

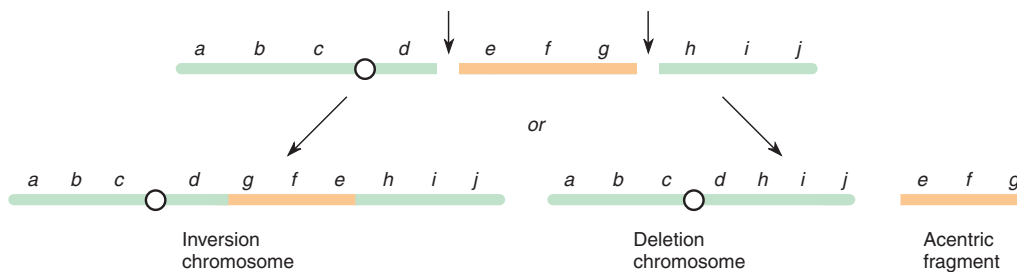
### Two Breaks in the Same Chromosome

#### Deletion

Figure 8.3 shows two of the possible results when two breaks occur in the same chromosome. One alternative is a reunion that omits an acentric fragment, which is then lost. The centric piece, missing the acentric fragment (*e-f-g* in fig. 8.3), is a deletion chromosome. An organism



**Figure 8.2** Breakage of a dicentric bridge causes duplications and additional deficiencies.



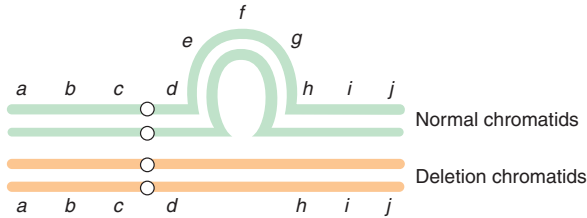
**Figure 8.3** Two possible consequences of a double break (top arrows) in the same chromosome.

having this chromosome and a normal homologue will have, during meiosis, a bulge in the tetrad if the deleted section is large enough (fig. 8.4). The bulge also appears in the paired, polytene giant salivary gland chromosomes of *Drosophila*. (Note that when a bulge like that illustrated in figure 8.4 is seen in paired chromosomes, it indicates that one chromosome has a piece that is missing in the other. In our example, the bulge resulted from a deletion in one chromosome; it could also result from an insertion of a piece in the other chromosome.)

#### Inversion

Two breaks in the same chromosome can also lead to **inversion**, in which the middle section is reattached but in the inverted configuration (see fig. 8.3). An inversion has several interesting properties. To begin with, fruit flies homozygous for an inversion show new linkage relations when their chromosomes are mapped. One outcome of this new linkage arrangement is the possibility of a **position effect**, a change in the expression of a gene due to a changed linkage arrangement. Position effects are either stable, as in *Bar* eye of *Drosophila* (to be discussed), or variegated, as with *Drosophila* eye color. A normal female fly that is heterozygous ( $X^{w+}X^+$ ) has red eyes. If, however, the white locus is moved through an inversion so that it comes to lie next to heterochromatin (fig. 8.5), the fly shows a **variegation**—patches of the eye are white. This is presumably caused by a spread of the tight coiling of the heterochromatin, “turning off” the expression of the locus. In a heterozygote, if the turned-off allele is the wild-type, the cell will express the normally recessive white-eye allele. Depending on what happens in each cell, patches of red and white eye color result.

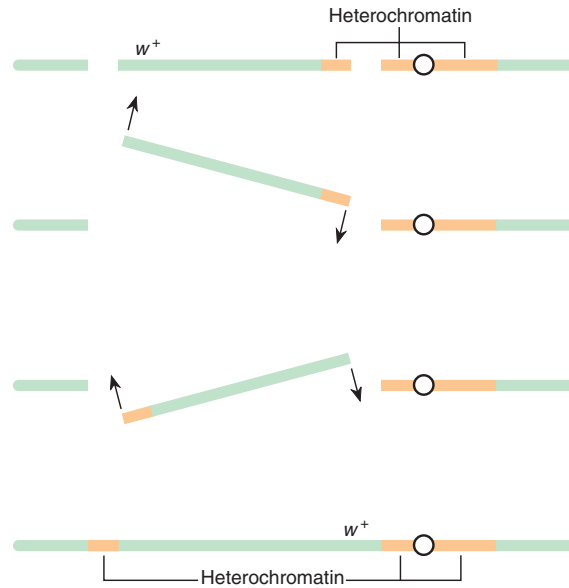
When synapsis occurs in an inversion heterozygote, either at meiosis or in the *Drosophila* salivary gland during endomitosis, a loop often forms to accommodate the point-for-point pairing process (figs. 8.6 and 8.7). An outcome of this looping tendency is **crossover suppression**. That is, an inversion heterozygote shows very little recombination of alleles within the inverted region. The reason is usually not that crossing over is actually



**Figure 8.4** A bulge can occur in a meiotic tetrad if a large deletion has occurred.

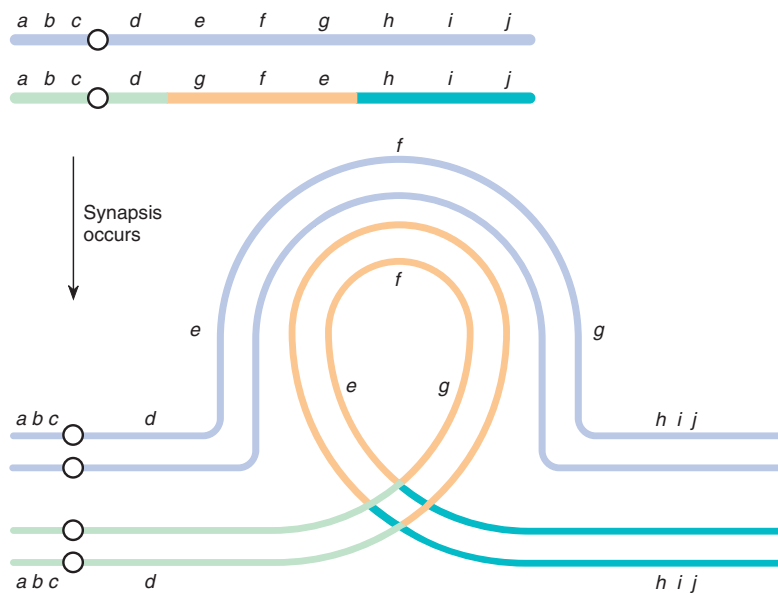
suppressed, but rather that the products of recombination within a loop are usually lost. (Suppression can also occur in small inversions where loops don't form.) Figure 8.8 shows a crossover within a loop. The two nonsister chromatids not involved in a crossover in the loop will end up in normal gametes (carrying either the normal chromosome or the intact inverted chromosome). The products of the crossover, rather than being a simple recombination of alleles, are a dicentric and an acentric chromatid. The acentric chromatid is not incorporated into a gamete nucleus, whereas the dicentric chromatid begins a breakage-fusion-bridge cycle that creates a genetic imbalance in the gametes. The gametes thus carry chromosomes with duplications and deficiencies.

The inversion pictured in figure 8.8 is a **paracentric inversion**, one in which the centromere is outside the inversion loop. A **pericentric inversion** is one in which the inverted section contains the centromere. It, too, suppresses crossovers, but for slightly different reasons



**Figure 8.5** An inversion in the X chromosome of *Drosophila* produces a variegation in eye color in a female if her other chromosome is normal and carries the white-eye allele ( $X^w$ ).

(fig. 8.9). All four chromatid products of a single crossover within the loop have centromeres and are thus incorporated into the nuclei of gametes. However, the two recombinant chromatids are unbalanced—they both have duplications and deficiencies. One has a duplication for



**Figure 8.6** Tetrad at meiosis showing the loop characteristic of an inversion heterozygote.



**Figure 8.7** A *Drosophila* heterozygous for an inversion will show a loop in the salivary gland chromosomes. (Compare with figure 8.6.)

*a-b-c-d* and is deficient for *b-i-j*, whereas the other is the reciprocal—deficient for *a-b-c-d* and duplicated for *b-i-j* (in fig. 8.9). These duplication-deletion gametes tend to form inviable zygotes. The result, as with the paracentric inversion, is the apparent suppression of crossing over.

**Results of Inversion**

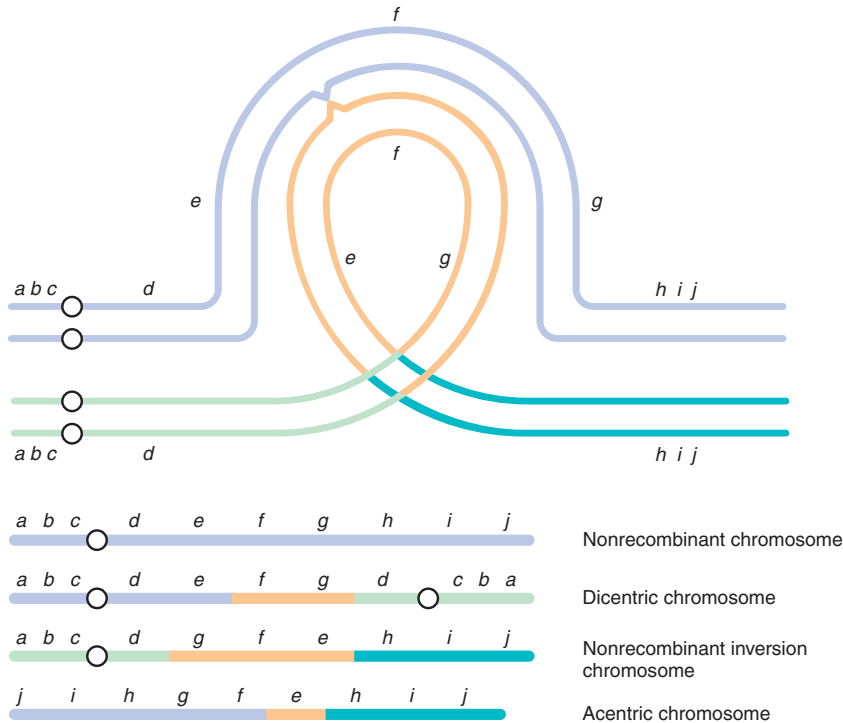
Crossing over within inversion loops results in **semisterility**. Almost all gametes that contain dicentric or imbalanced chromosomes form inviable zygotes. Thus, a certain proportion of the progeny of inversion heterozygotes are not viable.

Inversions have several evolutionary ramifications. Those alleles originally together in the noninversion chromosome and those found together within the inver-

sion loop tend to stay together because of the low rate of successful recombination within the inverted region. If several loci affect the same trait, the alleles are referred to as a **supergene**. Until careful genetic analysis is done, the loci in a supergene could be mistaken for a single locus; they affect the same trait and are inherited apparently as a single unit. Examples include shell color and pattern in land snails and mimicry in butterflies (see chapter 21). Supergenes can be beneficial when they involve favorable gene combinations. However, at the same time, their inversion structure prevents the formation of new complexes. Supergenes, therefore, have evolutionary advantages and disadvantages. Chapter 21 discusses these evolutionary topics in more detail.

Sometimes the inversion process produces a record of the evolutionary history of a group of species. As species evolve, inversions can occur on preexisting inversions. This leads to very complex arrangements of loci. We can readily study these patterns in Diptera by noting the changed patterns of bands in salivary gland chromosomes. Since certain arrangements can only come about by a specific sequence of inversions, it is possible to know which species evolved from which. The same series of events can occur within the same species (box 8.1).

In summary then, inversions result in suppressed crossing over, semisterility, variegation position effects, and new linkage arrangements. All of these events have evolutionary consequences.



**Figure 8.8** Consequences of a crossover in the loop region of a paracentric inversion heterozygote.

## BOX 8.1

In 1966, David Futch published a study of the chromosomes of a fruit fly, *Drosophila ananassae*, an organism widely distributed throughout the tropical Pacific. The study was designed to determine something about the species status of various melanic forms of the fly. In the course of his work, Futch looked at the salivary gland chromosomes of flies from twelve different localities. He discovered twelve paracentric inversions, three pericentric inversions, and one translocation. Because of the precise banding patterns of these chromosomes, it was possible

### Experimental Methods

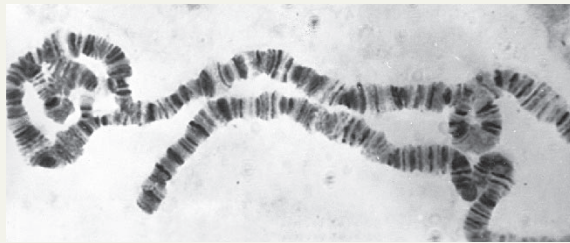
#### A Case History of the Use of Inversions to Determine Evolutionary Sequence

to determine the breakage points for each inversion.

Observation of several populations that have had sequential changes in their chromosomes makes

it possible to determine the sequence of successive changes. Once one knows the sequence of changes in different populations of *Drosophila ananassae*, along with the geographic locations of the populations, it is possible to determine the history of the way the flies colonized these tropical islands. *D. ananassae* is particularly suited to this type of work because it is believed to be a recent invader to most of the Pacific Islands that it occupies. It is of interest to know about the spread of this species as an adjunct to studies of human migration in the Pacific Islands

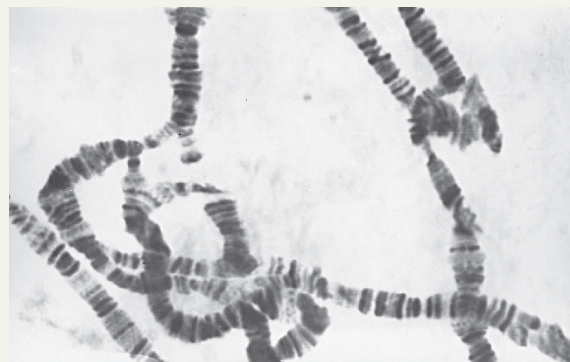
**Figure 1** Photomicrographs of the left arm of chromosome 2 (2L) from larval *Drosophila ananassae* heterozygous for various complex gene arrangements. (a) Pairing when heterozygous for standard gene sequence and overlapping inversions (2LC; 2LD) and inversion 2LB (Standard × Tutuila light). (b) Pairing when heterozygous for standard gene sequence and single inversion 2LC and overlapping inversions (2LE; 2LB: Standard × New Guinea). (c) Pairing when heterozygous for overlapping inversions (2LD; 2LE; 2LF: Tutuila light × New Guinea). (From David G. Futch, "A study of speciation in South Pacific populations of *Drosophila ananassae*," in Marshall R. Wheeler, ed., *Studies in Genetics*, no. 6615 [Austin: University of Texas Press, 1966]. Reproduced by permission.)



(a)



(b)



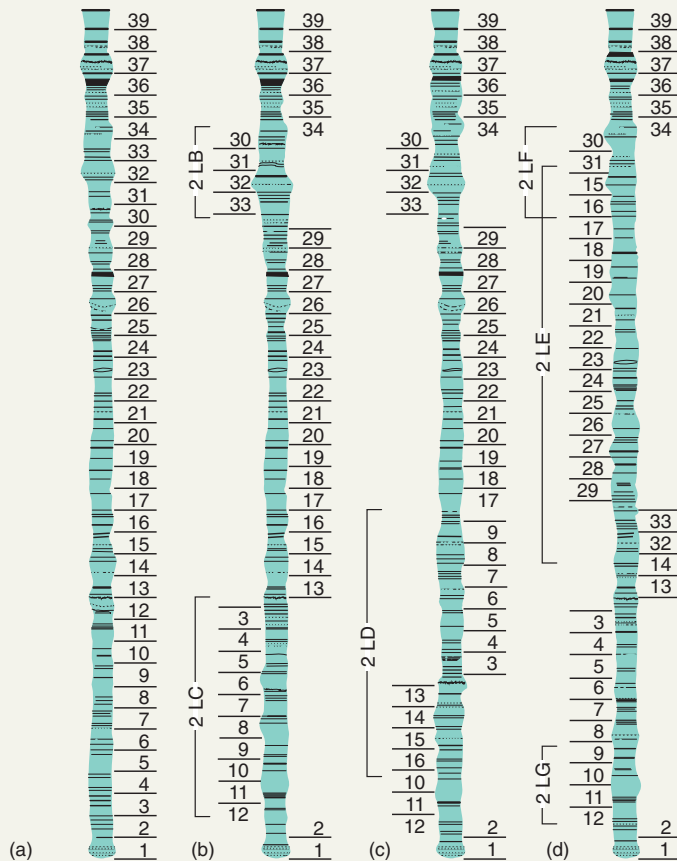
(c)

### Two Breaks in Nonhomologous Chromosomes

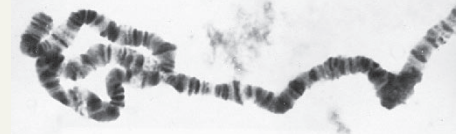
Breaks can occur simultaneously in two nonhomologous chromosomes. Reunion can then take place in various ways. The most interesting case occurs when the ends of two nonhomologous chromosomes are translocated to each other in a **reciprocal translocation** (fig. 8.10). The organism in which this has happened, a reciprocal translo-

cation heterozygote, has all the genetic material of the normal homozygote. Two outcomes of a reciprocal translocation, like those of an inversion, are new linkage arrangements in a homozygote—an organism with translocated chromosomes only—and variegation position effects.

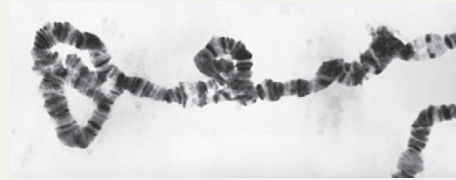
During synapsis, either at meiosis or endomitosis, a point-for-point pairing in the translocation heterozygote



**Figure 2** Chromosomal maps of 2L. (a) Standard gene sequence. (b) Ponape: breakpoints of 2LC and 2LB are indicated and the segments are shown inverted. (c) Tutuila light: breakpoints of 2LD are indicated. 2LC and 2LB are inverted. 2LD, which overlaps 2LC, is also shown inverted. (d) New Guinea: breakpoints of 2LE and 2LG are indicated. 2LC, 2LB, and 2LE are shown inverted. Note: only the breakpoints of 2LF and 2LG are shown; neither of these is inverted in the map. (From David G. Futch, "A study of speciation in South Pacific populations of *Drosophila ananassae*," in Marshall R. Wheeler, ed., *Studies in Genetics*, no. 6615 [Austin: University of Texas Press, 1966]. Reproduced by permission.)



(a)



(b)



(c)

**Figure 3** Photomicrographs of the right arm of chromosome 2 (2R) from larvae heterozygous for various complex gene arrangements. (a) Pairing when heterozygous for standard gene sequence and overlapping inversions (2RA; 2RB: Standard × Tutuila light). (b) Pairing when heterozygous for standard gene sequence and overlapping inversions (2RA; 2RC) and inversion 2RD (Standard × New Guinea). (c) Pairing when heterozygous for overlapping inversions 2RB, 2RC, and 2RD. Inversion 2RA is homozygous (Tutuila light × New Guinea). (From David G. Futch, "A study of speciation in South Pacific populations of *Drosophila ananassae*," in Marshall R. Wheeler, ed., *Studies in Genetics*, no. 6615 [Austin: University of Texas Press, 1966]. Reproduced by permission.)

*continued*

can be accomplished by the formation of a cross-shaped figure (fig. 8.10). Such a figure is diagnostic of a reciprocal translocation. A single crossover in a reciprocal translocation heterozygote will not produce chromatids that are further imbalanced, as it does in an inversion heterozygote. However, reciprocal translocation heterozygotes do produce nonviable progeny. Problems

can arise when centromeres separate at the first meiotic division.

### Segregation After Translocation

Since two homologous pairs of chromosomes are involved, we have to keep track of the independent

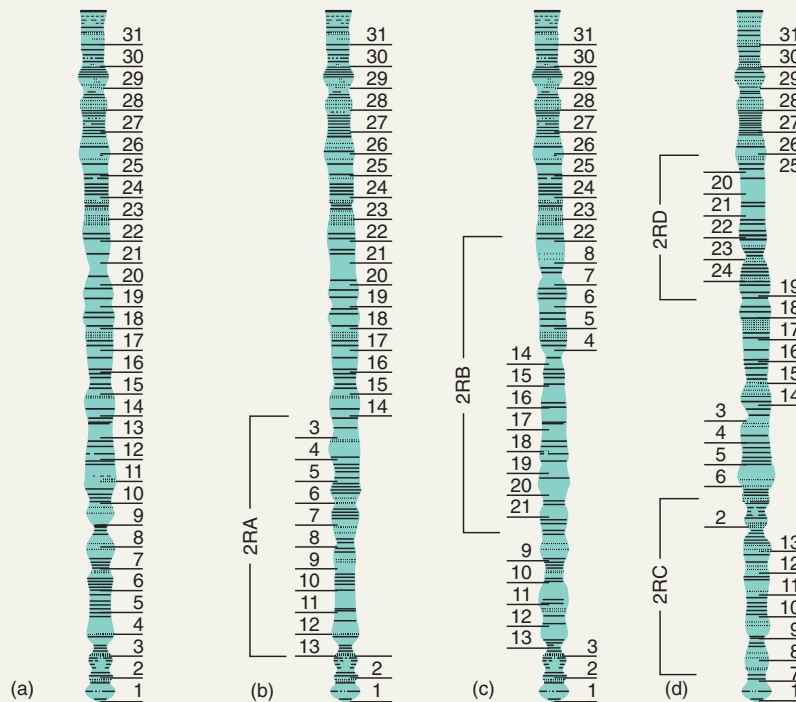
## BOX 8.1 CONTINUED

because *D. ananassae* is commensal with people.

Some of Futch's results are shown in figures 1–4, which diagram the left and right arms of the fly's second chromosome, as well as the synaptic patterns. We can see vividly the sequence of change in which one inversion occurs after a previous inver-

sion has already taken place. In figures 2 and 4, the standard (a) gave rise to (b), which then gave rise independently to (c) and (d). The standard is from Majuro in the Marshall Islands and is believed to be in the ancestral group of the species. Ponape is the home of (b), (c) is from Tutuila (eastern Samoa), and (d) is from New

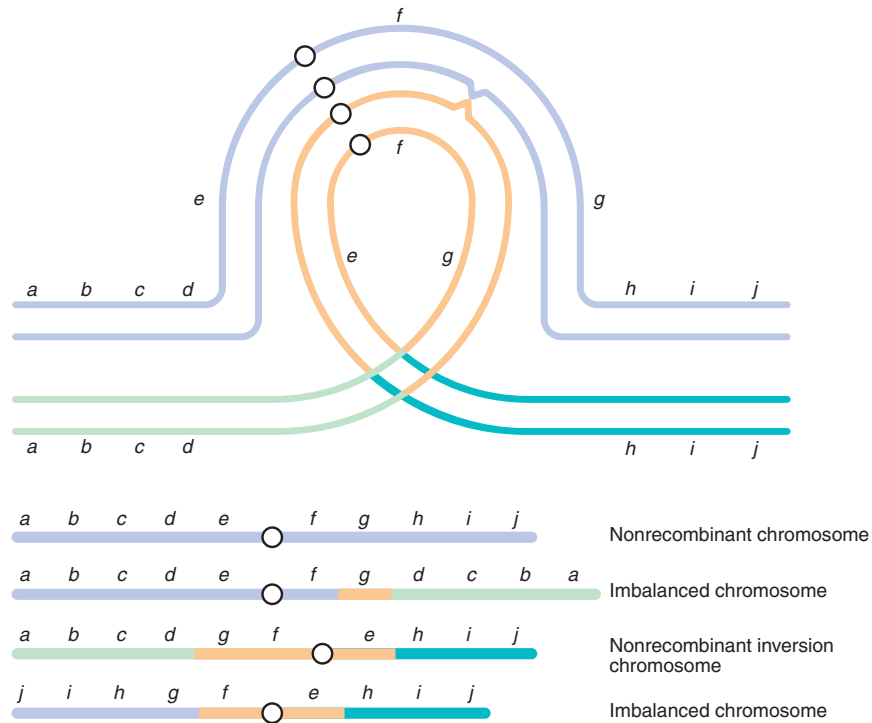
Guinea. Thus, the sequence is Majuro to Ponape, and from there the same stock was transferred to Tutuila and New Guinea. This type of analysis has been useful in the *Drosophila* group throughout its range but especially in the Pacific Island populations and in the southwestern United States.



**Figure 4** Chromosomal maps of 2R. (a) Standard gene sequence. (b) Ponape: breakpoints of 2RA are indicated and the segment is shown inverted. (c) Tutuila light: breakpoints of 2RB are indicated. 2RA is inverted and 2RB, which overlaps it, is also shown inverted. (d) New Guinea: breakpoints of 2RC and 2RD are indicated. 2RA is inverted; 2RC, which overlaps 2RA, and 2RD are shown inverted. (From David G. Futch, "A study of speciation in South Pacific populations of *Drosophila ananassae*," in Marshall R. Wheeler, ed., *Studies in Genetics*, no. 6615 [Austin: University of Texas Press, 1966]. Reproduced by permission.)

segregation of the centromeres of the two tetrads. There are two common possibilities and one that occurs less often (fig. 8.11). The first, called **alternate segregation**, occurs when the first centromere assort with the fourth centromere, leaving the second and third centromeres to go to the opposite pole. The result will be balanced

gametes, one with normal chromosomes and the other with a reciprocal translocation. Also likely is the **adjacent-1** type of segregation, in which the first and third centromeres segregate together in the opposite direction from the second and fourth centromeres. Here, both types of gametes are unbalanced, carrying duplica-



**Figure 8.9** Consequences of a crossover in the loop region of a pericentric inversion heterozygote.

tions and deficiencies that are usually lethal. Since adjacent-1 segregation occurs at a relatively high frequency, a significant amount of sterility results from the translocation (as much as 50%).

An **adjacent-2** type of segregation (fig. 8.11), in which homologous centromeres go to the same pole (first with second, third with fourth), is a third possibility. This can result when the cross-shaped double tetrad opens into a circle in late prophase I. In the German cockroach, adjacent-2 patterns have been observed in 10 to 25% of meioses, depending upon which chromosomes are involved.

In summary, then, reciprocal translocations result in new linkage arrangements, variegated position effects, a cross-shaped figure during synapsis, and semisterility.

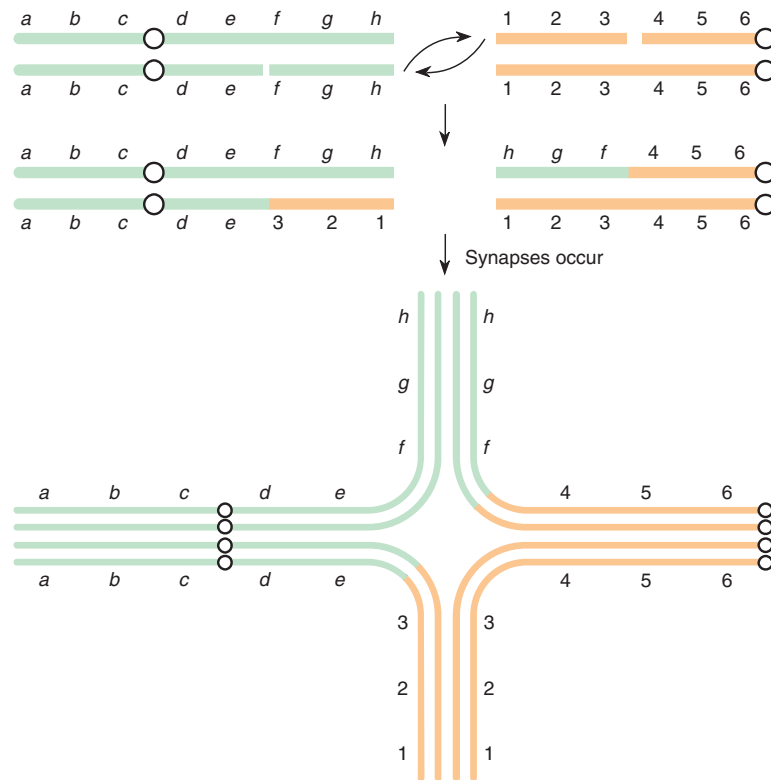
### Centromeric Breaks

Another interesting variant of the simple reciprocal translocation occurs when two acrocentric chromosomes join at or very near their centromeres. The process, called a **Robertsonian fusion** after cytologist W. Robertson, produces a decrease in the number of chromosomes, although virtually the same amount of genetic material is maintained. Often, closely related species undergo Robertsonian fusions and end up with

markedly different chromosome numbers without any significant difference in the quantity of their genetic material. Therefore, cytologists frequently count the number of chromosomal arms rather than the number of chromosomes to get a more accurate picture of species affinities. The number of arms is referred to as the **fundamental number**, or **NF** (French: *nombre fondamentale*). In a similar fashion, **centromeric fission** increases the chromosome number without changing the fundamental number.

### Duplications

Duplications of chromosomal segments can occur, as we have just seen, by the breakage-fusion-bridge cycle or by crossovers within the loop of an inversion. There is another way that duplications arise in small adjacent regions of a chromosome. We illustrate this with a particularly interesting example, the *Bar* eye phenotype in *Drosophila* (fig. 8.12). The wild-type fruit fly has about 800 facets in each eye. The *Bar* (*B*) homozygote has about 70 (a range of 20–120 facets). Another allele, *Doublebar* (*BB*; sometimes referred to as *Ultrabar*;  $B^U$ ), brings the facet number of the eye down to about 45 when heterozygous and to about 25 when homozygous. Around 1920, researchers



**Figure 8.10** A reciprocal translocation heterozygote forms after breaks occur in nonhomologous chromosomes. Synapsis at meiosis forms a cross-shaped figure.

showed that about one progeny in 1,600 from homozygous *Bar* females is *Doublebar*. This is much more frequent than we expect from mutation.

Alfred Sturtevant found that in every *Doublebar* fly, a crossover had occurred between loci on either side of the *Bar* locus. He suggested that the change to *Doublebar* was due to **unequal crossing over** rather than to a simple mutation of one allele to another (fig. 8.13). If the homologous chromosomes do not line up exactly during synapsis, a crossover produces an unequal distribution of chromosomal material. Later, an analysis of the banding pattern of the salivary glands confirmed Sturtevant's hypothesis. It was found that *Bar* is a duplication of several bands in the 16A region of the X chromosome (fig. 8.14). *Doublebar* is a triplication of the segment.

A position effect also occurs in the *Bar* system. A *Bar* homozygote ( $B/B$ ) and a *Doublebar*/wild-type heterozygote ( $BB/B^+$ ) both have four copies of the 16A region. It would therefore be reasonable to expect that both genotypes would produce the same phenotype. However, the *Bar* homozygote has about seventy facets in each eye, whereas the heterozygote only has about forty-five. Thus, not only the amount of genetic material, but also its con-

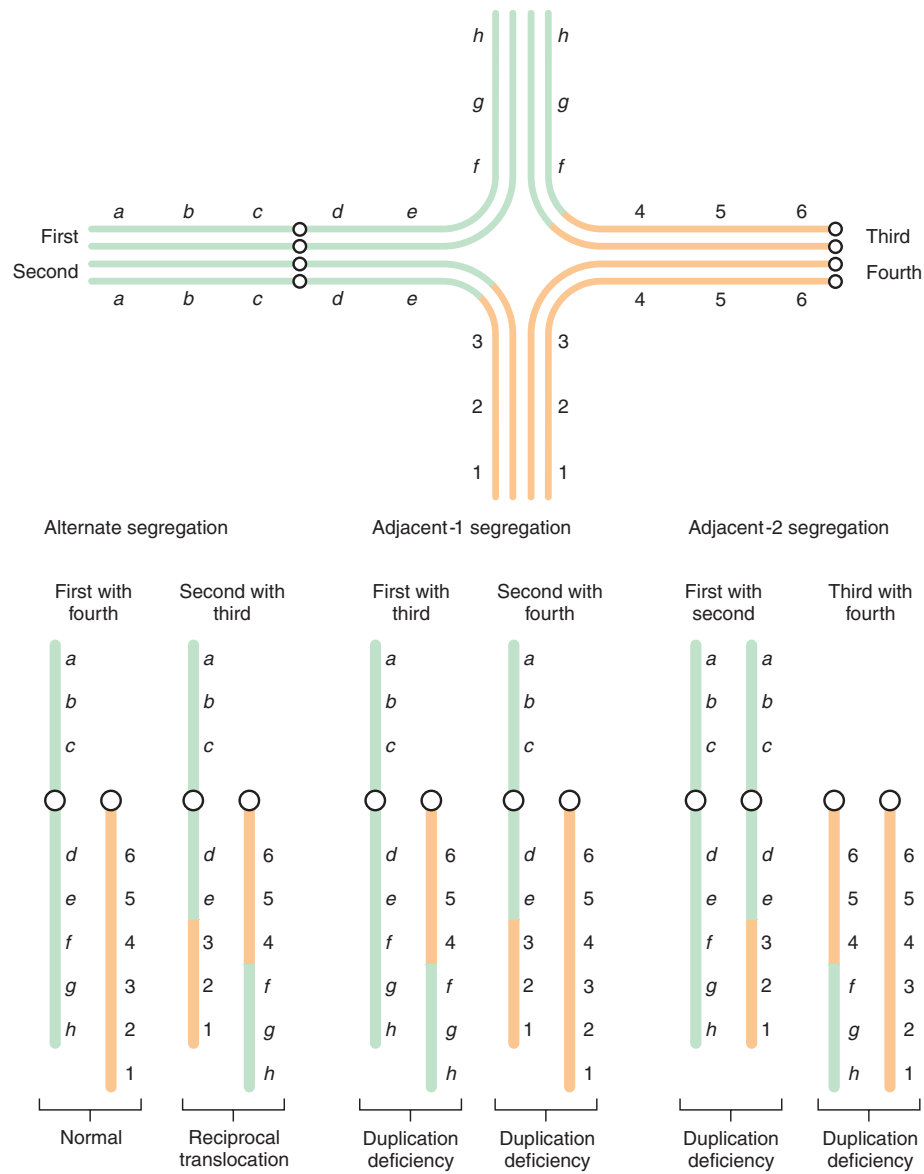
figuration, determines the extent of the phenotype. *Bar* eye was the first position effect discovered.

### Chromosomal Rearrangements in Human Beings

Several human syndromes and abnormalities are the result of chromosomal rearrangements, including deletions and translocations. The most common are described here. Keep three points in mind as you read. First, all of these disorders are rare. Second, the deletion syndromes are often caused by a balanced translocation in one of the parents. And third, about one in five hundred live births contains a balanced rearrangement of some kind, either a reciprocal translocation or inversion.

#### Fragile-X Syndrome

The most common cause of inherited mental retardation is the **fragile-X syndrome**. It occurs in about one in every 1,250 males and about one in every 2,000 females. Symptoms include mental retardation, altered speech patterns, and other physical attributes. The condition is



**Figure 8.11** Three possible results of chromatid separation during meiosis in a reciprocal translocation heterozygote.

called the fragile-X syndrome because it is related to a region at the X chromosome tip that breaks more frequently than other chromosomal regions. However, the break is not required for the syndrome to occur, and the fragile-X chromosome is usually identified by the lack of chromatin condensation at the site; in fact, under the microscope, it appears that the tip of the chromosome is being held in place by a thread (fig. 8.15). The gene responsible for the syndrome is called *FMR-1*, for fragile-X mental retardation-1.

Fragile-X syndrome has a highly unusual pattern of inheritance: the chance of inheriting the disease increases through generations. This is so unusual a pattern that it was termed the Sherman Paradox. Approximately 20% of males with the fragile-X chromosome do not have symptoms but have grandchildren who do have the symptoms. The daughters of the symptomatic males also don't have symptoms, but obviously, they have another X chromosome to mask the symptoms. As generations proceed, the percentage of affected sons of

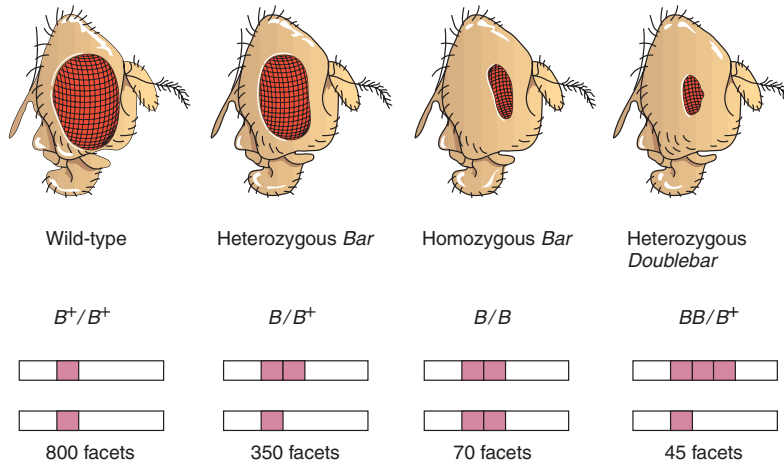


Figure 8.12 Bar eye in *Drosophila* females.

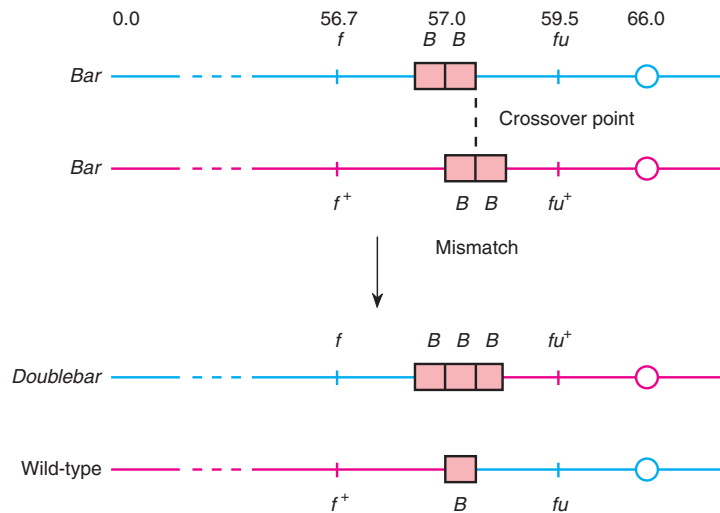


Figure 8.13 Unequal crossing over in a female *Bar*-eyed *Drosophila* homozygote as a result of improper pairing. A *Doublebar* chromosome (and concomitant wild-type chromosome) is produced by a crossover between forked (*f*) and fused (*fu*), two flanking loci.

carrier mothers increases. Molecular techniques, discussed in chapter 13, revealed the odd nature of this syndrome.

Basically, the *FMR-1* gene normally has between 6 and 50 copies of a three-nucleotide repeat, CCG. Chromosomes that have the fragile-site appearance have between 230 and 2,000 copies of the repeat. The number of repeats is very unstable; when carrier women transmit the chromosome, the number of repeats usually goes up. Repeat numbers above 230 inactivate the gene and thus cause the syndrome in men, who have only one copy of the X chromosome. The function of the gene is not currently known. This unusual form of inheritance, with un-

stable repeats in a gene, seems to be the mechanism in several other diseases as well, including muscular dystrophy and Huntington disease. We will discuss other unusual modes of inheritance in chapter 17.

### *Cri du Chat Syndrome, 46,XX or XY,5p-*

The syndrome known as *cri du chat* (French: cry of the cat) is so called because of the catlike cry that about half the affected infants make. Microcephaly (an abnormally small head), congenital heart disease, and severe mental retardation are also common symptoms. This disorder arises from a deletion in chromosome 5 (fig. 8.16); most

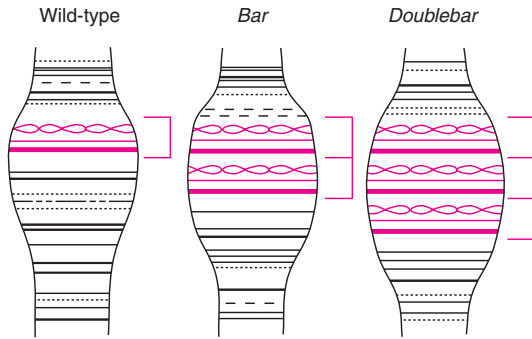


Figure 8.14 Bar region of the X chromosome of *Drosophila*.

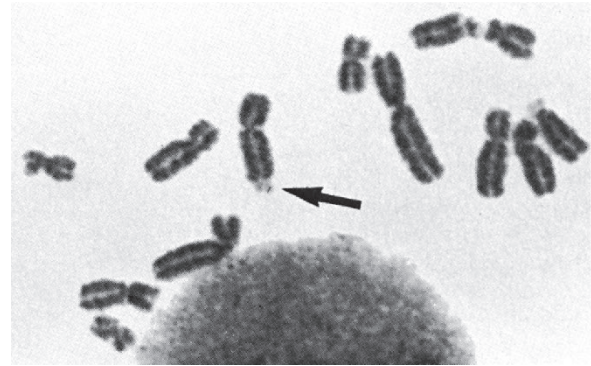


Figure 8.15 Human metaphase chromosomes with the fragile-X site indicated by an arrow. (From Ian Craig, "Methylation and the Fragile X," *Nature* [1991] 349:742. Copyright © 1991 Macmillan Magazines, Ltd.)

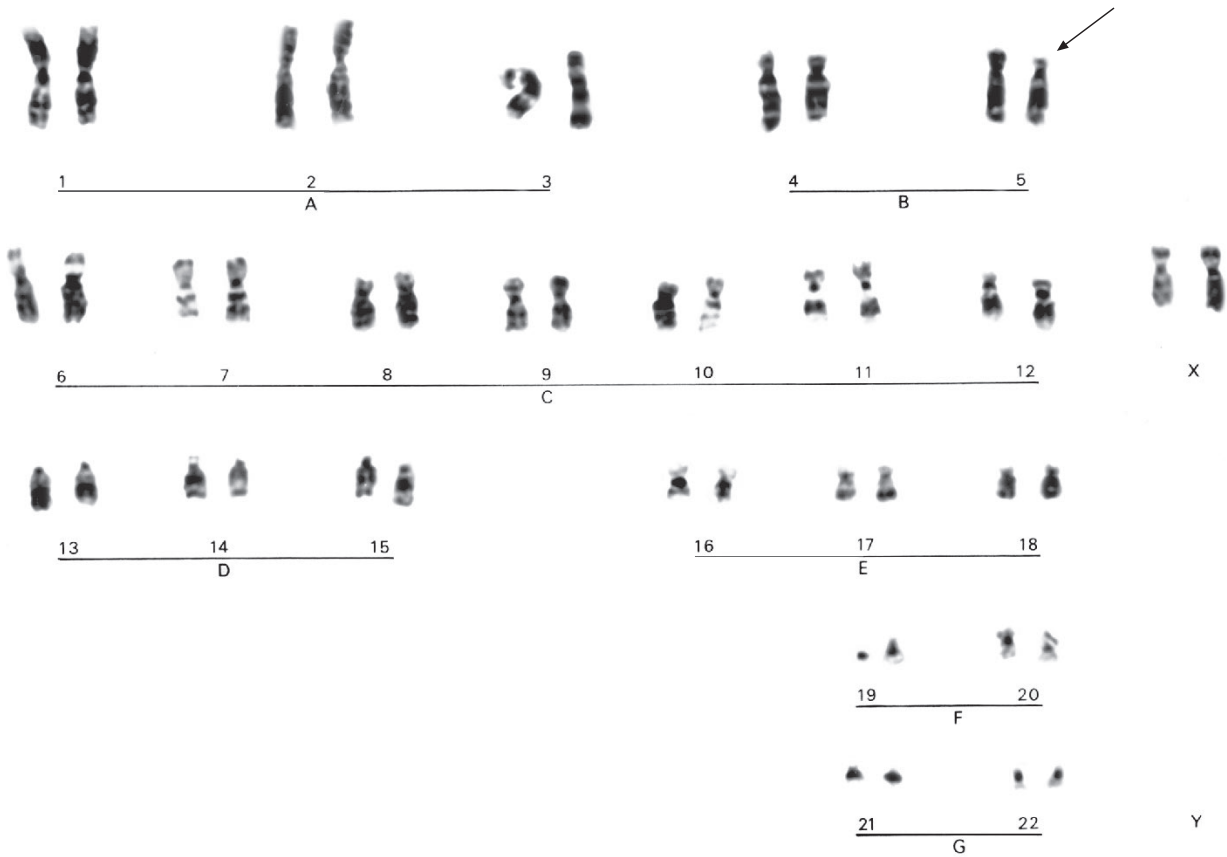


Figure 8.16 Karyotype of individual with cri du chat syndrome, due to a partial deletion of the short arm of chromosome 5 (5p-; arrow). (Reproduced courtesy of Dr. Thomas G. Brewster, Foundation for Blood Research, Scarborough, Maine.)

other deletions studied (4p-, 13q-, 18p-, 18q-) also result in microcephaly and severe mental retardation. The rarity of viable deletion heterozygotes is consistent with the fact that viable monosomics (having a single chromosome of a pair) are rare. An individual heterozygous for a deletion is, in effect, monosomic for the deleted region of the chromosome. Evidently, monosomy or heterozygosity for larger deleted regions of a chromosome is generally lethal in human beings.

## VARIATION IN CHROMOSOME NUMBER

Anomalies of chromosome number occur as either **euploidy** or **aneuploidy**. Euploidy involves changes in whole *sets* of chromosomes; aneuploidy involves changes in chromosome *number* by additions or deletions of less than a whole set.

### Aneuploidy

An explanation for the terminology of aneuploid change appears in table 8.1. A diploid cell missing a single chromosome is **monosomic**. A cell missing both copies of that chromosome is **nullisomic**. A cell missing two non-homologous chromosomes is a double monosomic. A similar terminology exists for extra chromosomes. For example, a diploid cell with an extra chromosome is **trisomic**. Aneuploidy results from nondisjunction in meiosis or by chromosomal lagging whereby one chromosome moves more slowly than the others during anaphase, is excluded from the telophase nucleus, and is thus lost. Here, nondisjunction is illustrated using the sex chromosomes in XY organisms such as human beings or fruit flies. Four examples are shown (fig. 8.17): nondisjunction in either the male or female at either the first or second meiotic divisions. Figure 8.18 shows the types of

zygotes that can result when these nondisjunctional gametes fuse with normal gametes. All of the offspring produced are chromosomally abnormal. The names and kinds of these imbalances in human beings are detailed later in this chapter.

Bridges first showed the occurrence of nondisjunction in *Drosophila* in 1916 with crosses involving the white-eye locus. When a white-eyed female was crossed with a wild-type male, typically the daughters were wild-type and the sons were white-eyed. However, occasionally (one or two per thousand), a white-eyed daughter or a wild-type son appeared. This could be explained most easily by a nondisjunctional event in the white-eyed females, where  $X^wX^w$  and 0 eggs (without sex chromosomes) were formed. Under this hypothesis, if a Y-bearing sperm fertilized an  $X^wX^w$  egg, the offspring would be an  $X^wX^wY$  white-eyed daughter. If a normal  $X^+$ -bearing sperm fertilized the egg without sex chromosomes, the result would be an  $X^+0$  wild-type son. Subsequently, these exceptional individuals were found by cytological examination to have precisely the predicted chromosomes (XXY daughters and X0 sons). The other types produced by this nondisjunctional event are the XX egg fertilized by an X-bearing sperm and the 0 egg fertilized by the Y-bearing sperm. The XXX zygotes are genotypically  $X^wX^wX^+$ , or wild-type daughters (which usually die), and Y0 flies (which always die).

### Mosaicism

Rarely, an individual is made up of several cell lines, each with different chromosome numbers. These individuals are referred to as **mosaics** or **chimeras**, depending on the sources of the cell lines. Such conditions can be the result of nondisjunction or chromosomal lagging during mitosis in the zygote or in nuclei in the early embryo (mosaic). This is demonstrated, again for sex chromosomes, in figure 8.19. A lagging chromosome is shown in figure 8.20; in the figure, the X chromosome is lost in one

**Table 8.1** Partial List of Terms to Describe Aneuploidy, Using *Drosophila* as an Example (Eight Chromosomes: X, X, 2, 2, 3, 3, 4, 4)

Type	Formula	Number of Chromosomes	Example
Normal	$2n$	8	X, X, 2, 2, 3, 3, 4, 4
Monosomic	$2n - 1$	7	X, X, 2, 2, 3, 4, 4
Nullisomic	$2n - 2$	6	X, X, 2, 2, 4, 4
Double monosomic	$2n - 1 - 1$	6	X, X, 2, 3, 4, 4
Trisomic	$2n + 1$	9	X, X, 2, 2, 3, 3, 4, 4, 4
Tetrasomic	$2n + 2$	10	X, X, 2, 2, 3, 3, 3, 3, 4, 4
Double trisomic	$2n + 1 + 1$	10	X, X, 2, 2, 2, 3, 3, 3, 4, 4

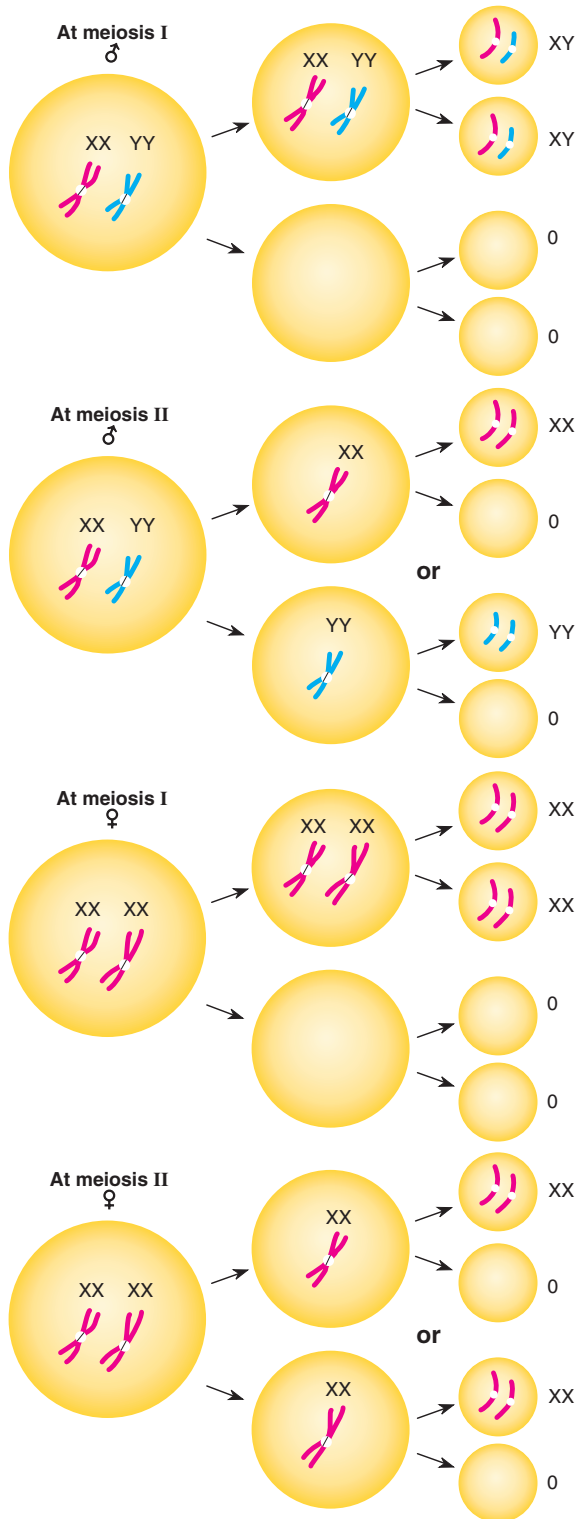


Figure 8.17 Nondisjunction of the sex chromosomes in *Drosophila* or human beings. "O" refers to the lack of sex chromosomes.

of the dividing somatic cells, resulting in an XX cell line and an XO cell line. In *Drosophila*, if this chromosomal lagging occurs early in development, an organism that is part male (XO) and part female (XX) develops. Figure 8.21 shows a fruit fly in which chromosomal lagging has occurred at the one-cell stage, causing the fly to be half male and half female. A mosaic of this type, involving male and female phenotypes, has a special name—**gynandromorph**. (A **hermaphrodite** is an individual, not necessarily mosaic, with both male and female reproductive organs.) Many sex-chromosomal mosaics are known in humans, including XX/X, XY/X, XX/XY, and XXX/X. At least one case is known of a human XX/XY chimera that resulted from the fusion of two zygotes, one

Nondisjunction

		♂				♀	
		XY	XX	YY	0	XX	0
Normal	♀X	XXY	XXX	XYY	X0		
	♂X					XXX	X0
	♂Y					XXY	Y0

Figure 8.18 Results of fusion of a nondisjunction gamete (top) with a normal gamete (side).

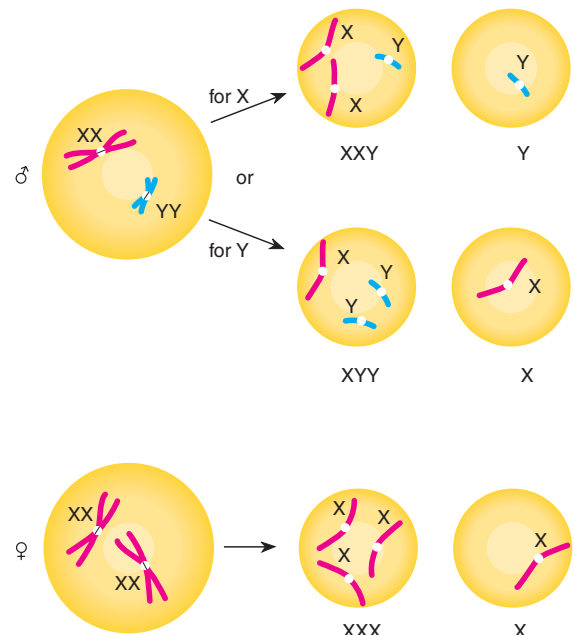
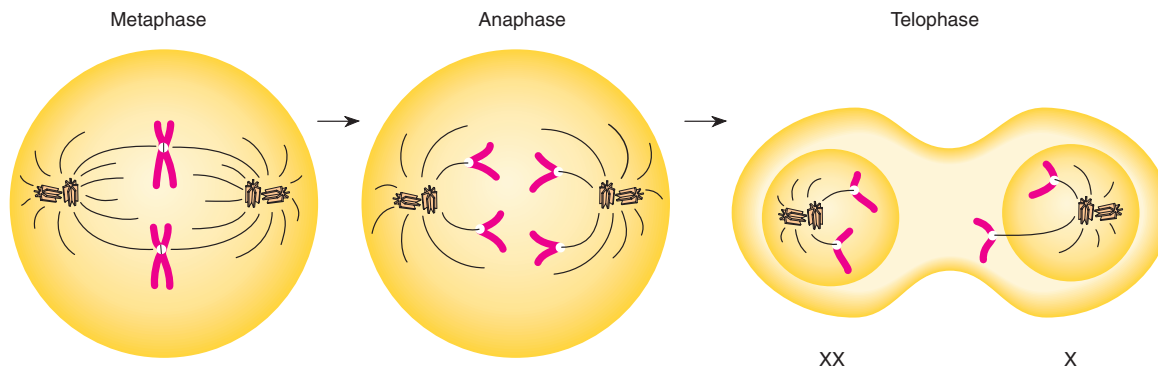
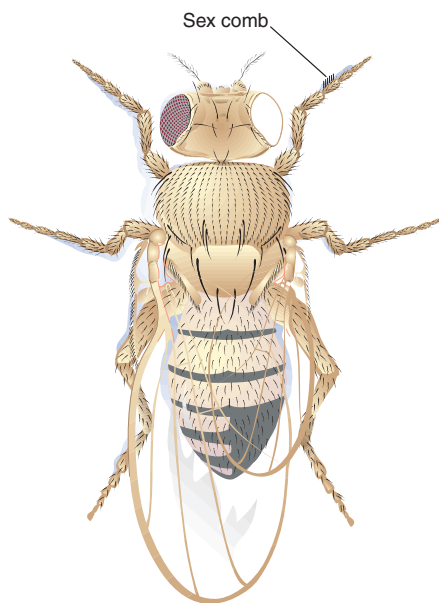


Figure 8.19 Mitotic nondisjunction of the sex chromosomes.



**Figure 8.20** Chromosomal lagging at mitosis in the X chromosomes of a female *Drosophila*.



**Figure 8.21** *Drosophila* gynandromorph. The left side is wild-type XX female; the right side is X0 male, hemizygous for white eye and miniature wing.

formed by a sperm fertilizing an ovum and the other formed by a second sperm fertilizing a polar body of that ovum.

### Aneuploidy in Human Beings

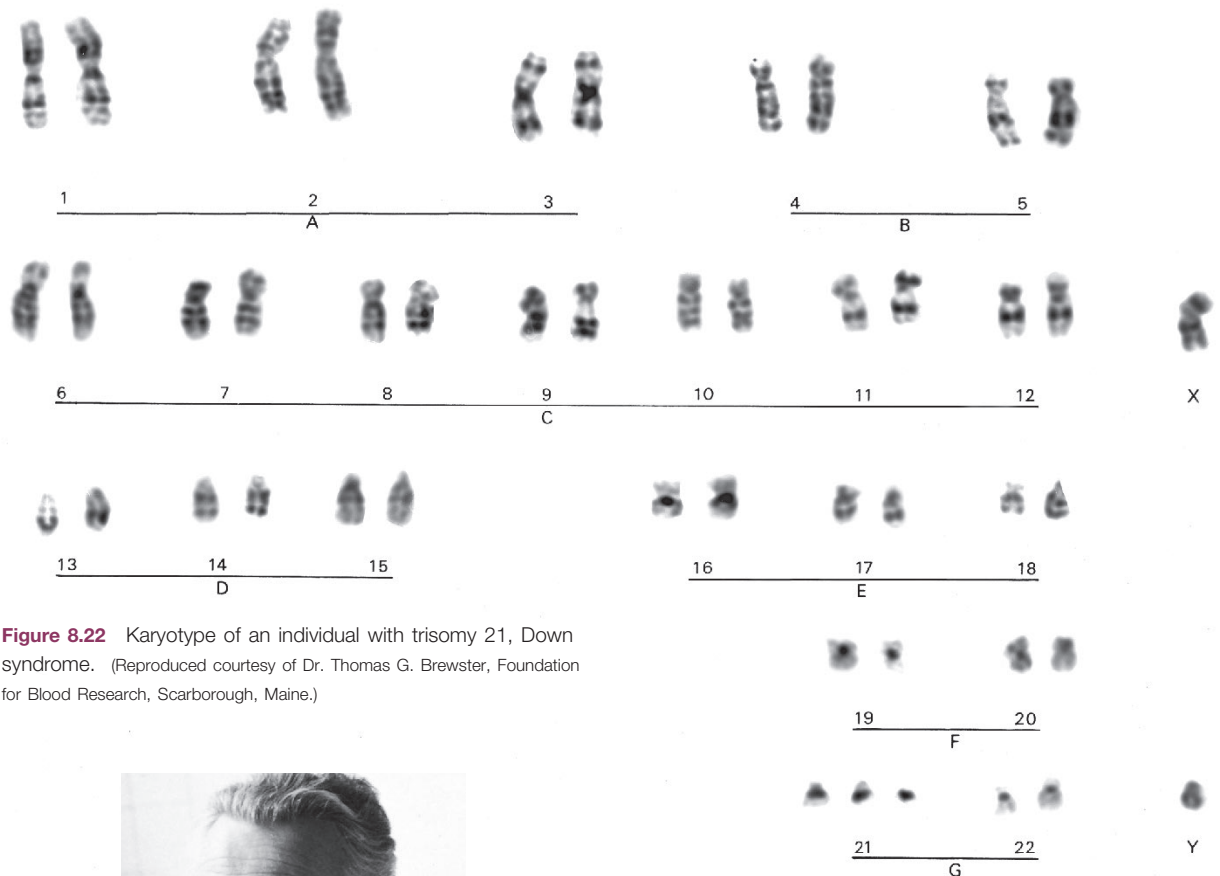
Approximately 50% of spontaneous abortions (miscarriages) among women in the United States involve fetuses with some chromosomal abnormality; about half of these are autosomal trisomics. About one in 160 live human births has some sort of chromosomal anomaly; most are balanced translocations, autosomal trisomics, or sex-chromosomal aneuploids.

In the standard system of nomenclature, a normal human chromosome complement is 46,XX for a female and 46,XY for a male. The total chromosome number appears first, then the description of the sex chromosomes, and, finally, a description of autosomes if some autosomal anomaly is evident. For example, a male with an extra X chromosome would be 47,XXY. A female with a single X chromosome would be 45,X. Since all the autosomes are numbered, we describe their changes by referring to their addition (+) or deletion (-). For example, a female with trisomy 21 would be 47,XX,+21. The short arm of a chromosome is designated p, the longer arm, q. When a change in part of the chromosome occurs, a + after the arm indicates an increase in the length of that arm, whereas a minus sign (-) indicates a decrease in its length. For example, a translocation (t) that transfers part of the short arm of chromosome 9 to the short arm of chromosome 18 would be 46,XX,t(9p-;18p+). The semicolon indicates that both chromosomes kept their centromeres.

Following are descriptions of viable human aneuploids who survive long enough after birth to have a named syndrome.

#### Trisomy 21 (Down Syndrome), 47,XX or XY,+21

Down syndrome (figs. 8.22 and 8.23) affects about one in seven hundred live births. Most affected individuals are mildly to moderately mentally retarded and have congenital heart defects and a very high (1/100) risk of acute leukemia. They are usually short and have a broad, short skull; hyperflexibility of joints; and excess skin on the back of the neck. The physician John Langdon Down first described this syndrome in 1866. (Modern convention is to avoid the possessive form of a name in referring to a syndrome.) Down syndrome was the first human syndrome attributed to a chromosomal disorder; Jérôme Lejeune, a physician in Paris, published this finding in



**Figure 8.22** Karyotype of an individual with trisomy 21, Down syndrome. (Reproduced courtesy of Dr. Thomas G. Brewster, Foundation for Blood Research, Scarborough, Maine.)



Jérôme Lejeune (1926–1994).  
(Courtesy of Dr. Jérôme Lejeune, Institut de Progenese, Paris.)

1959. An interesting aspect of this syndrome is its increased incidence among children of older mothers (fig. 8.24), a fact known more than twenty-five years before the discovery of the cause of the syndrome. Since the future ova are in prophase I of meiosis (dictyotene) since before the mother's birth, all ova are the same age as the female. Presumably, older ova are more susceptible to nondisjunction of chromosome 21.

Recently, techniques of molecular genetics (chapter 13) have been used to identify the origins of the three copies of chromosome 21 in a large sample of individuals with Down syndrome. As expected, the overwhelming majority of the extra copies of chromosome 21 (95%) were of maternal origin. About 5% of the cases of Down syndrome were of mitotic origin, occurring either in the gonad of one of the parents (evenly split between mothers and fathers) or possibly postzygotically in the fetus.

### Familial Down Syndrome

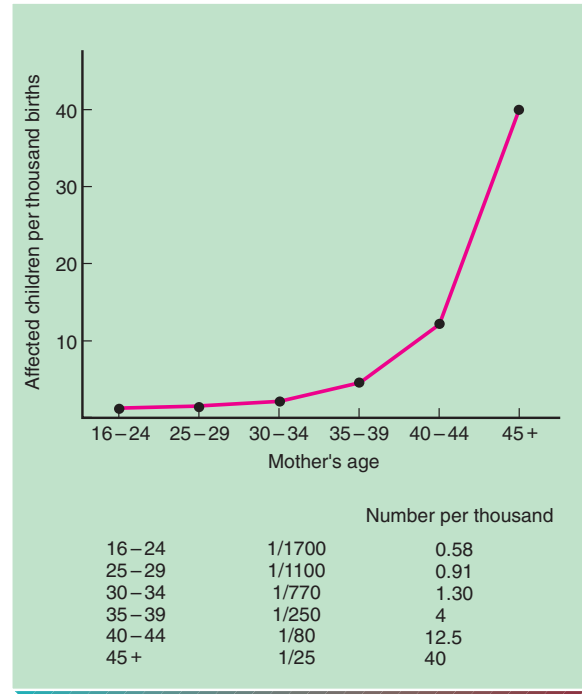
Down syndrome (trisomy 21), as described, is usually the result of either a nondisjunctional event during gametogenesis or, rarely, a mitotic event. It is a function of maternal age and is not inherited. (Although about half the children of a person with trisomy 21 will have trisomy 21 because of aneuploid gamete production, the possibility that an unaffected relative of the person will have abnormal children is no greater than for a person of the same age chosen at random from the general population.) However, about 4% of those with Down syndrome have been found to have a translocation of chromosome 21,



**Figure 8.23** Individual with trisomy 21. (© Hattie Young/SPL/Photo Researchers.)

usually associated with chromosome 14, 15, or 22. The translocational and nontranslocational types of Down syndrome have identical symptoms; however, a balanced translocation can be passed on to offspring (see fig. 8.11). Alternate segregation of centromeres in the translocation heterozygote produces either a normal gamete or one carrying the balanced translocation. Adjacent segregation causes partial trisomy for certain chromosomal parts. When this occurs for most of chromosome 21, Down syndrome results.

It is worth mentioning that aside from trisomy and translocation, Down syndrome can come about through mosaicism, as mentioned earlier, or a centromeric event. About 2% of individuals with Down syndrome are mosaic for cells with both two and three copies of chromosome 21. Some evidence suggests that the original zygotes were trisomic, but then a daughter cell lost one of the copies of chromosome 21. The severity of the symptoms in these individuals relates to the percentage of trisomic cells they possess. Mosaicism increases with maternal age, just as trisomy in general does. In extremely rare cases, Down syndrome is caused by an abnormal chromosome 21 that has, rather than a short and long arm, two identical long arms attached to the centromere. This



**Figure 8.24** Increased risk of trisomy 21 attributed to the age of the mother. (From E. Hook, "Estimates of Maternal Age-Specific Risks of a Down-Syndrome Birth in Women age 34-41," *Lancet*, 2:33-34, Copyright © 1976 by The Lancet Ltd.)

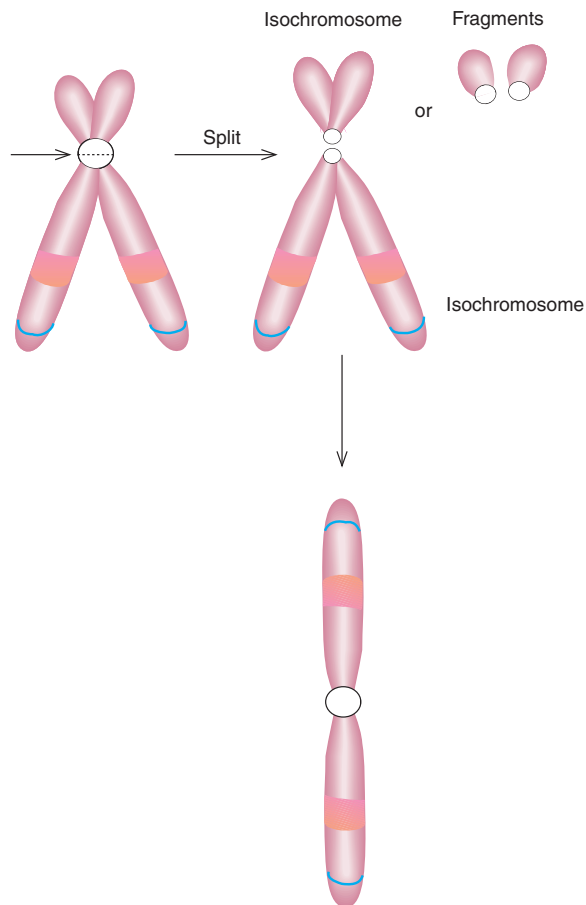
type of chromosome, called an **isochromosome**, presumably occurs by an odd centromeric fission (fig. 8.25). Hence, a person with a normal chromosome 21 and an isochromosome 21 has three copies of the long arm of the chromosome and has Down syndrome.

### **Trisomy 18 (Edward Syndrome), 47,XX or XY,+18**

Edward syndrome affects one in ten thousand live births (fig. 8.26). Most affected individuals are female, with 80 to 90% mortality by two years of age. The infant usually has an elfin appearance with small nose and mouth, a receding lower jaw, abnormal ears, and a lack of distal flexion creases on the fingers. The distal joints have limited motion, and the fingers display a characteristic posturing in which the little and index fingers overlap the middle two. The syndrome is usually accompanied by severe mental retardation.

### **Trisomy 13 (Patau Syndrome), 47,XX or XY,+13, and Other Trisomic Disorders**

Patau syndrome affects one in twenty thousand live births. Diagnostic features are cleft palate, cleft lip, con-



**Figure 8.25** If the centromere of chromosome 21 breaks perpendicular to the normal division axis, it can form an isochromosome of the long arms and either an isochromosome of the short arms or two separate fragments. This can happen during anaphase of mitosis or meiosis II.

genital heart defects, polydactyly, and severe mental retardation. Mortality is very high in the first year of life.

Other autosomal trisomies are known but are extremely rare. These include trisomy 8 ( $47,XX$  or  $XY,+8$ ) and cat's eye syndrome, a trisomy of an unidentified, small acrocentric chromosome ( $47,XX$  or  $XY,[+acrocentric]$ ). Several aneuploids involving sex chromosomes are also known.

### Turner Syndrome, $45,X$

About one in ten thousand live female births is of an infant with Turner syndrome. This and  $45,XX$  or  $XY,-21$  and

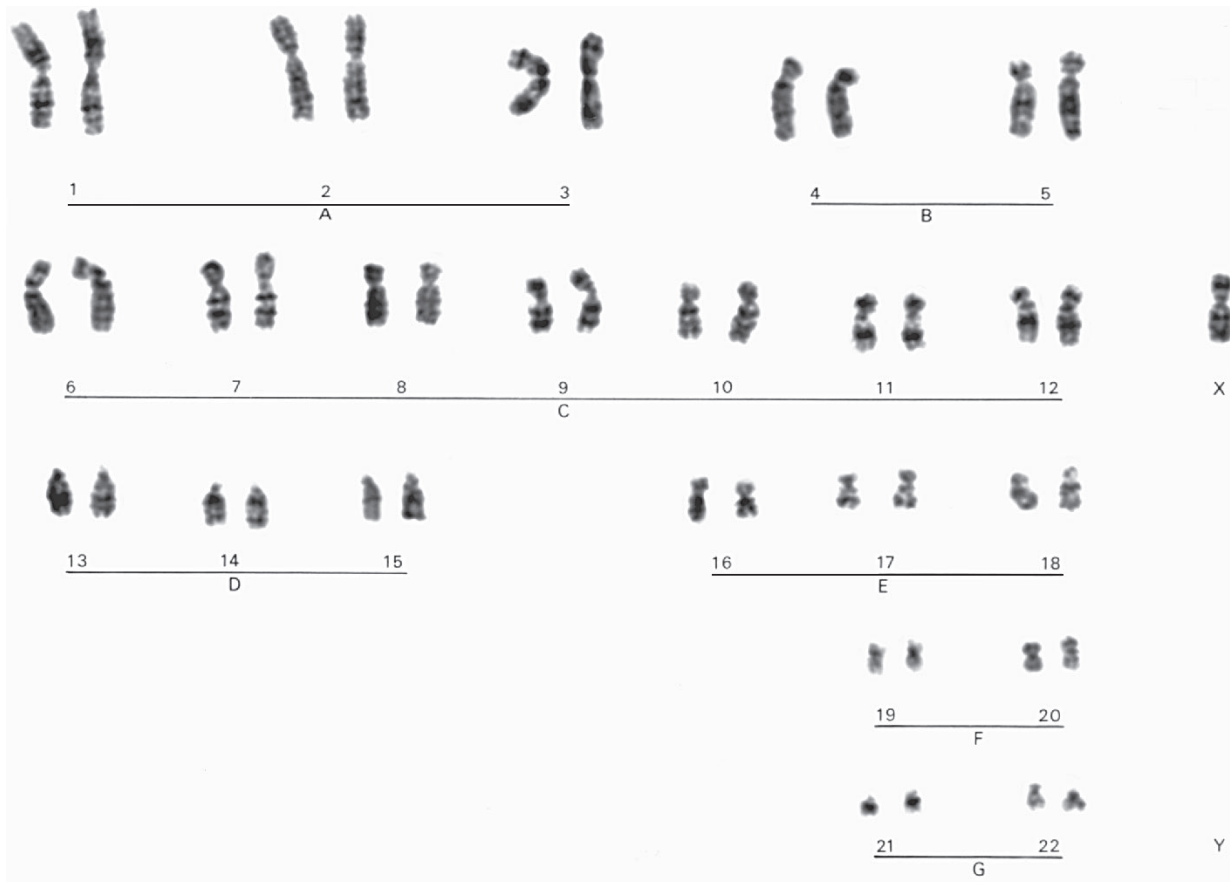


**Figure 8.26** Child with trisomy 18, Edward syndrome. (Reproduced courtesy of Dr. Jérôme Lejeune, Institut de Progenese, Paris.)

$45,XX$  or  $XY,-22$  are the only nonmosaic, viable monosomies recorded in human beings (fig. 8.27), indicating the severe consequences monosomy has on all but the two smallest autosomes and a sex chromosome. Individuals with Turner syndrome usually have normal intelligence but underdeveloped ovaries, abnormal jaws, webbed necks, and shieldlike chests.

The symptoms of Turner syndrome have been logically deduced to be caused by a single dosage of genes that are normally present and active in two dosages. Thus, these genes would be located on both the X and Y chromosomes (pseudoautosomal) to provide two dosages in normal XY males and also be active in both X chromosomes in normal XX females. Therefore, they should be located on regions of the X chromosome that escape inactivation (see chapter 5). Studies of persons with small X-chromosomal deletions and molecular analyses of the X and Y chromosomes (outlined in chapter 13) have caused two genes to emerge as candidates: *ZFY* (on the Y chromosome, termed *ZFX* on the X chromosome) and *RPS4Y* (on the Y chromosome, termed *RPS4X* on the X chromosome). *ZFY* (zinc finger on the Y chromosome) was once believed to be the male-determining gene in mammals. *RPS4Y* encodes a ribosomal protein, one of the many proteins making up the ribosome.

It is interesting to note a dosage-compensation difference in people and mice, which have analogous genes termed *Zfx* and *Rps4x*. In mice, unlike in people, these genes are inactivated in the "Lyonized" X chromosome in females and have restricted activity in the Y



**Figure 8.27** Karyotype of a person with Turner syndrome (X0). (Reproduced courtesy of Dr. Thomas G. Brewster, Foundation for Blood Research, Scarborough, Maine.)

chromosome. Hence, mouse cells seem normally to have only one copy of these genes functioning in normal XY males and XX females. Therefore, we would predict that the X0 genotype in mice would produce few if any negative effects as compared with a human X0 genotype, since mouse cells of both sexes normally only have one functional copy of each gene. In fact, human Turner syndrome fetuses have a 99% prenatal mortality rate, but virtually no prenatal mortality affects mouse fetuses with the X0 genotype (born of XX mothers). This confirms our predictions and points to differences between people and mice in dosage-compensation mechanisms for specific genes.

#### *XYY Karyotype, 47,XYY*

About one in one thousand live male births is of an individual with an XYY karyotype. (We avoid the term *syndrome* here because XYY men have no clearly defined series of attributes, other than often being taller

than normal.) Some controversy has surrounded this karyotype because it was once reported that it occurred in abundance in a group of mentally subnormal males in a prison hospital. Seven XYY males were found among 197 inmates, whereas only one in about two thousand control men were XYY. This study has subsequently been expanded and corroborated. Although it is now fairly well established that the incidence of XYY males in prison is about twentyfold higher than in society at large, the statistic is somewhat misleading: the overwhelming number of XYY men seem to lead normal lives. At most, about 4% of XYY men end up in penal or mental institutions, where they make up about 2% of the population.

There is some indication that the XYY men in prison had lower intelligence test levels. Thus, criminal tendency may be attributed to lower intelligence rather than a predisposition toward criminality caused by an extra Y chromosome. For the most part, expanded studies have indicated that XYY criminals do not commit violent crimes.

Research on this karyotype has produced its own problems. A research project at Harvard University on XYY males came under intense public pressure and was eventually terminated. The project, under the direction of Stanley Walzer (a psychiatrist) and Park Gerald (a geneticist), involved screening all newborn boys at the Boston Hospital for Women and following the development of those with chromosomal anomalies. The criticism of this work centered mainly on the necessity of informing parents that their sons had an XYY karyotype that might be associated with behavioral problems. Opponents of this work claimed that telling the parents could trigger a self-fulfilling prophecy; that is, parents who heard that their children were not normal and *might* cause trouble might then behave toward their children in a manner that would increase the probability that their children *would* cause trouble. The opponents claimed that the risks of this research outweighed the benefits. The project was terminated in 1975 primarily because of the harassment Walzer faced.

### Klinefelter Syndrome, 47,XXY

The incidence of Klinefelter syndrome is about one in one thousand live births. Tall stature and infertility are common symptoms. Diagnosis is usually by buccal (cheek tissue) smear to ascertain the presence of a Barr body in a male, indicating an XXY karyotype. Some problems with behavior and speech development are associated with this syndrome.

### Triple-X Female, 47,XXX, and Other Aneuploid Disorders of Sex Chromosomes

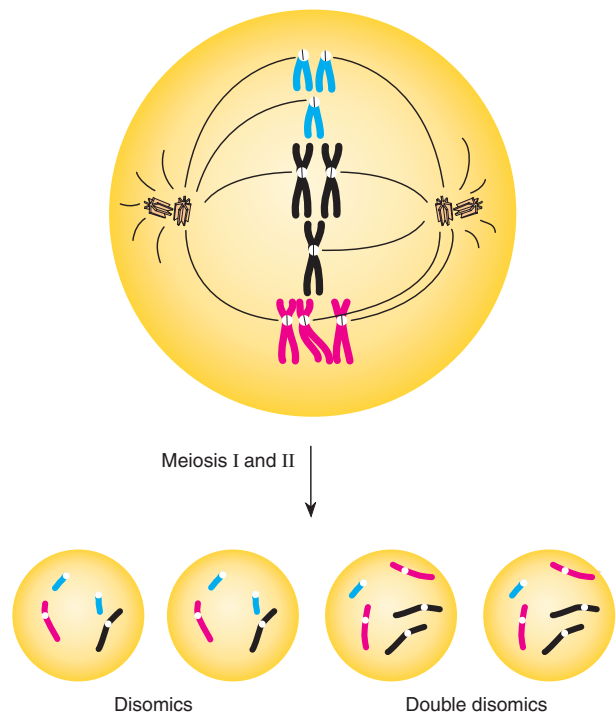
A triple-X female appears in about one in one thousand female live births. Fertility can be normal, but these individuals are usually mildly mentally retarded. Delayed growth, as well as congenital malformations, are also sometimes present. Other sex-chromosomal aneuploids, including XXXX, XXXXX, and XXXXY, are extremely rare. All seem to be characterized by mental retardation and growth deficiencies.

### Euploidy

Euploid organisms have varying numbers of complete haploid chromosomal sets. We are already familiar with haploids ( $n$ ) and diploids ( $2n$ ). Organisms with higher numbers of sets, such as **triploids** ( $3n$ ) and **tetraploids** ( $4n$ ), are called polyploids. Three kinds of problems plague polyploids. First, the potential exists for a general imbalance in the organism due to the extra genetic material in each cell. For example, a triploid human fetus has about a one in a million chance to survive to birth, at which time death usually occurs due to problems in all

organ systems. Second, if there is a chromosomal sex-determining mechanism, it may be disrupted by polyploidy. And third, meiosis produces unbalanced gametes in many polyploids.

If the polyploid has an odd number of sets of chromosomes, such as triploid ( $3n$ ), two of the three homologues will tend to pair at prophase I of meiosis, producing a bivalent and a univalent. The bivalent separates normally, but the third chromosome goes independently to one of the poles. This separation results in a 50% chance of aneuploidy in each of the  $n$ -different chromosomes, rapidly decreasing the probability of a balanced gamete as  $n$  increases. Therefore, as  $n$  increases, so does the likelihood of sterility. An alternative to the bivalent-univalent type of synapsis is the formation of trivalents, which have similar problems (fig. 8.28). Even-numbered polyploids, such as tetraploids ( $4n$ ), can do better during meiosis. If the centromeres segregate two by two in each of the  $n$  meiotic figures, balanced gametes can result. Often, however, the multiple copies of the chromosomes form complex figures during synapsis, including monovalents, bivalents, trivalents, and quadrivalents, tending to result in aneuploid gametes and sterility.

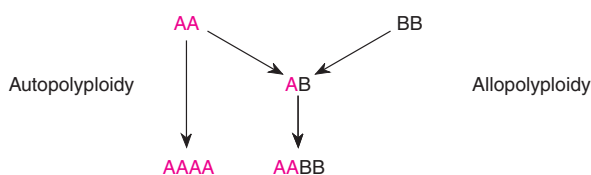


**Figure 8.28** Meiosis in a triploid ( $3n = 9$ ) and one possible resulting arrangement of gametes. The probability of a “normal” gamete is  $(1/2)^n$  where  $n$  equals the haploid chromosome number. Here,  $n = 3$  and  $(1/2)^3 = 1/8$ .

Some groups of organisms, primarily plants, have many polyploid members. An estimated 30 to 80% of all flowering plant species (angiosperms) are polyploids, as are 95% of ferns. (Polyploidy is apparently rare in gymnosperms and fungi.) For example, the genus of wheat, *Triticum*, has members with fourteen, twenty-eight, and forty-two chromosomes. Because the basic *Triticum* chromosome number is  $n = 7$ , these forms are  $2n$ ,  $4n$ , and  $6n$  species, respectively. Chrysanthemums have species of eighteen, thirty-six, fifty-four, seventy-two, and ninety chromosomes. With a basic number of  $n = 9$ , these species represent a  $2n$ ,  $4n$ ,  $6n$ ,  $8n$ , and  $10n$  series. In both these examples, the even-numbered polyploids are viable and fertile, but the odd-numbered polyploids are not.

### Autopolyploidy

Polyploidy can come about in two different ways. In **autopolyploidy**, all of the chromosomes come from within the same species. In **allopolyploidy**, the chromosomes come from the hybridization of two different species (fig. 8.29). Autopolyploidy occurs in several different ways. The fusion of nonreduced gametes creates polyploidy. For example, if a diploid gamete fertilizes a normal haploid gamete, the result is a triploid. Similarly, if a diploid gamete fertilizes another diploid gamete, the result is a tetraploid. The equivalent of a nonreduced gamete comes about in meiosis if the parent cell is polyploid to begin with. For example, if one branch of a diploid plant is tetraploid, its flowers produce diploid gametes. These gametes are not the result of a failure to reduce chromosome numbers meiotically, but rather the result of successful meiotic reduction in a polyploid flower. The tetraploid tissue of the



**Figure 8.29** Autopolyploidy and allopolyploidy. If A and B are the haploid genomes of species A and B, respectively, then autopolyploidy produces a species with an AAAA karyotype, and allopolyploidy (with chromosome doubling) produces a species with AABB karyotype. If A represents seven chromosomes, then an AA diploid has fourteen chromosomes and an AAAA tetraploid has twenty-eight chromosomes. If B represents five chromosomes, then a BB diploid has ten chromosomes and an AABB allotetraploid has twenty-four chromosomes.

plant in this example can originate by the **somatic doubling** of diploid tissues.

Somatic doubling can come about spontaneously or be caused by anything that disrupts the normal sequence of a nuclear division. For example, colchicine induces somatic doubling by inhibiting microtubule formation. This prevents the formation of a spindle and thus prevents the chromosomes from moving apart during either mitosis or meiosis. The result is a cell with double the chromosome number. Other chemicals, temperature shock, and physical shock can produce the same effect.

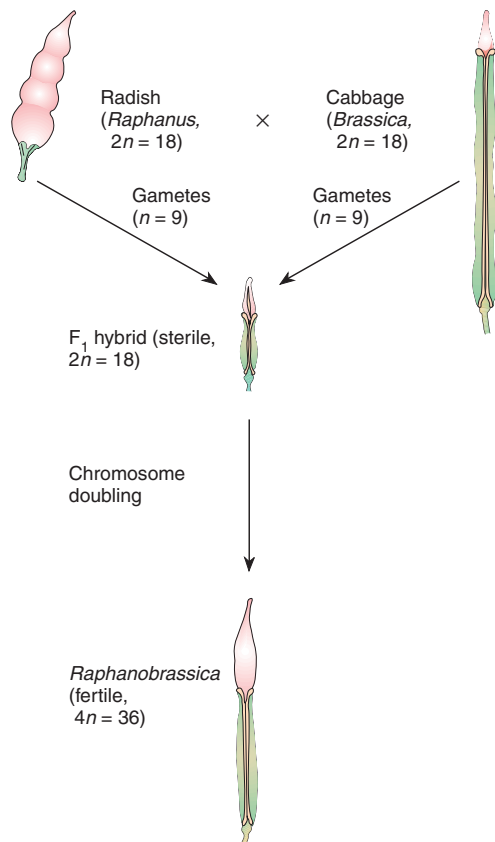
### Allopolyploidy

Allopolyploidy comes about by cross-fertilization between two species. The resulting offspring have the sum of the reduced chromosome number of each parent species. If each chromosome set is distinctly different, the new organisms have difficulty in meiosis because no two chromosomes are sufficiently homologous to pair. Then every chromosome forms a univalent (unpaired) figure, and they separate independently during meiosis, producing aneuploid gametes. However, if an organism can survive by vegetative growth until somatic doubling takes place in gamete precursor cells ( $2n \rightarrow 4n$ ), or alternatively, if the zygote was formed by two unreduced gametes ( $2n + 2n$ ), the resulting offspring will be fully fertile because each chromosome has a pairing partner at meiosis. We can draw an example from the work of Russian geneticist G. D. Karpechenko.

In 1928, Karpechenko worked with the radish (*Raphanus sativus*,  $2n = 18$ ,  $n = 9$ ) and cabbage (*Brassica oleracea*,  $2n = 18$ ,  $n = 9$ ). When these two plants are crossed, an  $F_1$  results with  $n + n = 18$  ( $9 + 9$ ). This plant, which is an allodiploid, has characteristics intermediate between the two parental species (fig. 8.30). If somatic doubling takes place, the chromosome number is doubled to thirty-six, and the plant becomes an allopolyploid (an allotetraploid of  $4n$ ). Since each chromosome has a homologue, this allotetraploid is also referred to as an **amphidiploid**. If we did not know its past history, this plant would simply be classified as a diploid with  $2n = 36$ . In this case, the new amphidiploid cannot successfully breed with either parent because the offspring are sterile triploids. It is, therefore, a new species and has been named *Raphanobrassica*. As an agricultural experiment, however, it was not a success because it did not combine the best features of the cabbage and radish.

### Polyploidy in Plants and Animals

Although polyploids in the animal kingdom are known (in some species of lizards, fish, invertebrates, and a



**Figure 8.30** Hybridization of cabbage and radish, showing the resulting hybrid fruiting structures.

tetraploid mammal, the red viscacha rat), polyploidy as a successful evolutionary strategy is primarily a plant phenomenon. There are several reasons for this. To begin with, many more animals than plants have chromosomal sex-determining mechanisms. Polyploidy severely disrupts these mechanisms. For example, Bridges discovered a tetraploid female fruit fly, but it has not been possible to produce a tetraploid male. The tetraploid female's progeny were triploids and intersexes. A second reason why polyploidy is more common in plants is because plants can generally avoid the meiotic problems of polyploidy longer than most animals. Some plants can exist vegetatively, allowing more time for the rare somatic doubling event to occur that will produce an amphidiploid; animal life spans are more precisely defined, allowing less time for a somatic doubling. And third, many plants depend on the wind or insect pollinators to fertilize them and thus have more of an opportunity for hybridization. Many animals have relatively elaborate courting rituals that tend to restrict hybridization.

Polyploidy has been used in agriculture to produce "seedless" as well as "jumbo" varieties of crops. Seedless watermelon, for example, is a triploid. Its seeds are mostly sterile and do not develop. It is produced by growing seeds from the cross between a tetraploid variety and a diploid variety. Jumbo Macintosh apples are tetraploid.

## S U M M A R Y

**STUDY OBJECTIVE 1:** To observe the nature and consequences of chromosomal breakage and reunion 178–190

Variation can occur in the structure and number of chromosomes in the cells of an organism. When chromosomes break, the ends become "sticky"; they tend to reunite with other broken ends. A single break can lead to deletions or the formation of acentric or dicentric chromosomes. Dicentrics tend to go through breakage-fusion-bridge cycles, which result in duplications and deficiencies.

Two breaks in the same chromosome can yield deletions and inversions. Variational position effects, as well as new linkage arrangements, can result. Inversion heterozygotes produce loop figures during synapsis, which can form either at meiosis or in polytene chromosomes. Heterozygosity for an inversion suppresses crossovers; organisms that are heterozygotes are semisterile.

Reciprocal translocations can result from single breaks in nonhomologous chromosomes. These produce cross-shaped figures at synapsis and result in semisterility. The *Bar* eye phenotype of *Drosophila* is an example of a duplication that causes a position effect.

**STUDY OBJECTIVE 2:** To observe the nature and consequences of variation in chromosome numbers in human and nonhuman organisms 190–199

Changes in chromosome number can involve whole sets (euploidy) or partial sets (aneuploidy) of chromosomes. Aneuploidy usually results from nondisjunction or chromosomal lagging. Several medical syndromes, such as Down, Turner, and Klinefelter syndromes, and the XYY karyotype are caused by aneuploidy.

Polyploidy leads to difficulties in chromosomal sex-determining mechanisms, general chromosomal imbalance, and problems during meiotic segregation. It has been more successful in plants than in animals because plants generally lack chromosomal sex-determining mechanisms. Plants can also avoid meiotic problems by propagating vegetatively. In both animals and plants, even-numbered poly-

ploids do better than odd-numbered polyploids because they have a better chance of producing balanced gametes during meiosis. Somatic doubling provides each chromosome in a hybrid organism with a homologue, and thus makes possible tetrad formation at meiosis. New species have arisen by polyploidy.

## SOLVED PROBLEMS

**PROBLEM 1:** What are the consequences of an inversion?

**Answer:** In an inversion homozygote, the consequences are change in linkage arrangements, including new orders and map distances, and the possibility of position effects if a locus is placed into or near heterochromatin. In an inversion heterozygote, crossover suppression causes semisterility because zygotes that carry genic imbalances are lost. Inversion heterozygotes can be seen as meiotic loop structures or loops formed in endomitotic chromosomes such as those found in the salivary glands of fruit flies. In an evolutionary sense, inversions result in supergenes, locking together allelic combinations.

**PROBLEM 2:** What are the consequences of a monosomic chromosome in human beings?

**Answer:** In human beings, monosomy is rare, meaning that, with few exceptions, it is lethal. In fact, monosomies are also rare in spontaneous abortions, indicating that most monosomic fetuses are lost before the woman is aware of the pregnancy. The only monosomies known to

be viable in human beings are Turner syndrome (45,X) and monosomies of chromosomes 21 and 22, the two smallest autosomal chromosomes.

**PROBLEM 3:** Ebony body (*e*) in flies is an autosomal recessive trait. A true-breeding ebony female (*ee*) is mated with a true-breeding wild-type male that has been irradiated. Among the wild-type progeny is a single ebony male. Explain this observation.

**Answer:** The cross is  $ee \times e^+e^+$ , and all  $F_1$ s should be  $e^+e$  (wild-type). The use of irradiation alerts us to the possibility of chromosomal breaks, as well as simple mutations. What type of chromosomal aberration would allow a recessive trait to appear unexpectedly? A deletion, which creates pseudodominance when there is no second allele, is a good possibility. The male in question could have gotten the ebony allele from its mother and no homologous allele from its father. Alternatively, the wild-type allele from the father could have mutated to an ebony allele.

## EXERCISES AND PROBLEMS\*

### VARIATION IN CHROMOSOMAL STRUCTURE

1. What kind of figure is observed in meiosis of a reciprocal translocation homozygote?
2. Can a deletion result in the formation of a variegated position effect? If so, how?
3. Does crossover suppression occur in an inversion homozygote? Explain.
4. Which rearrangements of chromosomal structure cause semisterility?
5. What are the consequences of single crossovers during tetrad formation in a reciprocal translocation heterozygote?
6. Give the gametic complement, in terms of acentrics, dicentrics, duplications, and deficiencies, when a three-strand double crossover occurs within a paracentric inversion loop.
7. In studying a new sample of fruit flies, a geneticist noted phenotypic variegation, semisterility, and the nonlinkage of previously linked genes. What probably caused this, and what cytological evidence would strengthen your hypothesis?
8. In a second sample of flies, the geneticist found a position effect and semisterility. The linkage groups were correct, but the order was changed and crossing over was suppressed. What probably caused this, and what cytological evidence would strengthen your hypothesis?

\* Answers to selected exercises and problems are on page A-9.

9. Diagram the results of alternate segregation for a three-strand double crossover between a centromere and the cross center in a reciprocal translocation heterozygote.
10. A heterozygous plant  $A B C D E/a b c d e$  is testcrossed with an  $a b c d e/a b c d e$  plant. Only the following progeny appear:
- $A B C D E/a b c d e$   
 $a b c d e/a b c d e$   
 $A b c d e/a b c d e$   
 $a B C D E/a b c d e$   
 $A B C D e/a b c d e$   
 $a b c d E/a b c d e$

What is unusual about the results? How can you explain them?

11. White eye color in *Drosophila* is an X-linked recessive trait. A wild-type male is irradiated and mated with a white-eyed female. Among the progeny is a white-eyed female.
- a. Why is this result unexpected, and how could you explain it?
- b. What type of progeny would you expect if this white-eyed female is crossed with a normal, non-irradiated male?
12. You are trying to locate an enzyme-producing gene in *Drosophila*, which you know is located on the third chromosome. You have five strains with deletions for different regions of the third chromosome (a slash — / — indicates a deleted region):

	0	10	20	30	40	50	60	map units
Normal								
Strain A	/////	_____						
Strain B	_____	//////////	_____					
Strain C	_____	_____	//////////	_____				
Strain D	_____	_____	_____	//////////	_____			
Strain E	_____	_____	_____	_____	//////////	_____		

You cross each strain with wild-type flies and measure the amount of enzyme in the  $F_1$  progeny. The results appear as follows. In what region is the gene located?

Strain Crossed	Percentage of Wild-Type Enzyme Produced in $F_1$ Progeny
A	100
B	45
C	54
D	98
E	101

13. Consider the following table, which shows the number of viable progeny produced by a plant under standard conditions. Provide an explanation for the results.

$P_1$ :	Strain A × Strain A	Strain B × Strain B	Strain A × Strain B
$F_1$ :	765	750	775
$F_2$ :	712	783	416

14. The map position for three X-linked recessive genes in *Drosophila* ( $v$ , vermilion eyes;  $m$ , miniature wings; and  $s$ , sable body) is:

$v$	$m$	$s$
33.0	36.1	43.0

A wild-type male is X-rayed and mated to a vermilion, miniature, sable female. Among the progeny is a single vermilion-eyed, long-winged, tan-bodied female. The following shows the progeny when this female is mated with a  $v m s$  hemizygot male.

Females	Males
87 vermilion, miniature, sable	89 vermilion, miniature, sable
93 vermilion	1 vermilion

Explain these results by drawing a genetic map.

15. In *Drosophila*, recessive genes clot ( $ct$ ) and black body ( $b$ ) are located at 16.5 and 48.5 map units, respectively, on the second chromosome. In one cross, wild-type females that are  $ct^+ b^+/ct b$  are mated with  $ct b/ct b$  males. They produce these progeny:

wild-type	1,250
clot, black	1,200
black	30
clot	20

What is unusual about the results? How can you explain them?

16. You have four strains of *Drosophila* (1–4) that were isolated from different geographic regions. You compare the banding patterns of the second chromosome and obtain these results (each letter corresponds to a band):

- (1) m n r q p o s t u v  
 (2) m n o p q r s t u v  
 (3) m n r q t s u p o v  
 (4) m n r q t s o p u v

If (3) is presumed to be the ancestral strain, in what order did the other strains arise?

17. In *Drosophila*, the recessive gene for white eyes is located near the tip of the X chromosome. A wild-type male is irradiated and mated with a white-eyed female. Among the progeny is one red-eyed male. How can you explain the red-eyed male, and how could you test your hypothesis?

**VARIATION IN CHROMOSOME NUMBER**

18. Is a tetraploid more likely to show irregularities in meiosis or mitosis? Explain. What about these processes in a triploid?
19. How many chromosomes would a human tetraploid have? How many chromosomes would a human monosomic have?
20. Do autopolyploids or allopolyploids experience more difficulties during meiosis? Do amphidiploids have more or less trouble than auto- or allopolyploids?
21. If a diploid species of  $2n = 16$  hybridizes with one of  $2n = 12$ , and the resulting hybrid doubles its chromosome number to produce an allotetraploid (amphidiploid), how many chromosomes will it have? How many chromosomes will an allotetraploid have if both parent species had  $2n = 20$ ?
22. If nondisjunction of the sex chromosomes occurs in a female at the second meiotic division, what type of eggs will arise?
23. How might an X0/XYY human mosaic arise? An XX/XXY mosaic? How might a trisomy 21 individual arise?
24. Plant species P has  $2n = 18$ , and species U has  $2n = 14$ . A fertile hybrid is found. How many chromosomes does it have?
25. A woman with normal vision whose father was color-blind mates with a man with normal vision. They have a color-blind daughter with Turner syndrome. In which parent did nondisjunction occur?
26. A color-blind man mates with a woman with normal vision whose father was color-blind. They have a color-blind son with Klinefelter syndrome. In which parent did nondisjunction occur?
27. Describe a genetic event that can produce an XYY man.
28. Chromosomal analysis of a spontaneously aborted fetus revealed that the fetus was 92,XXYY. Propose an explanation to account for this unusual karyotype.

**C R I T I C A L   T H I N K I N G   Q U E S T I O N S**

1. Various species in the grass genus *Bromus* have chromosome numbers of 14, 28, 42, 56, 70, 84, 98, and 112. What can you tell about the genetic relationships among these species and how they might have arisen?
2. There was a humorous television commercial in which someone accidentally discovered the desirability of combining chocolate and peanut butter. Could this combination be achieved by crossing peanut and cocoa plants?

*Suggested Readings for chapter 8 are on page B-4.*