CHAPTER

4

Genetic and Congenital Disorders

Genetic and congenital defects are important at all levels of health care because they affect all age groups and can involve almost any of the body tissues and organs. Congenital defects, sometimes called *birth defects,* develop during prenatal life and usually are apparent at birth or shortly thereafter. Spina bifida and cleft lip, for example, are apparent at birth, but other malformations, such as kidney and heart defects, may be present at birth but may not become apparent until they begin to produce symptoms. Not all genetic disorders are congenital, and many are not apparent until later in life.

Birth defects, which affect more than 150,000 infants each year, are the leading cause of infant death.[1] Birth defects may be caused by genetic factors (*i.e.*, single-gene or multifactorial inheritance or chromosomal aberrations), or they may be caused by environmental factors that occurred during embryonic or fetal development (*i.e.*, maternal disease, infections, or drugs taken during pregnancy). In rare cases, congenital defects may be the result of intrauterine factors such as fetal crowding, positioning, or entanglement of fetal parts with the amnion.

This chapter provides an overview of genetic and congenital disorders and is divided into three parts: (1) genetic and chromosomal disorders, (2) disorders caused by environmental agents, and (3) diagnosis and counseling.

GENETIC AND CHROMOSOMAL DISORDERS

Genetic disorders involve a permanent change (or mutation) in the genome. A genetic disorder can involve a single-gene trait, multifactorial inheritance, or a chromosome disorder.

Single-Gene Disorders

Single-gene disorders are caused by a single defective or mutant gene. The defective gene may be present on an autosome or the X chromosome and it may affect only one member of an autosomal gene pair (matched with a normal gene) or both members of the pair. Single-gene defects follow the mendelian patterns of inheritance (see Chapter 3) and are often called

KEY CONCEPTS

GENETIC AND CHROMOSOMAL DISORDERS

- Genetic disorders are inherited as autosomal dominant disorders, in which each child has a 50% chance of inheriting the disorder, and as autosomal recessive disorders, in which each child has a 25% chance of being affected, a 50% chance of being a carrier, and a 25% chance of being unaffected.
- Sex-linked disorders almost always are associated with the X chromosome and are predominantly recessive.
- Chromosomal disorders reflect events that occur at the time of meiosis and result from defective movement of an entire chromosome or from breakage of a chromosome with loss or translocation of genetic material.

mendelian disorders. At last count, there were more than 8000 single-gene disorders, many of which have been mapped to a specific chromosome.[2]

The genes on each chromosome are arranged in pairs and in strict order, with each gene occupying a specific location or locus. The two members of a gene pair, one inherited from the mother and the other from the father, are called *alleles.* If the members of a gene pair are identical (*i.e.*, code the exact same gene product), the person is *homozygous,* and if the two members are different, the person is *heterozygous.* The genetic composition of a person is called a *genotype,* whereas the *phenotype* is the observable expression of a genotype in terms of morphologic, biochemical, or molecular traits. If the trait is expressed in the heterozygote (one member of the gene pair codes for the trait), it is said to be *dominant;* if it is expressed only in the homozygote (both members of the gene pair code for the trait), it is *recessive.*

Although gene expression usually follows a dominant or recessive pattern, it is possible for both alleles (members) of a gene pair to be fully expressed in the heterozygote, a condition called *codominance.* Many genes have only one normal version, called a *wild-type* allele. Other genes have more than one normal allele (alternate forms) at the same locus. This is called *polymorphism.* Blood group inheritance (*e.g.*, AO, BO, AB) is an example of codominance and polymorphism.

A single mutant gene may be expressed in many different parts of the body. Marfan's syndrome is a defect in connective tissue that has widespread effects involving skeletal, eye, and cardiovascular structures. In other single-gene disorders, the same defect can be caused by mutations at several different loci. Childhood deafness can result from 16 different types of autosomal recessive mutations.

Single-gene disorders are characterized by their patterns of transmission, which usually are obtained through a family genetic history. The patterns of inheritance depend on whether the phenotype is dominant or recessive, and whether the gene is located on an autosomal or sex chromosome (see Chapter 3). Disorders of autosomal inheritance include autosomal dominant and autosomal recessive traits. Among the approximate 8000 single-gene disorders, more than half are autosomal dominant. Autosomal recessive phenotypes are less common, accounting for approximately one third of single-gene disorders.[3] Currently, all sex-linked genetic disorders are thought to be X-linked, and most are recessive. The only mutations affecting the Y-linked genes are involved in spermatogenesis and male fertility and thus are not transmitted. A few additional genes with homologs on the X chromosome have been mapped to the Y chromosome, but to date, no disorders resulting from mutations in these genes have been described.

Virtually all single-gene disorders lead to formation of an abnormal protein or decreased production of a gene product. The defect can result in defective or decreased amounts of an enzyme, defects in receptor proteins and their function, alterations in nonenzyme proteins, or mutations resulting in unusual reactions to drugs. Table 4-1 lists some of the common single-gene disorders and their manifestations.

Autosomal Dominant Disorders

In autosomal dominant disorders, a single mutant allele from an affected parent is transmitted to an offspring regardless of sex. The affected parent has a 50% chance of transmitting the disorder to each offspring (Fig. 4-1). The unaffected relatives of the parent or unaffected siblings of the offspring do not transmit the disorder. In many conditions, the age of onset is delayed, and the signs and symptoms of the disorder do not appear until later in life, as in Huntington's chorea (see Chapter 37).

Autosomal dominant disorders also may manifest as a new mutation. Whether the mutation is passed on to the next generation depends on the affected person's reproductive capacity. Many new autosomal dominant mutations are accompanied by reduced reproductive capacity; therefore, the defect is not perpetuated in future generations. If an autosomal defect is accompanied by a total inability to reproduce, essentially all new cases of the disorder will be due to new mutations. If the defect does not affect reproductive capacity, it is more likely to be inherited.

Although there is a 50% chance of inheriting a dominant genetic disorder from an affected parent, there can be wide variation in gene penetration and expression. When a person inherits a dominant mutant gene but fails to express it, the trait is described as having *reduced penetrance.* Penetrance is expressed in mathematical terms; a 50% penetrance indicates that a person who inherits the defective gene has a 50% chance of expressing the disorder. The person who has a mutant gene but does not express it is an important exception to the rule that unaffected persons do not transmit an autosomal dominant trait. These persons can transmit the gene to their descendants and so produce a skipped generation. Autosomal dominant disorders also can display *variable expressivity,* meaning that they can be expressed differently among individuals. For example, polydactyly or the presence of more than the usual number of digits may be expressed in the fingers or the toes.

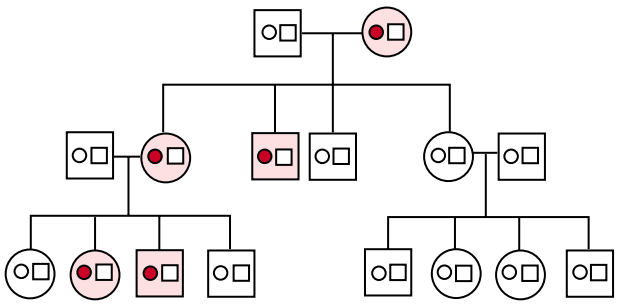
The gene products of autosomal dominant disorders usually are regulatory proteins involved in rate-limiting components of complex metabolic pathways or key components of structural proteins such as collagen.[4,5] Two disorders of autosomal inheritance, Marfan's syndrome and neurofibromatosis (NF), are described in this chapter.

Marfan's Syndrome. Marfan's syndrome is a connective tissue disorder that is manifested by changes in the skeleton, eyes, and cardiovascular system. There is a wide range of variation in expression of the disorder. Persons may have abnormalities of one or all three systems. The skeletal deformities, which are the most obvious features of the disorder, include a long, thin body with exceptionally long extremities and long, tapering fingers, sometimes called *arachnodactyly* or *spider fingers* (Fig. 4-2), hyperextensible joints, and a variety of spinal deformities including kyphoscoliosis. Chest deformity, pectus excavatum (*i.e.*, deeply depressed sternum), or pigeon chest deformity, often is present. The most common eye disorder is bilateral dislocation of the lens caused by weakness of the suspensory ligaments. Myopia and predisposition to retinal detachment also are common, the result of increased optic globe length due to altered connective tissue support of ocular structures. However, the most life-threatening aspects of the disorder are the cardiovascular defects, which include mitral valve prolapse, progressive dilation of the aortic valve ring, and weakness of the aorta and other arteries. Dissection and rupture of the aorta often lead to premature death. The average age of death in persons with Marfan's syndrome is 30 to 40 years.[4]

TABLE 4-1 Some Disorders of Mendelian or Single-Gene Inheritance and Their Significance

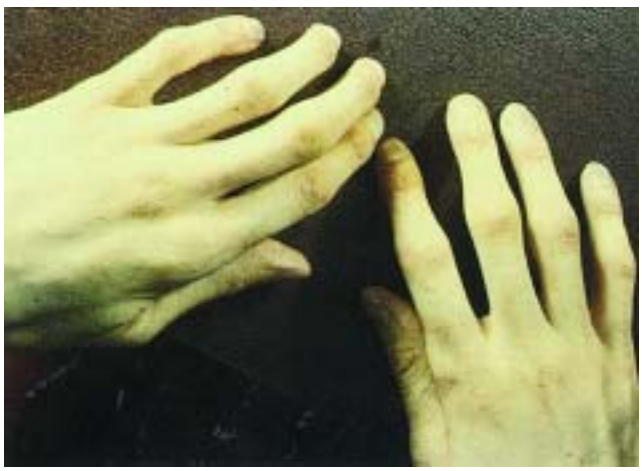
Disorder	Significance
Autosomal Dominant	
Achondroplasia	Short-limb dwarfism
Adult polycystic kidney disease	Kidney failure
Huntington's chorea	Neurodegenerative disorder
Familial hypercholesterolemia	Premature atherosclerosis
Marfan's syndrome	Connective tissue disorder with abnormalities in skeletal, ocular, cardiovascular systems
Neurofibromatosis (NF)	Neurogenic tumors: fibromatous skin tumors, pigmented skin lesions, and ocular nodules in NF-1; bilateral acoustic neuromas in NF-2
Osteogenesis imperfecta	Molecular defects of collagen
Spherocytosis	Disorder of red blood cells
von Willebrand's disease	Bleeding disorder
Autosomal Recessive	
Color blindness	Color blindness
Cystic fibrosis	Disorder of membrane transport of ions in exocrine glands causing lung and pancreatic disease
Glycogen storage diseases	Excess accumulation of glycogen in the liver and hypoglycemia (von Gierke's disease); glycogen accumulation in striated muscle in myopathic forms
Oculocutaneous albinism	Hypopigmentation of skin, hair, eyes as result of inability to synthesize melanin
Phenylketonuria (PKU)	Lack of phenylalanine hydroxylase with hyperphenylalaninemia and impaired brain development
Sickle cell disease	Red blood cell defect
Tay-Sachs disease	Deficiency of hexosaminidase A; severe mental and physical deterioration beginning in infancy
X-Linked Recessive	
Bruton-type hypogammaglobulinemia	Immunodeficiency
Hemophilia A	Bleeding disorder
Duchenne dystrophy	Muscular dystrophy
Fragile X syndrome	Mental retardation

Neurofibromatosis. Neurofibromatosis is a condition involving neurogenic tumors that arise from Schwann cells and other elements of the peripheral nervous system.[4,5] There are at least two genetically and clinically distinct forms of the disorder: type 1 NF (NF-1), also known as *von Recklinghausen's disease,* and type 2 bilateral acoustic NF (NF-2). Both of these disorders result from a genetic defect in a protein that regulates cell growth. The gene for NF-1 has been mapped to chromosome 17, and the gene for NF-2 has been mapped to chromosome 22.



■ **FIGURE 4-1** ■ Simple pedigree for inheritance of an autosomal dominant trait. The small, colored circle represents the mutant gene. An affected parent with an autosomal dominant trait has a 50% chance of passing the mutant gene on to each child regardless of sex.

NF-1 is a relatively common disorder with a frequency of 1 in 3000.[5] Approximately 50% of cases have a family history of autosomal dominant transmission, and the remaining 50% appear to represent a new mutation. In more than 90% of persons with NF-1, cutaneous and subcutaneous neurofibromas



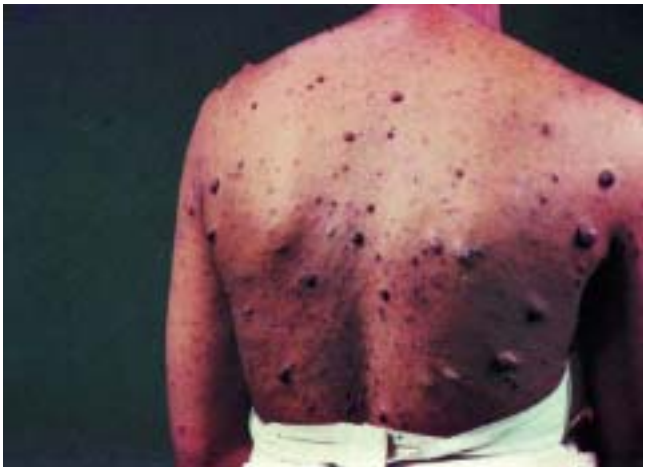
■ **FIGURE 4-2** ■ Long, slender fingers (arachnodactyly) in a patient with Marfan's syndrome. (Rubin E., Farber J.L. [1999]. *Pathology* [3rd ed., p. 242]. Philadelphia: Lippincott Williams & Wilkins)

develop in late childhood or adolescence. The cutaneous neurofibromas, which vary in number from a few to many hundreds, manifest as soft, pedunculated lesions that project from the skin. They are the most common type of lesion, often are not apparent until puberty, and are present in greatest density over the trunk (Fig. 4-3). The subcutaneous lesions grow just below the skin; they are firm and round, and may be painful. Plexiform neurofibromas involve the larger peripheral nerves. They tend to form large tumors that cause severe disfigurement of the face or an extremity. Pigmented nodules of the iris (Lisch nodules), which are specific for NF-1, usually are present after 6 years of age. They do not present any clinical problem but are useful in establishing a diagnosis.

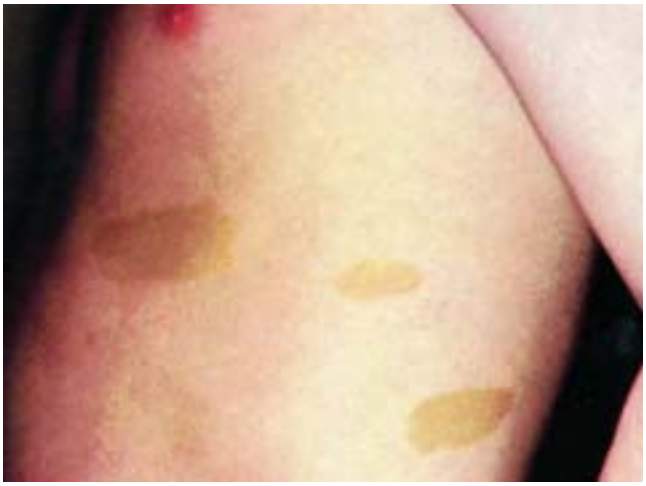
A second major component of NF-1 is the presence of large (usually ≥15 mm in diameter), flat cutaneous pigmentations, known as *café-au-lait spots*. They are usually a uniform light brown in whites and darker brown in African Americans and have sharply demarcated edges (Fig. 4-4). Although small single lesions may be found in normal children, larger lesions of six or more spots larger than 1.5 cm in diameter suggest NF-1. The skin pigmentations become more evident with age as the melanosomes in the epidermal cells accumulate melanin.

In addition to neurofibromatoses, persons with NF-1 have a variety of other associated lesions, the most common being skeletal lesions such as scoliosis and erosive bone defects. Persons with NF-1 also are at increased risk for development of other nervous system tumors such as meningiomas, optic gliomas, and pheochromocytomas.

NF-2 is characterized by tumors of the acoustic nerve. Most often, the disorder is asymptomatic through the first 15 years of life. The most frequently reported symptoms are headaches, hearing loss, and tinnitus (*i.e.*, ringing in the ears). There may be associated intracranial and spinal meningiomas. The condition is made worse by pregnancy, and oral contraceptives may increase the growth and symptoms of tumors. Persons with the disorder should be warned that severe disorientation may occur during diving or swimming underwater, and drowning may result. Surgery may be indicated for debulking or removal of the tumors.



■ **FIGURE 4-3** ■ Neurofibromatosis on the back. (Reed and Carnick Pharmaceuticals) (Sauer G.C., Hall J.C. [1996]. *Manual of skin diseases.* Philadelphia: Lippincott-Raven)

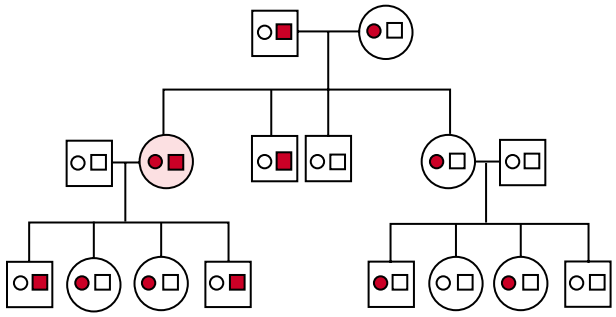


■ **FIGURE 4-4** ■ Neurofibromatosis with early café-au-lait spots in a 5-year-old child. (Owen Laboratories, Inc.) (Sauer G.C., Hall J.C. [1996]. *Manual of skin diseases.* Philadelphia: Lippincott-Raven)

Autosomal Recessive Disorders

Autosomal recessive disorders are manifested only when both members of the gene pair are affected. In this case, both parents may be unaffected but are carriers of the defective gene. Autosomal recessive disorders affect both sexes. The occurrence risk in each pregnancy is one in four for an affected child, two in four for a carrier child, and one in four for a normal (noncarrier, unaffected) homozygous child (Fig. 4-5).

With autosomal recessive disorders, the age of onset is frequently early in life; the symptomatology tends to be more uniform than with autosomal dominant disorders; and the disorders are characteristically caused by deficiencies in enzymes, rather than abnormalities in structural proteins. In the case of a heterozygous carrier, the presence of a mutant gene usually does not produce symptoms because equal amounts of normal and defective enzymes are synthesized. The "margin of safety" ensures that cells with half their usual amount of enzyme function normally. By contrast, the inactivation of both alleles in a



■ **FIGURE 4-5** ■ Simple pedigree for inheritance of an autosomal recessive trait. The small, colored circle and square represent a mutant gene. When both parents are carriers of a mutant gene, there is a 25% chance of having an affected child, a 50% chance of a carrier child, and a 25% chance of a nonaffected or noncarrier child, regardless of sex. All children (100%) of an affected parent are carriers.

homozygote results in complete loss of enzyme activity. Autosomal recessive disorders include almost all inborn errors of metabolism. Enzyme disorders that impair catabolic pathways result in an accumulation of dietary substances (*e.g.*, phenylketonuria [PKU]) or cellular constituents (*e.g.*, lysosomal storage diseases). Other disorders result from a defect in the enzyme-mediated synthesis of an essential protein (*e.g.*, the cystic fibrosis transmembrane conductance regulator in cystic fibrosis). Two examples of autosomal recessive disorders that are not covered elsewhere in this book are PKU and Tay-Sachs disease.

Phenylketonuria. Phenylketonuria is a genetically inherited enzyme defect. It is characterized by a deficiency of phenylalanine hydroxylase, the enzyme needed for conversion of phenylalanine to tyrosine. As a result of this deficiency, toxic levels of phenylalanine accumulate in the blood. Like other inborn errors of metabolism, PKU is inherited as a recessive trait and is manifested only in the homozygote. Untreated, PKU results in severe mental retardation.

PKU occurs once in approximately 10,000 births, and damage to the developing brain almost always results when high concentrations of phenylalanine and other metabolites persist in the blood.[4] Because the symptoms of untreated PKU develop gradually and would often go undetected until irreversible mental retardation had occurred, newborn infants are routinely screened for abnormal levels of serum phenylalanine. It is important that blood samples for PKU screening be obtained at least 12 hours after birth to ensure accuracy.[6] It also is possible to identify carriers of the trait by subjecting them to a phenylalanine test, in which a large dose of phenylalanine is administered orally and the rate at which it disappears from the bloodstream is measured.

Infants with the disorder are treated with a special diet that restricts phenylalanine intake. Dietary treatment must be started early in neonatal life to prevent brain damage. The results of dietary therapy of children with PKU have been impressive. The diet can prevent mental retardation as well as other neurodegenerative effects of untreated PKU.

Tay-Sachs Disease. Tay-Sachs disease is a variant of a class of lysosomal storage diseases, known as *gangliosidoses*, in which substances (gangliosides) found in membranes of nervous tissue are deposited in neurons of the central nervous system and retina because of a failure of lysosomal degradation.[4,5] The disease is particularly prevalent among eastern European (Ashkenazi) Jews. Infants with Tay-Sachs disease appear normal at birth but begin to manifest progressive weakness, muscle flaccidity, and decreased attentiveness at approximately 6 to 10 months of age. This is followed by rapid deterioration of motor and mental function, often with development of generalized seizures. Retinal involvement leads to visual impairment and eventual blindness. Death usually occurs before 4 years of age. Although there is no cure for the disease, analysis of the blood serum for a deficiency of the lysosomal enzyme, hexosaminidase A, which is deficient in Tay-Sachs disease, allows for accurate identification of the genetic carriers for the disease.

X-Linked Disorders

Sex-linked disorders are almost always associated with the X, or female, chromosome, and the inheritance pattern is predominantly recessive. Because of a normal paired gene, female heterozygotes rarely experience the effects of a defective gene. The common pattern of inheritance is one in which an unaffected mother carries one normal and one mutant allele on the X chromosome. This means that she has a 50% chance of transmitting the defective gene to her sons, and her daughters have a 50% chance of being carriers of the mutant gene. When the affected son procreates, he transmits the defective gene to all of his daughters, who become carriers of the mutant gene. Because the genes of the Y chromosome are unaffected, the affected male does not transmit the defect to any of his sons, and they will not be carriers or transmit the disorder to their children. X-linked recessive disorders include the fragile X syndrome, glucose-6-phosphate dehydrogenase deficiency (see Chapter 13), hemophilia A (see Chapter 12), and X-linked agammaglobulinemia (see Chapter 10).

Fragile X Syndrome. Fragile X syndrome is an X-linked disorder associated with a fragile site on the X chromosome where the chromatin fails to condense during mitosis. As with other X-linked disorders, fragile X syndrome affects males more often than females. The disorder, which affects approximately 1 in 1000 male infants, is the second most common cause of mental retardation, after Down syndrome.[7]

Affected males are mentally retarded and share a common physical phenotype that includes a long face with large mandible; large, everted ears; and large testicles (macroorchidism). Hyperextensible joints, a high-arched palate, and mitral valve prolapse, which is observed in some cases, mimic a connective tissue disorder. Some physical abnormalities may be subtle or absent. The most distinctive feature, which is present in 90% of prepubertal males, is macroorchidism.[5,8]

In 1991, the fragile X syndrome was mapped to a small area on the X chromosome (Xq27), now designated FMR-1 (fragile X, mental retardation 1) site.[7] The mechanism by which the normal FMR-1 gene is converted to an altered, or mutant, gene capable of producing disease symptoms involves an increase in the length of the gene. A small region of the gene that contains the CCG triplet code undergoes repeated duplication, resulting in a longer gene. The longer gene is susceptible to methylation, a chemical process that results in inactivation of the gene. When the number of repeats is small (<200), the person often has few or no manifestations of the disorder, compared with those evidenced in persons with a larger number of repeats.

In fragile X families, the probability of being affected with the disorder is related to the position in the pedigree. Later generations are more likely to be affected than earlier generations. For example, brothers of transmitting males are at a 9% risk of having mental retardation, whereas grandsons of transmitting males are at a 40% risk.[5] Approximately 20% of males who have been shown to carry the fragile X mutation are clinically and cytogenetically normal. Because male carriers transmit the trait through all their daughters (who are phenotypically normal) to affected grandchildren, they are called *transmitting males*. Approximately 50% of female carriers are affected (mentally retarded), a proportion that is higher than with other X-linked disorders.[5]

Multifactorial Inheritance Disorders

Multifactorial inheritance disorders are caused by multiple genes and, in many cases, environmental factors. The exact number of genes contributing to multifactorial traits is not

known, and these traits do not follow a clear-cut pattern of inheritance, as do single-gene disorders. Multifactorial inheritance has been described as a threshold phenomenon in which the factors contributing to the trait might be compared with water filling a glass.[9] Using this analogy, one might say that expression of the disorder occurs when the glass overflows. Disorders of multifactorial inheritance can be expressed during fetal life and be present at birth, or they may be expressed later in life. Congenital disorders that are thought to arise through multifactorial inheritance include cleft lip or palate, clubfoot, congenital dislocation of the hip, congenital heart disease, pyloric stenosis, and urinary tract malformation. Environmental factors are thought to play a significant role in disorders of multifactorial inheritance that develop in adult life, such as coronary artery disease, diabetes mellitus, hypertension, cancer, and common psychiatric disorders such as manic-depressive psychoses and schizophrenia.

Although multifactorial traits cannot be predicted with the same degree of accuracy as the mendelian single-gene mutations, characteristic patterns exist. First, multifactorial congenital malformations tend to involve a single organ or tissue derived from the same embryonic developmental field. Second, the risk of recurrence in future pregnancies is for the same or a similar defect. This means that parents of a child with a cleft palate defect have an increased risk of having another child with a cleft palate, but not with spina bifida. Third, the increased risk (compared with the general population) among first-degree relatives of the affected person is 2% to 7%, and among second-degree relatives, it is approximately one-half that amount.[5] The risk increases with increasing incidence of the defect among relatives. This means that the risk is greatly increased when a second child with the defect is born to a couple. The risk also increases with severity of the disorder and when the defect occurs in the sex not usually affected by the disorder.

Chromosomal Disorders

Chromosomal disorders form a major category of genetic disease, accounting for a large proportion of reproductive wastage (early gestational abortions), congenital malformations, and mental retardation. Specific chromosomal abnormalities can be linked to more than 60 identifiable syndromes that are present in 0.7% of all live births, 2% of all pregnancies in women older than 35 years of age, and 50% of all first-term abortions.[3]

During cell division (*i.e.*, mitosis) in nongerm cells, the chromosomes replicate so that each cell receives a full diploid number. In germ cells, a different form of division (*i.e.*, meiosis) takes place. During meiosis, the double sets of 22 autosomes and the 2 sex chromosomes (normal diploid number) are reduced to single sets (haploid number) in each gamete. At the time of conception, the haploid number in the ovum and that in the sperm join and restore the diploid number of chromosomes. Chromosomal defects usually develop because of defective movement during meiosis or because of breakage of a chromosome with loss or translocation of genetic material.

Chromosome abnormalities are commonly described according to the shorthand description of the karyotype. In this system, the total number of chromosomes is given first, followed by the sex chromosome complement, and then the description of any abnormality. For example, a male with trisomy 21 is designated 47,XY,+21.

Alterations in Chromosome Duplication

Mosaicism is the presence in one individual of two or more cell lines characterized by distinctive karyotypes. This defect results from an accident during chromosomal duplication. Sometimes, mosaicism consists of an abnormal karyotype and a normal one, in which case the physical deformities caused by the abnormal cell line usually are less severe.

Alterations in Chromosome Number

A change in chromosome number is called *aneuploidy*. Among the causes of aneuploidy is failure of the chromosomes to separate during oogenesis or spermatogenesis. This can occur in the autosomes or the sex chromosomes and is called *nondisjunction*. Nondisjunction gives rise to germ cells that have an even number of chromosomes (22 or 24). The products of conception formed from this even number of chromosomes have an uneven number of chromosomes, 45 or 47. *Monosomy* refers to the presence of only one member of a chromosome pair. The defects associated with monosomy of the autosomes are severe and usually cause abortion. Monosomy of the X chromosome (45,X/O), or Turner's syndrome, causes less severe defects. *Polysomy*, or the presence of more than two chromosomes to a set, occurs when a germ cell containing more than 23 chromosomes is involved in conception. This defect has been described for the autosomes and the sex chromosomes. Trisomies of chromosomes 8, 13, 18, and 21 are the more common forms of polysomy of the autosomes. There are several forms of polysomy of the sex chromosomes in which extra X or Y chromosomes are present.

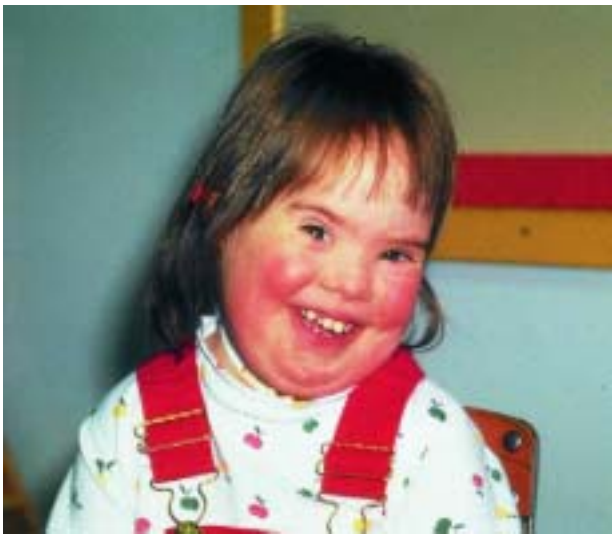
Trisomy 21. First described in 1866 by John Langon Down, trisomy 21, or Down syndrome, causes a combination of birth defects, including characteristic facial features, some degree of mental retardation, and other health problems. According to the National Down Syndrome Association, it is the most common chromosomal disorder, occurring approximately once in every 800 to 1000 births. Currently, there are approximately 350,000 people in the United States with Down syndrome.[10]

Approximately 95% of cases of Down syndrome are caused by nondisjunction or an error in cell division during meiosis, resulting in a trisomy of chromosome 21. Most of the remaining cases are due to a translocation in which part of chromosome 21 breaks off and attaches to another chromosome (usually chromosome 14). Although there still are only 46 chromosomes in the cell, the presence of the extra part of chromosome 21 causes the features of Down syndrome.

The risk of having a child with Down syndrome increases with maternal age: it is 1/1300 at 25 years of age, 1/365 at 35 years, and 1/30 at 45 years of age.[11] The reason for the correlation between maternal age and nondisjunction is unknown, but is thought to reflect some aspect of aging of the oocyte. Although males continue to produce sperm throughout their reproductive life, females are born with all the oocytes they ever will have. These oocytes may change as a result of the aging process. With increasing age, there is a greater chance of a woman having been exposed to damaging environmental agents such as drugs, chemicals, and radiation.

The physical features of a child with Down syndrome are distinctive, and therefore the condition usually is apparent at birth. These features include a small and rather square head. There is upward slanting of the eyes; small, low-set, and malformed ears; a fat pad at the back of the neck; an open mouth; and a large, protruding tongue (Fig. 4-6). The child's hands usually are short and stubby, with fingers that curl inward, and there usually is only a single palmar (*i.e.*, simian) crease. Hypotonia and joint laxity also are present in infants and young children. There often are accompanying congenital heart defects and an increased risk of gastrointestinal malformations. Approximately 1% of persons with trisomy 21 Down syndrome have mosaicism (*i.e.*, cell populations with the normal chromosome number and trisomy 21); these persons may be less severely affected. Of particular concern is the much greater risk of development of acute leukemia among children with Down syndrome—10 to 20 times greater than that of other children.[5] With increased life expectancy due to improved health care, it has been found that there is an increased risk of Alzheimer's disease among older persons with Down syndrome.

There are several prenatal screening tests that can be done to determine the risk of having a child with Down syndrome. The most commonly used test is the triple screen—α-fetoprotein (AFP), human chorionic gonadotropin (HCG), and unconjugated estriol. The results of these tests, which usually are done between 15 and 20 weeks of gestation, together with the woman's age often are used to determine the probability of a pregnant woman having a child with Down syndrome. These tests are able to accurately detect only approximately 60% of fetuses with Down syndrome. Some women are given false-positive readings, and some are given false-negative readings. In 1992, fetal nuchal (back of neck) translucency, as measured by ultrasonography in the first trimester, was proposed as another screening measure; the nucha was found to be thicker in fetuses with Down syndrome.[12] This test, which must be done by a highly trained professional, continues to be investigated as a screening method. The only way to accurately determine the presence of Down syndrome in the fetus is through chromosome analysis using chorionic villus sampling, amniocentesis, or percutaneous umbilical blood sampling.



■ **FIGURE 4-6** ■ A child with Down syndrome. (Courtesy of March of Dimes Birth Defects Foundation, White Plains, NY)

Monosomy X. Monosomy X, or Turner's syndrome, describes a monosomy of the X chromosome (45,X/0) with gonadal agenesis, or absence of the ovaries. This disorder affects approximately 1 of every 2500 live births, and it has been estimated that more than 99% of fetuses with the 45,X/0 karyotype are spontaneously aborted during the first trimester.[13] There are variations in the syndrome, with abnormalities ranging from essentially none to webbing of the neck with redundant skin folds, nonpitting lymphedema of the hands and feet, and congenital heart defects, particularly coarctation of the aorta. There also may be abnormalities in kidney development (*i.e.*, abnormal location, abnormal vascular supply, or double collecting system). There may be other abnormalities, such as changes in nail growth, high-arched palate, short fourth metacarpal, and strabismus.

Characteristically, the female with Turner's syndrome is short in stature, but her body proportions are normal. She does not menstruate and shows no signs of secondary sex characteristics. When a mosaic cell line (*i.e.*, 45,X/0 and 46,X/X or 45,X/0 and 46,X/Y) is present, the manifestations associated with the chromosomal defect tend to be less severe.

Administration of female sex hormones (*i.e.*, estrogens) is used to promote development of secondary sexual characteristics and produce additional skeletal growth in women with Turner's syndrome. Growth hormone also may be used to increase skeletal growth.[14]

The diagnosis of Turner's syndrome often is delayed until late childhood or early adolescence in girls who do not present with the classic features of the syndrome.[15] Early diagnosis is an important aspect of treatment for Turner's syndrome. It allows for counseling about the phenotypic characteristics of the disorder; screening for cardiac, renal, thyroid, and other abnormalities; provision of emotional support for the girl and her family; and planning for growth hormone therapy, if appropriate.[13] Because of the potential for delay in diagnosis, it has been recommended that girls with unexplained short stature (height below the fifth percentile), webbed neck, peripheral lymphedema, coarctation of the aorta, or delayed puberty have chromosome studies done. In addition, chromosome analysis should be considered for girls who remain above the fifth percentile but have two or more features of Turner's syndrome, including high palate, nail deformities, short fourth metacarpal, and strabismus.[15]

Polysomy X. Polysomy X, or Klinefelter's syndrome, is a condition of testicular dysgenesis accompanied by the presence of one or more extra X chromosomes in excess of the normal male XY complement. Most males with Klinefelter's syndrome have one extra X chromosome (XXY). In rare cases, there may be more than one extra X chromosome (XXXY). The syndrome is characterized by enlarged breasts, sparse facial and body hair, small testes, and the inability to produce sperm.[15] Regardless of the number of X chromosomes present, the male phenotype is retained. Based on studies conducted in the 1970s, including one sponsored by the National Institutes of Health and Human Development that checked the chromosomes of more than 40,000 infants, it has been estimated that

the XXY syndrome is one of the most common genetic abnormalities known, occurring as frequently as 1 in 500 to 1 in 1000 male births.[16] Although the presence of the extra chromosome is fairly common, the syndrome with its accompanying signs and symptoms that may result from the extra chromosome is uncommon. Many men live their lives without being aware that they have an additional chromosome. For this reason, it has been suggested that the term *Klinefelter's syndrome* be replaced with XXY male.

The condition often goes undetected at birth. The infant usually has normal male genitalia, with a small penis and small, firm testicles. At puberty, the intrinsically abnormal testes do not respond to stimulation from the gonadotropins and undergo degeneration. This leads to a tall stature with abnormal body proportions in which the lower part of the body is longer than the upper part. Later in life, the body build may become heavy, with a female distribution of subcutaneous fat and variable degrees of breast enlargement. There may be deficient secondary male sex characteristics, such as a voice that remains feminine in pitch and sparse beard and pubic hair. There may be sexual dysfunction along with the complete infertility that occurs owing to the inability to produce sperm. Regular administration of testosterone, beginning at puberty, can promote more normal growth and development of secondary sexual characteristics. Although the intellect usually is normal, most XXY males have some degree of language impairment. They often learn to talk later than do other children and often have trouble with learning to read and write.

The presence of the extra X chromosome in the XXY male results from nondisjunction during meiotic division in one of the parents. The additional X chromosome (or chromosomes) is of maternal origin in approximately two thirds of cases and of paternal origin in the remaining one third.[4] The cause of the nondisjunction is unknown. Advanced maternal age increases the risk, but only slightly.

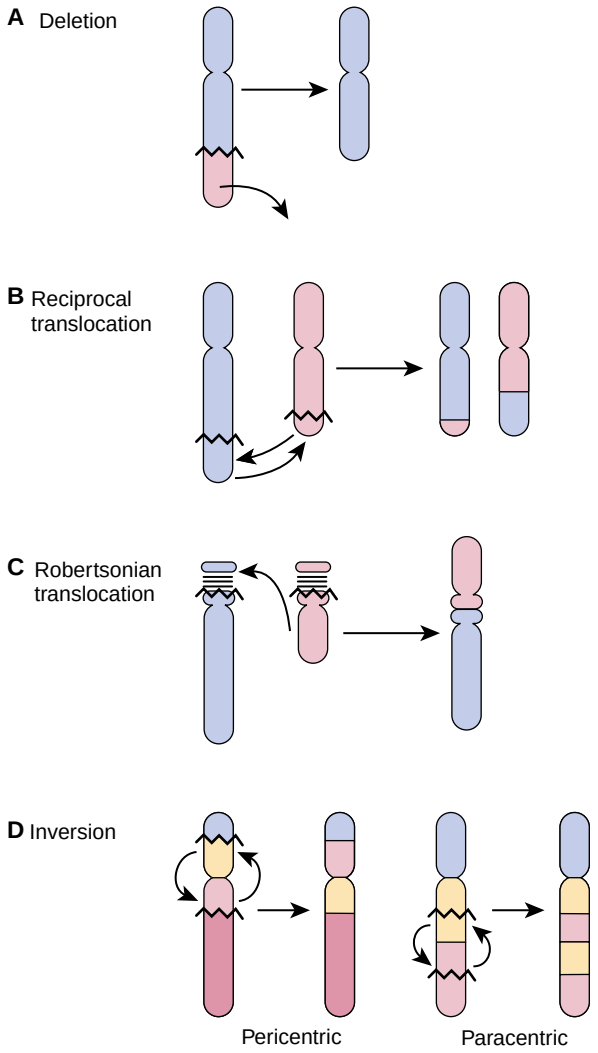
Alterations in Chromosome Structure

Aberrations in chromosome structure occur when there is a break in one or more of the chromosomes followed by rearrangement or deletion of the chromosome parts. Among the factors believed to cause chromosome breakage are exposure to radiation sources, such as x-rays; influence of certain chemicals; extreme changes in the cellular environment; and viral infections.

Several patterns of chromosome breakage and rearrangement can occur (Fig. 4-7). There can be a *deletion* of the broken portion of the chromosome. When one chromosome is involved, the broken parts may be *inverted*. *Isochromosome formation* occurs when the centromere, or central portion, of the chromosome separates horizontally instead of vertically. *Ring formation* results when deletion is followed by uniting of the chromatids to form a ring. *Translocation* occurs when there are simultaneous breaks in two chromosomes from different pairs, with exchange of chromosome parts. With a balanced reciprocal translocation, no genetic information is lost; therefore, persons with translocations usually are normal. However, these persons are translocation carriers and may have normal and abnormal children.

A special form of translocation called a *centric fusion* or *Robertsonian translocation* involves two acrocentric chromosomes in which the centromere is near the end. Typically, the break occurs near the centromere affecting the short arm in one chromosome and the long arm in the other. Transfer of the chromosome fragments leads to one long and one extremely short chromosome. The short fragments commonly are lost. In this case, the person has only 45 chromosomes, but the amount of genetic material that is lost is so small that it often goes unnoticed. However, difficulty arises during meiosis; the result is gametes with an unbalanced number of chromosomes.

A rare form of Down syndrome can occur in the offspring of persons in whom there has been a translocation involving the



■ **FIGURE 4-7** ■ Examples of structural abnormalities of human chromosomes: (**A**) deletion of part of a chromosome leads to loss of genetic material and shortening of the chromosome; (**B**) a reciprocal translocation involves breaks in two nonhomologous chromosomes, with exchange of the acentric segment; (**C**) robertsonian translocation in which two nonhomologous chromosomes break near their centromeres, after which the long arms fuse to form one large metacentric chromosome; (**D**) inversion, which requires two breaks in a single chromosome with inversion to the opposite side of the centromere (pericentric), or paracentric if the breaks are on the same arm. (Adapted from Rubin E., Farber J.L. [1999]. *Pathology* [3rd ed., p. 225]. Philadelphia: Lippincott Williams & Wilkins)

long arm of chromosome 21q and the long arm of one of the acrocentric chromosomes (most often 14 or 22). The translocation adds to the normal long arm of chromosome 21; therefore, the person with this type of Down syndrome has 46 chromosomes, but essentially a trisomy of 21q.[3]

The manifestations of aberrations in chromosome structure depend to a great extent on the amount of genetic material that is lost. Many cells sustaining unrestored breaks are eliminated within the next few mitoses because of deficiencies that may in themselves be fatal. This is beneficial because it prevents the damaged cells from becoming a permanent part of the organism or, if it occurs in the gametes, from giving rise to grossly defective zygotes. Some altered chromosomes, such as those that occur with translocations, are passed on to the next generation.

In summary, genetic disorders can affect a single gene (mendelian inheritance) or several genes (polygenic inheritance). Single-gene disorders may be present on an autosome or on the X chromosome and they may be expressed as a dominant or recessive trait. In autosomal dominant disorders, a single mutant allele from an affected parent is transmitted to an offspring regardless of sex. The affected parent has a 50% chance of transmitting the disorder to each offspring. Autosomal recessive disorders are manifested only when both members of the gene pair are affected. Usually, both parents are unaffected but are carriers of the defective gene. Their chances of having an affected child are one in four; of having a carrier child, two in four; and of having a noncarrier unaffected child, one in four. Sex-linked disorders, which are associated with the X chromosome, are those in which an unaffected mother carries one normal and one mutant allele on the X chromosome. She has a 50% chance of transmitting the defective gene to her sons, and her daughters have a 50% chance of being carriers of the mutant gene. Because of a normal paired gene, female heterozygotes rarely experience the effects of a defective gene. Multifactorial inheritance disorders are caused by multiple genes and, in many cases, environmental factors.

Chromosomal disorders result from a change in chromosome number or structure. A change in chromosome number is called *aneuploidy. Monosomy* involves the presence of only one member of a chromosome pair; it is seen in Turner's syndrome, in which there is monosomy of the X chromosome. *Polysomy* refers to the presence of more than two chromosomes in a set. Klinefelter's syndrome involves polysomy of the X chromosome. Trisomy 21 (*i.e.,* Down syndrome) is the most common form of chromosome disorder. Alterations in chromosome structure involve deletion or addition of genetic material, which may involve a translocation of genetic material from one chromosome pair to another.

DISORDERS DUE TO ENVIRONMENTAL INFLUENCES

The developing embryo is subject to many nongenetic influences. After conception, development is influenced by the environmental factors that the embryo shares with the mother. The physiologic status of the mother—her hormone balance, her general state of health, her nutritional status, and the drugs she takes—undoubtedly influences the development of the unborn child. For example, diabetes mellitus is associated with increased risk of congenital anomalies. Smoking is associated with lower than normal neonatal weight. Alcohol, in the context of chronic alcoholism, is known to cause fetal abnormalities. Some agents cause early abortion. Measles and other infectious agents cause congenital malformations. Other agents, such as radiation, can cause chromosomal and genetic defects and produce developmental disorders.

Period of Vulnerability

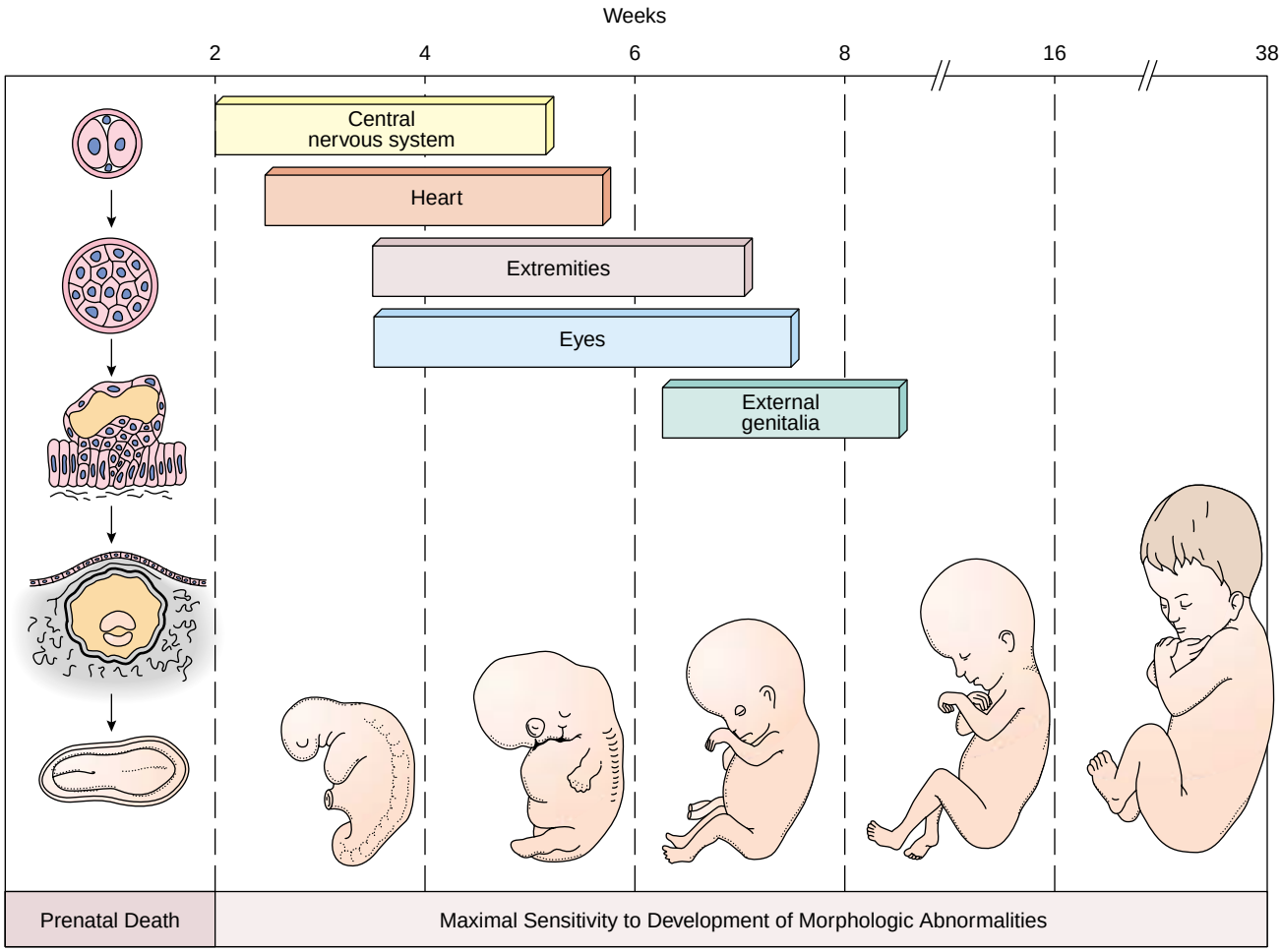
The embryo's development is most easily disturbed during the period when differentiation and development of the organs are taking place. This time interval, which is often referred to as the period of *organogenesis,* extends from day 15 to day 60 after conception. Environmental influences during the first 2 weeks after fertilization may interfere with implantation and result in abortion or early resorption of the products of conception. Each organ has a critical period during which it is highly susceptible to environmental derangements (Fig. 4-8). Often, the effect is expressed at the biochemical level just before the organ begins to develop. The same agent may affect different organ systems that are developing at the same time.

Teratogenic Agents

A teratogenic agent is an environmental agent that produces abnormalities during embryonic or fetal development. It is important to remember that, in this case, the environment is that of the embryo and fetus. Maternal disease or altered metabolic state also can affect the environment of the embryo or fetus. For discussion purposes, teratogenic agents have been divided into three groups: radiation, drugs and chemical substances, and infectious agents. Chart 4-1 lists commonly identified agents in each of these groups. Theoretically, environmental agents can cause birth defects in three ways: by direct exposure of the pregnant woman and the embryo or fetus to the agent; through exposure of the soon-to-be-pregnant woman with an agent that has a slow clearance rate such that a teratogenic dose is retained during early pregnancy; or as a result of mutagenic effects of an environmental agent that occur before pregnancy, causing permanent damage to a woman's (or a man's) reproductive cells.

Radiation

Heavy doses of ionizing radiation have been shown to cause microcephaly, skeletal malformations, and mental retardation. There is no evidence that diagnostic levels of radiation cause congenital abnormalities. However, because the question of safety remains many agencies require that the day of a woman's last menstrual period be noted on all radiologic requisitions. Other institutions may require a pregnancy test before any extensive diagnostic x-ray studies are performed. Radiation is teratogenic and mutagenic, and there is the possibility of effecting inheritable changes in genetic materials. Administration of therapeutic doses of radioactive iodine (^{131}I) during the 13th week of gestation, the time when the fetal thyroid is beginning to concentrate iodine, has been shown to interfere with thyroid development.



■ **FIGURE 4-8** ■ Sensitivity of specific organs to teratogenic agents at critical periods in embryogenesis. Exposure of adverse influences in the preimplantation and early postimplantation stages of development (*far left*) leads to prenatal death. Periods of maximal sensitivity to teratogens (*horizontal bars*) vary for different organ systems but overall are limited to the first 8 weeks of pregnancy. (Rubin E., Farber J.L. [1999]. *Pathology* [3rd ed., p. 216]. Philadelphia: Lippincott Williams & Wilkins)

Chemicals and Drugs

Environmental chemicals and drugs can cross the placenta and cause damage to the developing embryo and fetus. It has been estimated that only 2% to 3% of developmental defects have a known drug or environmental origin. Some of the best-documented environmental teratogens are the organic mercurials, which cause neurologic deficits and blindness. Sources of exposure to mercury include contaminated food (fish) and water.[17] The precise mechanism by which chemicals and drugs exert their teratogenic effects is largely unknown. They may produce cytotoxic (cell-killing), antimetabolic, or growth-inhibiting properties. Often their effects depend on the time of exposure (in terms of embryonic and fetal development) and extent of exposure (dosage).

Drugs top the list of chemical teratogens, probably because they are regularly used at elevated doses. Most drugs can cross the placenta and expose the fetus to both the pharmacologic and teratogenic effects. Factors that affect placental drug transfer and drug effects on the fetus include the rate at which the drug crosses the placenta, the duration of exposure, and the stage of placental and fetal development at the time of exposure.[18] Lipid-soluble drugs tend to cross the placenta more readily and enter the fetal circulation. The molecular weight of a drug also influences the rate of transfer and the amount of drug transferred across the placenta. Drugs with a molecular weight less than 500 can cross the placenta easily, depending on lipid solubility and degree of ionization; those with a

KEY CONCEPTS

TERATOGENIC AGENTS

- Teratogenic agents such as radiation, chemicals and drugs, and infectious organisms are agents that produce abnormalities in the developing embryo.
- The stage of development of the embryo determines the susceptibility to teratogens. The period during which the embryo is most susceptible to teratogenic agents is the time during which rapid differentiation and development of body organs and tissues are taking place, usually from days 15 to 60 postconception.

CHART 4-1 Teratogenic Agents*

Radiation

Drugs and Chemical Substances

Alcohol
Anticoagulants
  Warfarin
Anticonvulsants
Cancer drugs
  Aminopterin
  Methotrexate
  6-Mercaptopurine
Isotretinoin (Accutane)
Propylthiouracil
Tetracycline
Thalidomide

Infectious Agents

Viruses
  Cytomegalovirus
  Herpes simplex virus
  Measles (rubella)
  Mumps
  Varicella-zoster virus (chickenpox)
Nonviral factors
  Syphilis
  Toxoplasmosis

*Not inclusive.

molecular weight of 500 to 1000 cross the placenta with more difficulty; and those with molecular weights greater than 1000 cross very poorly.[18]

A number of drugs are suspected of being teratogens, but only a few have been identified with certainty.[19] Perhaps the best known of these drugs is thalidomide, which has been shown to give rise to a full range of malformations, including phocomelia (*i.e.*, short, flipper-like appendages) of all four extremities. Other drugs known to cause fetal abnormalities are the antimetabolites that are used in the treatment of cancer, the anticoagulant drug warfarin, several of the anticonvulsant drugs, ethyl alcohol, and cocaine. Some drugs affect a single developing structure; for example, propylthiouracil can impair thyroid development and tetracycline can interfere with the mineralization phase of tooth development. More recently, vitamin A and its derivatives (the retinoids) have been targeted for concern because of their teratogenic potential. Concern over the teratogenic effects of vitamin A derivatives became evident with the introduction of the acne drug isotretinoin (Accutane). Fetal abnormalities such as cleft palate, heart defects, retinal and optic nerve abnormalities, and central nervous system malformations were observed in women ingesting therapeutic doses of the drug during the first trimester of pregnancy.[20] There also is concern about the teratogenic effects when a woman consumes high doses of vitamin A, such as those contained in some dietary supplements or vitamin pills. It is currently recommended that doses greater than 10,000 IU should be avoided.[21]

In 1983, the U.S. Food and Drug Administration established a system for classifying drugs according to probable risks to the fetus. According to this system, drugs are put into five categories: A, B, C, D, and X. Drugs in category A are the least dangerous, and categories B, C, and D are increasingly more dangerous. Those in category X are contraindicated during pregnancy because of proven teratogenicity.[22] The law does not require classification of drugs that were in use before 1983.

Because many drugs are suspected of causing fetal abnormalities, and even those that were once thought to be safe are now being viewed critically, it is recommended that women in their childbearing years avoid unnecessary use of drugs. This pertains to nonpregnant women as well as pregnant women because many developmental defects occur early in pregnancy. As happened with thalidomide, the damage to the embryo may occur before pregnancy is suspected or confirmed. Two drugs of particular importance are alcohol and cocaine.

Fetal Alcohol Syndrome. The term *fetal alcohol syndrome* (FAS) refers to a constellation of physical, behavioral, and cognitive abnormalities resulting from maternal alcohol consumption. It has been reported that 1 in 1000 infants born in the United States manifests some characteristics of the syndrome.[23] Alcohol, which is lipid soluble and has a molecular weight between 600 and 1000, passes freely across the placental barrier; concentrations of alcohol in the fetus are at least as high as in the mother. Unlike other teratogens, the harmful effects of alcohol are not restricted to the sensitive period of early gestation but extend throughout pregnancy.

Alcohol has widely variable effects on fetal development, ranging from minor abnormalities to FAS. Criteria for defining FAS were standardized by the Fetal Alcohol Study Group of the Research Society on Alcoholism in 1980,[24] and modifications were proposed in 1989 by Sokol and Clarren.[25] The proposed criteria are prenatal or postnatal growth retardation (*i.e.*, weight or length below the 10th percentile); central nervous system involvement, including neurologic abnormalities, developmental delays, behavioral dysfunction, intellectual impairment, and skull and brain malformation; and a characteristic face with short palpebral fissures (*i.e.*, eye openings), a thin upper lip, and an elongated, flattened midface and philtrum (*i.e.*, the groove in the middle of the upper lip). The facial features of FAS may not be as apparent in the newborn but become more prominent as the infant develops. As the children grow into adulthood, the facial features become more subtle, making diagnosis of FAS in older individuals more difficult.[26] Each of these defects can vary in severity, probably reflecting the timing of alcohol consumption in terms of the period of fetal development, amount of alcohol consumed, and hereditary and environmental influences. Because of problems with terminology and the diagnostic criteria, the Institute of Medicine in 1996 proposed the terms *alcohol-related neurodevelopmental disorder* (ARND) and *alcohol-related birth defects* (ARBD) to describe conditions in which there is a history of maternal alcohol consumption.[27] This new terminology uses pathophysiologic diagnostic categories to describe the conditions resulting from confirmed alcohol exposure. For example, facial abnormalities, growth retardation, and central nervous system abnormalities would be classified as FAS; central nervous system and cognitive abnor-

malities would be classified as ARND; and birth defects as ARBD.[28]

The mechanisms whereby alcohol exerts its teratogenic effects are unclear. Evidence suggests that the effects of alcohol observed in children with FAS are related to the timing of alcohol consumption and peak alcohol dose.

The amount of alcohol that can be safely consumed during pregnancy also is unknown. Animal studies suggest that the fetotoxic effects of alcohol are dose dependent, rather than threshold dependent. Studies suggest that even three drinks per day may be associated with a lower IQ at 4 years of age.[29] However, it may be that the time during which alcohol is consumed is equally important. Even small amounts of alcohol consumed during critical periods of fetal development may be teratogenic. For example, if alcohol is consumed during the period of organogenesis, a variety of skeletal and organ defects may result. When alcohol is consumed later in gestation, when the brain is undergoing rapid development, there may be behavioral and cognitive disorders in the absence of physical abnormalities. Chronic alcohol consumption throughout pregnancy may result in a variety of effects, ranging from physical abnormalities to growth retardation and compromised central nervous system functioning. Evidence suggests that short-lived high concentrations of alcohol such as those that occur with binge drinking may be particularly significant, with abnormalities being unique to the period of exposure. The recommendation of the U.S. Surgeon General is that women abstain from alcohol during pregnancy.[30]

Cocaine Babies. Of concern is the increasing use of cocaine by pregnant women. In 1992, approximately 45,000 women in this country used cocaine during their pregnancy.[31] Determining exposure of infants to maternal cocaine use often is difficult. In utero exposure often is ascertained by testing maternal urine for cocaine and its metabolites and by interviewing the mother. Urine testing provides evidence only of recent cocaine use, and information from an interview may be inaccurate. Urine testing of infants provides evidence only of recent exposure to cocaine.

Among the effects of cocaine use during pregnancy is a decrease in uteroplacental blood flow, maternal hypertension, stimulation of uterine contractions, and fetal vasoconstriction. The decrease in uteroplacental blood flow is associated with an increase in preterm births, intrauterine growth retardation, microcephaly, and neurologic abnormalities.[32,33] Furthermore, there appears to be a dose-related relationship between increasing levels of chronic cocaine abuse and impaired fetal growth and neurologic function.[33] Maternal hypertension may increase the risk of abruptio placentae, particularly if it is accompanied by a decrease in uteroplacental blood flow.[31] Fetal vasoconstriction has been suggested as the cause of fetal anomalies, particularly limb reduction defects and urogenital tract defects such as hydronephrosis, hypospadias, and undescended testicles, as well as ambiguous genitalia.[34,35] Exposure of the fetus to cocaine also may lead to destructive lesions of the brain, including cerebral infarction and intracranial hemorrhage. Sudden infant death syndrome (SIDS) also has been more common in infants of mothers who have used cocaine during their pregnancy.[36]

Although the immediate effects of maternal cocaine use on infant behavior are being reported, the long-term effects are largely unknown. Unfortunately, cocaine addiction often affects the behavior of the pregnant woman to the extent that the need to procure larger amounts of the drug overwhelms all other considerations of maternal and fetal well-being; other factors such as malnutrition, use of other drugs and teratogens, and lack of prenatal care also may contribute to fetal disorders.

Folic Acid Deficiency. Although most birth defects are related to exposure to a teratogenic agent, deficiencies of nutrients and vitamins also may be a factor. Folic acid deficiency has been implicated in the development of neural tube defects (*e.g.*, anencephaly, spina bifida, encephalocele). Studies have shown a reduction in neural tube defects when folic acid was taken before conception and continued during the first trimester of pregnancy.[37,38] The Public Health Service recommends that all women of childbearing age should take 400 micrograms (µg) of folic acid daily. It has been suggested that this recommendation may help to prevent as many as 50% of neural tube defects.[39] The Institute of Medicine Panel for Folate and Other B Vitamins and Choline has recently revised the Recommended Dietary Allowance for pregnant women to 600 µg.[40] These recommendations are particularly important for women who have previously had an affected pregnancy, for couples with a close relative with the disorder, and for women with diabetes mellitus and those taking anticonvulsant drugs who are at increased risk for having infants with birth defects.

Since 1998, all enriched cereal grain products in the United States have been fortified with folic acid. To achieve an adequate intake of folic acid, pregnant women should couple a diet that contains folate-rich foods (*e.g.*, orange juice, dark, leafy green vegetables, and legumes) with sources of synthetic folic acid, such as fortified food products.[40]

Infectious Agents

Many microorganisms cross the placenta and enter the fetal circulation, often producing multiple malformations. The acronym TORCH stands for *t*oxoplasmosis, *o*ther, *r*ubella (*i.e.*, German measles), *c*ytomegalovirus, and *h*erpes, which are the agents most frequently implicated in fetal anomalies.[3] Other infections include varicella-zoster virus infection, listeriosis, leptospirosis, Epstein-Barr virus infection, tuberculosis, and syphilis. The TORCH screening test examines the infant's serum for the presence of antibodies to these agents. These infections tend to cause similar clinical manifestations, including microcephaly, hydrocephalus, defects of the eye, and hearing problems.

Toxoplasmosis is a protozoal infection that can be contracted by eating raw or poorly cooked meat. The domestic cat also seems to carry the organism, excreting the protozoa in its stools. It has been suggested that pregnant women should avoid contact with excrement from the family cat. The introduction of the rubella vaccine in the United States has virtually eliminated congenital rubella. The epidemiology of cytomegalovirus infection is largely unknown. Some infants are severely affected at birth, and others, although having evidence of the infection, have no symptoms. In some symptom-free infants, brain damage becomes evident over a span of several years. There also is evidence that some infants contract the infection during the first year of life, and in some of them the

infection leads to retardation a year or two later. Herpes simplex type 2 infection is considered to be a genital infection and usually is transmitted through sexual contact. The infant acquires this infection in utero or in passage through the birth canal.

In summary, a teratogenic agent is one that produces abnormalities during embryonic or fetal life. It is during the early part of pregnancy (15 to 60 days after conception) that environmental agents are most apt to produce their deleterious effects on the developing embryo. A number of environmental agents can be damaging to the unborn child, including radiation, drugs and chemicals, and infectious agents. FAS is a risk for infants of women who regularly consume alcohol during pregnancy. Of recent concern is the use of cocaine by pregnant women. Because many drugs have the potential for causing fetal abnormalities, often at an early stage of pregnancy, it is recommended that women of childbearing age avoid unnecessary use of drugs. It also has been shown that folic acid deficiency can contribute to neural tube defects. The acronym TORCH stands for *t*oxoplasmosis, *o*ther, *r*ubella, *c*ytomegalovirus, and *h*erpes, which are the infectious agents most frequently implicated in fetal anomalies.

REVIEW QUESTIONS

- Explain the difference between a hereditary and congenital defect.
- Contrast disorders attributable to multifactorial inheritance with those caused by single-gene inheritance.
- Describe two chromosomal abnormalities that demonstrate aneuploidy.
- Relate maternal age and the occurrence of Down syndrome.
- Cite the most susceptible period of intrauterine life for development of defects caused by environmental agents.
- State the cautions that should be observed when considering the use of drugs during pregnancy.
- Describe the effects of alcohol and cocaine abuse on fetal development and birth outcomes.
- List four infectious agents that cause congenital defects.

connection

Visit the Connection site at connection.lww.com/go/porth for links to chapter-related resources on the Internet.

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