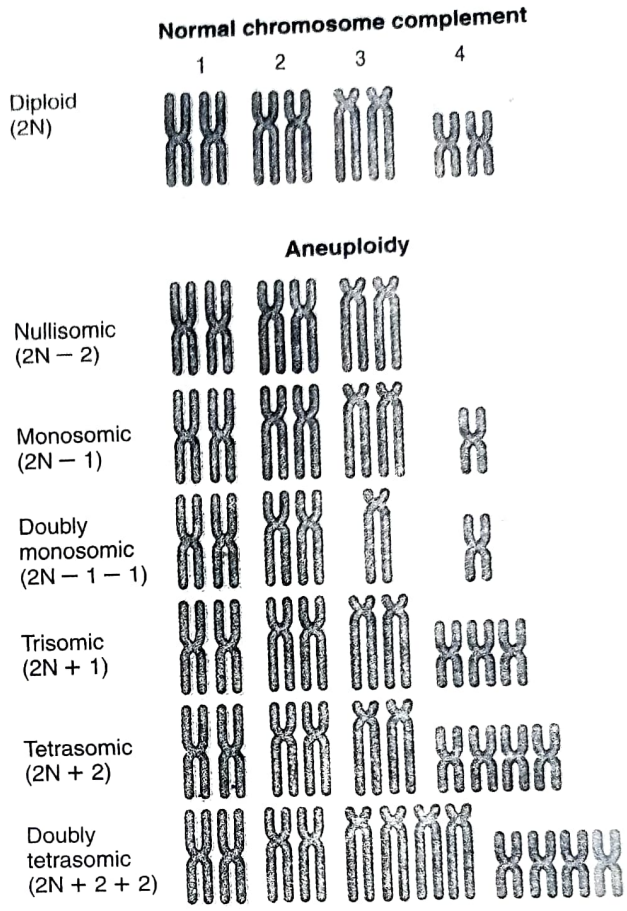
of unusual complements of X chromosomes, with Figure 12.18 (p. 344) illustrating the consequences of nondisjunction at the first and second meiotic divisions. Referring to that figure and considering just one particular chromosome, one can see that nondisjunction at meiosis I produces four abnormal gametes: two with a chromosome duplicated and two with the corresponding chromosome missing. In a male, nondisjunction at meiosis I can produce a gamete with both the X and the Y chromosome; in a female, it produces a gamete with both sets of homologs (and thus possible heterozygotes). Fusion of the former gamete type with a normal gamete produces a zygote with three copies of the particular chromosome instead of the normal two and, unless nondisjunction also involves other chromosomes, there will be two copies of all other chromosomes. The latter gamete type may well be inviable. If it is viable, fusion with a normal gamete produces a zygote with only one copy of the particular chromosome instead of the normal two, and two copies of all other chromosomes. Nondisjunction in meiosis II (see Figure 12.18) is different from nondisjunction in meiosis I in that some normal gametes are produced. As Figure 12.19 shows, nondisjunction in meiosis II results in two normal gametes and two abnormal gametes—that is, a single gamete with two daughter chromosomes and one gamete with that same chromosome missing. Fusion of these with normal gametes gives the zygote types just discussed. Nondisjunction can occur in mitosis, giving rise to somatic cells with unusual chromosome complements.

Figure 16.15
Normal (theoretical) set of metaphase chromosomes in a diploid (2N) organism *(top)* and examples of aneuploidy *(bottom)*.



Types of Aneuploidy. In aneuploidy, one or more chromosomes are lost from or added to the normal set of chromosomes (Figure 16.15). Aneuploidy can occur, for example, from the loss of individual chromosomes in meiosis or (rarely) in mitosis by nondisjunction. In animals, autosomal aneuploidy is almost always lethal, so in mammals it is detected mainly in aborted fetuses. Aneuploidy is tolerated more by plants, especially in species that are considered polyploid (having more sets of chromosomes than the usual two).

In diploid organisms, there are four main types of aneuploidy (see Figure 16.15):

1. **Nullisomy** (a nullisomic cell) involves a loss of one homologous chromosome pair—the cell is 2N − 2. (Nullisomy can arise, for example, if nondisjunction occurs for the same chromosome in meiosis in both parents, producing gametes with no copies of that chromosome and one copy of all other chromosomes in the set.)
2. **Monosomy** (a monosomic cell) involves a loss of a single chromosome—the cell is 2N − 1. (Monosomy can arise, for example, if nondisjunction in meiosis in a parent produces a gamete with no copies of a particular chromosome and one copy of all other chromosomes in the set.)
3. **Trisomy** (a trisomic cell) involves a single extra chromosome—the cell has three copies of a particular chromosome and two copies of all other chromosomes. A trisomic cell is 2N + 1. (Trisomy can arise, for example, if nondisjunction in meiosis in a parent produces a gamete with two copies of a particular chromosome and one copy of all other chromosomes in the set.)
4. **Tetrasomy** (a tetrasomic cell) involves an extra chromosome pair; that is, there are four copies of one particular chromosome and two copies of all other chromosomes—the cell is 2N + 2. (Tetrasomy can arise, for example, if nondisjunction occurs for the same chromosome in meiosis in both parents, producing gametes with two copies of that chromosome and one copy of all other chromosomes in the set.)

Aneuploidy may involve the loss or the addition of more than one specific chromosome or chromosome pair. For example, a *double monosomic* has two separate chromosomes present in only one copy each; that is, it is 2N − 1 − 1. A *double tetrasomic* has two chromosomes present in four copies each; that is, it is 2N + 2 + 2. In both cases, meiotic nondisjunction involved two different chromosomes in one parent's gamete production.

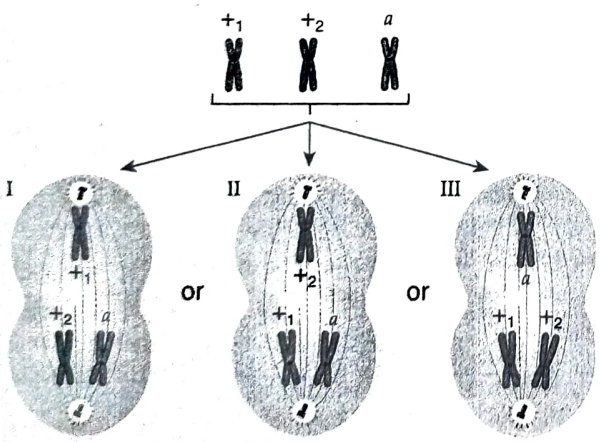
Most forms of aneuploidy have serious consequences in meiosis. Monosomics, for example, produce two kinds

of haploid gametes: N and N − 1. Alternatively, the odd, unpaired chromosome in the 2N − 1 cell may be lost during meiotic anaphase and not be included in either daughter nucleus, thereby producing two N − 1 gametes. For trisomics, there are more segregation possibilities in meiosis. Consider a trisomic of genotype +/+/*a* in an organism that can tolerate trisomy, and assume no crossing-over between the *a* locus and its centromere. Then, as shown in Figure 16.16, random segregation of the three types of chromosomes produces four genotypic classes of gametes: 2 (+ *a*) : 2 (+) : 1 (+ +) : 1 (*a*). In a cross of a +/+/*a* trisomic with an *a*/*a* individual, the predicted phenotypic ratio among the progeny is 5 wild type (+) : 1 mutant (*a*). This ratio is seen in many actual crosses of this kind.

In the sections that follow, we examine some examples of aneuploidy as they are found in the human population. Table 16.1 summarizes various aneuploid abnormalities for autosomes and for sex chromosomes in the human population. Examples of aneuploidy of the X and Y chromosomes are discussed in Chapter 12. Recall that, in mammals, aneuploidy of the sex chromosomes is more often found in adults than is aneuploidy of the autosomes, because of a dosage compensation mechanism (lyonization) by which excess X chromosomes are inactivated.

Figure 16.16

Meiotic segregation possibilities in a trisomic individual. Shown is segregation in an individual of genotype +/+/*a* when two chromosomes migrate to one pole and one goes to the other pole, and assuming no crossing-over between the *a* locus and its centromere. The two + alleles are labeled $+_1$ and $+_2$ to distinguish them.



Gametes produced after 2nd meiotic division

	haploid	disomic
I	$+_1$	$+_2/a$
II	$+_2$	$+_1/a$
III	*a*	$+_1/+_2$

In sum: 2 +/*a* : 2 + : 1 +/+ : 1 *a*

Table 16.1 Aneuploid Abnormalities in the Human Population

Chromosomes	Syndrome	Frequency at Birth
Autosomes		
Trisomic 21	Down	14.3/10,000
Trisomic 13	Patau	2/10,000
Trisomic 18	Edwards	2.5/10,000
Sex chromosomes, females		
XO, monosomic	Turner	4/10,000 females
XXX, trisomic	Viable; most	
XXXX, tetrasomic	are fertile	14.3/10,000 females
XXXXX, pentasomic		
Sex chromosomes, males		
XYY, trisomic	Normal	25/10,000 males
XXY, trisomic		
XXYY tetrasomic	Klinefelter	40/10,000
XXXY, tetrasomic		

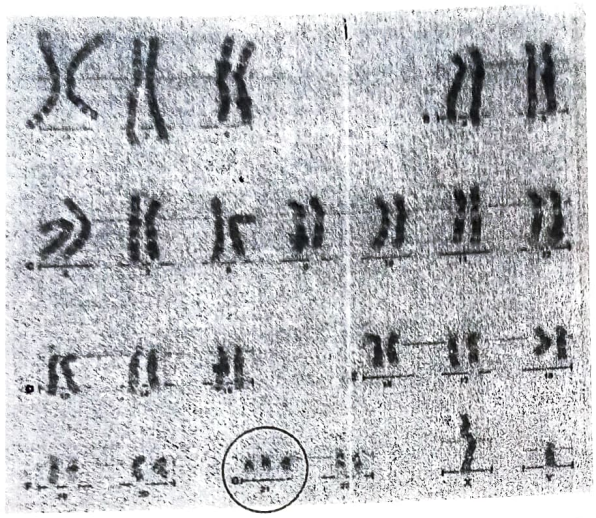
In humans, autosomal monosomy is rare. Presumably, monosomic embryos do not develop significantly and are lost early in pregnancy. In contrast, autosomal trisomy accounts for about one-half of chromosomal abnormalities producing fetal deaths. In fact, only a few autosomal trisomies are seen in live births. Most of these (trisomy-8, -13, and -18) result in early death. Only in trisomy-21 (Down syndrome) does survival to adulthood occur.

Trisomy-21. **Trisomy-21** (OMIM 190685) occurs when there are three copies of chromosome 21 (Figure 16.17a) and with a frequency of about 3,510 per 1 million conceptions and about 1,430 per 1 million live births. Individuals with trisomy-21 have Down syndrome (Figure 16.17b), characterized by such abnormalities as low IQ, epicanthal folds (in which the skin of the upper eyelid forms a layer that covers the inner corner of the eye), short and broad hands, and below-average height. Down syndrome is named for the late-nineteenth-century English physician John Langdon Down, who, in 1866, became the first to publish an accurate description of a person with the condition.

A direct relationship exists between maternal age and probability of giving birth to an individual with trisomy-21. (Table 16.2). (For many years, it was thought that there was no correlation with age of the father. Recent evidence, however, indicates that paternal age has an effect on Down syndrome if the mother is 35 years old or older; in younger women, there is no paternal effect.) During the development of a female fetus before birth, the primary oocytes in the ovary undergo meiosis, but stop at prophase I. In a fertile female, each month at ovulation the nucleus of a secondary oocyte (see Chapter 12) begins the second meiotic division, but progresses only to metaphase, when division

Figure 16.17
Trisomy-21 (Down syndrome).

a) Karyotype (G banding)



b) Individual with trisomy-21 (Down syndrome)

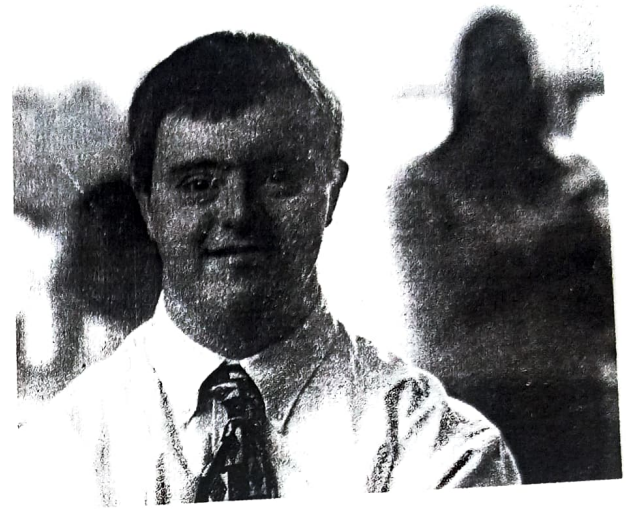


Table 16.2 Relationship Between Age of Mother and Risk of Trisomy-21

Age of Mother	Risk of Trisomy-21 in Child
16–26	7.7/10,000
27–34	4/10,000
35–39	29/10,000
40–44	100/10,000
45–47	333/10,000
All mothers combined	14.3/10,000

again stops. If a sperm penetrates the secondary oocyte, the second meiotic division is completed. The probability of nondisjunction increases with the length of time the primary oocyte is in the ovary. It is important, then, that older mothers-to-be consider testing—for example, by undergoing amniocentesis or chorionic villus sampling (see Chapter 4, p. 74)—to determine whether the fetus has a normal complement of chromosomes.

Are there other risk factors for having a Down syndrome baby? Where a person lives, social class, and race have no influence on the chance of having a baby with Down syndrome. However, mothers under 35 years of age who smoke are at an increased risk of having children with the syndrome. If mothers with these characteristics use cigarettes and oral contraceptives, the risk is increased over using cigarettes alone. Oral contraceptive use alone for this class of mothers has no effect on the incidence of Down syndrome.

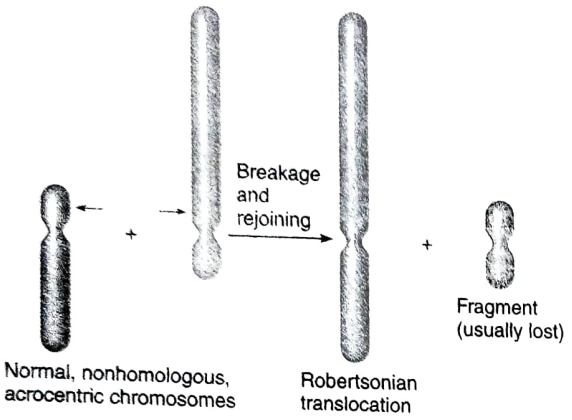
Down syndrome can also result from a different sort of chromosomal mutation called centric fusion or **Robertsonian translocation**, which produces three copies of the long arm of chromosome 21. (The translocation is named for W. R. B. Robertson, an insect geneticist who first described this type of chromosomal mutation.) This form of Down syndrome, called familial Down syndrome, is responsible for 2–3% of Down syndrome cases. A Robertsonian translocation is a type of reciprocal translocation in which two nonhomologous acrocentric chromosomes (chromosomes with centromeres near their ends) break at their centromeres and then the long arms become attached to a single centromere (Figure 16.18). The short arms also join to form the reciprocal product, which typically contains nonessential genes and usually is lost within a few cell divisions. In humans, when a Robertsonian translocation joins the long arm of chromosome 21 with the long arm of chromosome 14 (or 15), the heterozygous carrier is phenotypically normal, because there are two copies of all major chromosome arms and hence two copies of all essential genes.

Animation
Down Syndrome Caused by a Robertsonian Translocation

There is a high risk of Down syndrome among the offspring of pairings between heterozygous carriers and normal individuals (Figure 16.19). The normal parent produces gametes with one copy each of chromosomes 14 and 21. The heterozygous carrier parent produces three reciprocal pairs of gametes, each as a result of different segregation of the three chromosomes involved: (1) 14/21 (translocated 14 and 21) + 21, and 14; (2) 14/21 + 14, and 21; and (3) 14/21, and 14 + 21 (The three gamete pairs do not occur with equal frequency.) The zygotes are produced by pairing these gametes with gametes of normal chromosomal constitution: 14 and 21. Figure 16.19 shows the result of the gamete fusions. In only one case is

Figure 16.18

Robertsonian translocation. Production of a Robertsonian translocation (centric fusion) by breakage of two acrocentric chromosomes at their centromeres (indicated by arrows) and fusion of the two large chromosome arms and of the two small chromosome arms.



a normal zygote produced with chromosomes 14, 14, 21, and 21. One other zygote that leads to a normal phenotype is a carrier zygote with chromosomes 14, 21, and 14/21. A viable trisomy-21 zygote is produced with chromosomes 14, 14/21, 21, and 21. Three inviable zygotes are produced, one with monosomy-21, one with trisomy-14, and one with monosomy-14.

Trisomy-13. **Trisomy-13** produces Patau syndrome (Figure 16.20). About 2 in 10,000 live births produce individuals with trisomy-13. Characteristics of individuals with trisomy-13 include cleft lip and palate, small eyes, polydactyly (extra fingers and toes), mental and developmental retardation, and cardiac anomalies, among many other abnormalities. Most infants die before the age of 3 months.

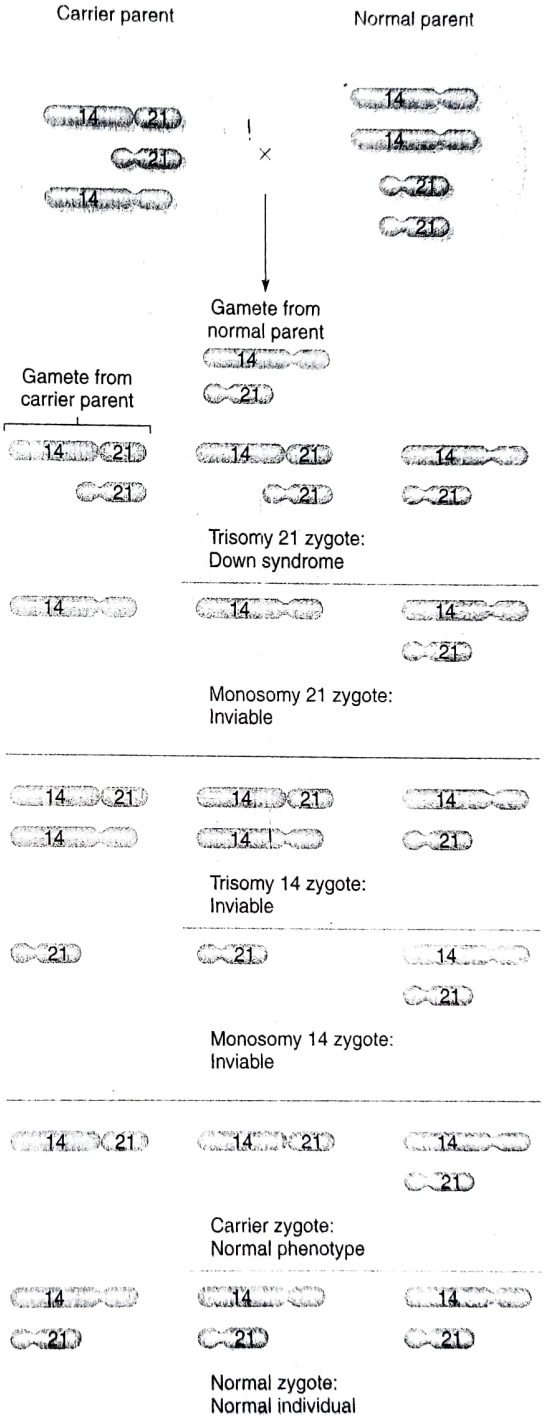
Trisomy-18. **Trisomy-18** produces Edwards syndrome (Figure 16.21), which occurs in about 2.5 in 10,000 live births. For reasons that are not known, about 80 percent of infants with Edwards syndrome are female. Individuals with trisomy-18 are small at birth and have multiple congenital malformations affecting almost every organ in the body. Clenched fists, an elongated skull, low-set malformed ears, mental and developmental retardation, and many other abnormalities are associated with the syndrome. Ninety percent of infants with trisomy-18 die within 6 months, often from cardiac problems.

Changes in Complete Sets of Chromosomes

Monoploidy and **polyploidy** involve variations from the normal state in the number of complete sets of chromosomes. Because the number of complete sets of chromosomes is involved in each case, monoploids and polyploids are euploids. Monoploidy and polyploidy are lethal in most animal species, but are less consequential in plants.

Figure 16.19

The three segregation patterns of a heterozygous Robertsonian translocation involving human chromosomes 14 and 21. Fusion of the resulting gametes with gametes from a normal parent produces zygotes with various combinations of normal and translocated chromosomes.



CONCEPTS

The sexual phenotype of a fruit fly is determined by the ratio of the number of X chromosomes to the number of haploid sets of autosomal chromosomes (the X:A ratio).

✔ CONCEPT CHECK 4

What is the sexual phenotype of a fruit fly that has XXYYY sex chromosomes and two sets of autosomes?

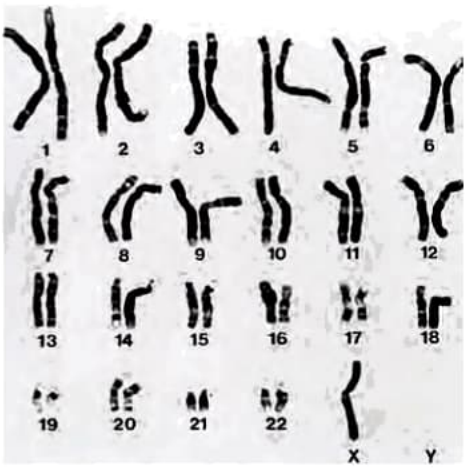
a. Male
b. Female
c. Intersex
d. Metamale

Sex Determination in Humans

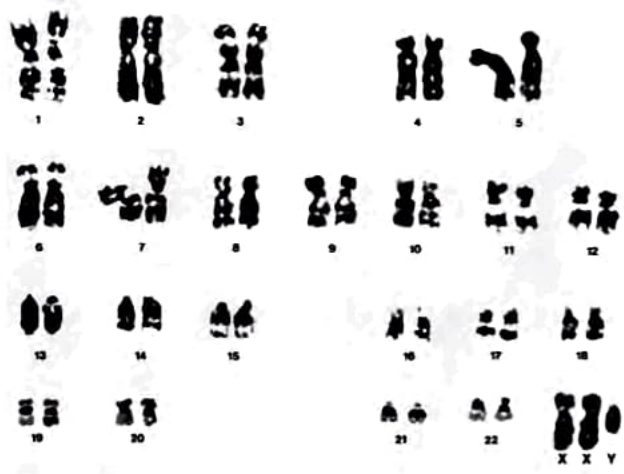
Humans, like *Drosophila*, have XX-XY sex determination, but, in humans, the presence of a gene (*SRY*) on the Y chromosome determines maleness. The phenotypes that result from abnormal numbers of sex chromosomes, which arise when the sex chromosomes do not segregate properly in meiosis or mitosis, illustrate the importance of the Y chromosome in human sex determination.

Turner syndrome Persons who have **Turner syndrome** are female and often have underdeveloped secondary sex characteristics. This syndrome is seen in 1 of 3000 female births. Affected women are frequently short and have a low hairline, a relatively broad chest, and folds of skin on the neck. Their intelligence is usually normal. Most women who have Turner syndrome are sterile. In 1959, Charles Ford used new techniques to study human chromosomes and discovered that cells from a 14-year-old girl with Turner syndrome had only a single X chromosome (**Figure 4.8**); this chromosome complement is usually referred to as XO.

There are no known cases in which a person is missing both X chromosomes, an indication that at least one X chromosome is necessary for human development. Presumably, embryos missing both Xs spontaneously abort in the early stages of development.



4.8 Persons with Turner syndrome have a single X chromosome in their cells. [Department of Clinical Cytogenetics, Addenbrookes Hospital/Science Photo Library/Photo Reseachers.]



4.9 Persons with Klinefelter syndrome have a Y chromosome and two or more X chromosomes in their cells. [Biophoto Associates/Science Source/Photo Researchers.]

Klinefelter syndrome Persons who have **Klinefelter syndrome**, which occurs with a frequency of about 1 in 1000 male births, have cells with one or more Y chromosomes and multiple X chromosomes. The cells of most males having this condition are XXY (**Figure 4.9**), but the cells of a few Klinefelter males are XXXY, XXXXY, or XXYY. Men with this condition frequently have small testes and reduced facial and pubic hair. They are often taller than normal and sterile; most have normal intelligence.

Poly-X females In about 1 in 1000 female births, the infant's cells possess three X chromosomes, a condition often referred to as **triplo-X syndrome**. These persons have no distinctive features other than a tendency to be tall and thin. Although a few are sterile, many menstruate regularly and are fertile. The incidence of mental retardation among triple-X females is slightly greater than that in the general population, but most XXX females have normal intelligence. Much rarer are females whose cells contain four or five X chromosomes. These females usually have normal female anatomy but are mentally retarded and have a number of physical problems. The severity of mental retardation increases as the number of X chromosomes increases beyond three.

The role of sex chromosomes The phenotypes associated with sex-chromosome anomalies allow us to make several inferences about the role of sex chromosomes in human sex determination.

1. The X chromosome contains genetic information essential for both sexes; at least one copy of an X chromosome is required for human development.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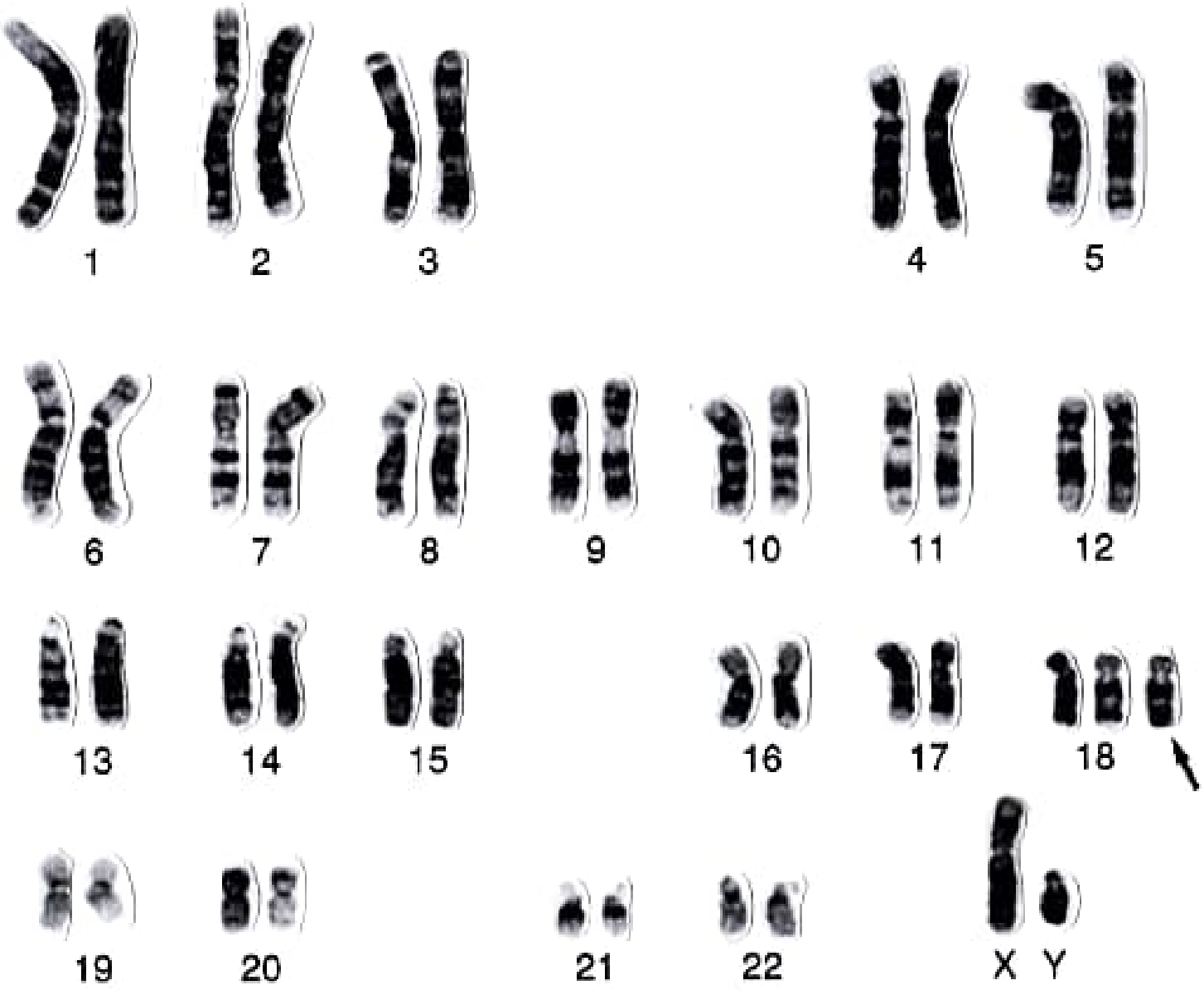
47,XY,+18
TRISOMY 18 (EDWARD'S SYNDROME)



Klinefelter Syndrome