6
Developmental and Genetic Diseases

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Glossary

The following terms are used in the text or figures of this chapter:

Allele–An alternative form of a gene.
Alternative splicing–A regulatory mechanism by which variations in the incorporation of a gene’s exons, or coding regions, into messenger RNA (mRNA) lead to the production of more than one related protein, or isoform.
Autosomes–All of the nuclear chromosomes except for the sex chromosomes.
Centromere–The constricted region near the center of a chromosome, which has a critical role in cell division.
Codon–A three-base sequence of DNA or RNA that specifies a single amino acid.
Conservative mutation–A change in a DNA or RNA sequence that leads to the replacement of one amino acid with a biochemically similar one.
Epigenetic–A term describing nonmutational phenomena, such as methylation and histone modification, that alter the expression of a gene.
Exon–A region of a gene that codes for a protein.
Frame-shift mutation–The addition or deletion of a number of DNA bases that is not a multiple of three, thus causing a shift in the reading frame of the gene. This shift leads to a change in the reading frame of all parts of the gene that are downstream from the mutation, often creating a premature stop codon and ultimately, a truncated protein.
Gain-of-function mutation–A mutation that produces a protein that takes on a new or enhanced function.
Genomics–The study of the functions and interactions of all the genes in the genome, including their interactions with environmental factors.
Genotype–A person’s genetic makeup, as reflected by his or her DNA sequence.
Haplotyp–A group of nearby alleles that are inherited together.
Hemizygous–Having a gene on one chromosome for which there is no counterpart on the opposite chromosome.
Heterozygous–Having two different alleles at a specific autosomal (or X chromosomal in a female) gene locus.
Homozygous–Having two identical alleles at a specific autosomal (or X chromosomal in a female) gene locus.
The fetus may also be injured by adverse transplacental influences or deformities and injuries caused by intrauterine trauma or during parturition. After birth, acquired diseases of infancy and childhood are also important causes of morbidity and mortality.

Magnitude of the Problem

Each year, about one quarter of a million babies in the United States are born with a birth defect. Worldwide, at least 1 in 50 newborns has a major congenital anomaly, 1 in 100 has a single-gene abnormality, and 1 in 200 has a major chromosomal abnormality.

In more than two thirds of all birth defects, the cause is not apparent (Fig. 6-1). No more than 6% of total birth defects can be attributed to uterine factors; maternal disorders such as metabolic imbalances or infections during pregnancy; and other environmental hazards, including exposure to drugs, chemicals, and radiation. Most of the remainder are accounted for by genomic defects, either hereditary traits or spontaneous mutations, and a smaller number by chromosomal abnormalities.

Although chromosomal abnormalities account for only a small fraction of birth defects in newborns, cytogenetic analyses of fetuses spontaneously aborted early in pregnancy show that up to 50% have chromosomal abnormalities. The incidence of specific numerical chromosomal abnormalities in abortuses is several times higher than in term infants, indicating that most such chromosomal defects are lethal. Thus only a small number of children with cytogenetic abnormalities are born alive.

In Western countries, developmental and genetic birth defects account for half of the deaths in infancy and childhood.
In less-developed countries, in contrast, 95% of infant mortality reflects environmental causes such as infectious diseases and malnutrition. Further reduction in the incidence of birth anomalies in industrialized societies will require genetic counseling, early prenatal diagnosis, identification of high-risk pregnancies, and avoidance of possible exogenous teratogens. Thus, prenatal dietary folic acid supplements have reduced the incidence of congenital neural tube defects.

**Principles of Teratology**

Teratology is the study of developmental anomalies (Greek, teraton, monster). **Teratogens** are chemical, physical, and biological agents that cause developmental anomalies. There are few proven teratogens in humans. However, many drugs and chemicals are teratogenic in animals and should, thus, be treated as potentially dangerous for humans.

**Malformations** are morphologic defects or abnormalities of an organ, part of an organ, or anatomical region due to perturbed morphogenesis. Exposure to a teratogen may result in a malformation, but this is not invariably the case. Such observations have led to the formulation of general principles of teratology:

- **Susceptibility to teratogens is variable.** Presumably the principal determinants of this variability are the genotypes of the fetus and the mother. Experimental evidence for this concept comes from the demonstration that certain strains of inbred mice are susceptible to some teratogens whereas others are not. An example of human variability in the vulnerability to teratogens is the fetal alcohol syndrome, which affects some children of alcoholic mothers, but not others.

- **Susceptibility to teratogens is specific for each embryologic stage.** Most agents are teratogenic only at particular times in development (Fig. 6-2). For example, maternal rubella infection only causes fetal abnormalities if it occurs during the first trimester of pregnancy.

- **The mechanism of is specific for each teratogen.** Teratogenic drugs inhibit crucial enzymes or receptors, interfere with formation of mitotic spindles or block energy production, thereby inhibiting metabolic steps critical for normal morphogenesis. Many drugs and viruses affect specific tissues (e.g., neurotropism, cardiotropism) and so damage some developing organs more than others.

- **Teratogenesis is dose-dependent.** Theoretically, this means that each teratogen should have a “safe” dose, below which no teratogenesis occurs. In practice, however, because of the multiple determinants of teratogenesis, all established

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**FIGURE 6-2. Sensitivity of specific organs to teratogenic agents at critical stages of human embryogenesis.** Exposure to 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.
Teratogens should be avoided during pregnancy; an absolutely safe dose cannot be predicted for every woman.

- **Teratogens produce death, growth retardation, malformation, or functional impairment.** The outcome depends on the interaction between the teratogenic influences, the maternal organism and the fetal–placental unit.

  The search for human teratogens requires (1) population surveys, (2) prospective and retrospective studies of single malformations, and (3) investigation of reported adverse effects of drugs or other chemicals. The list of proven teratogens is long and includes most cytotoxic drugs, alcohol, some antiepileptic drugs, heavy metals, and thalidomide. Many drugs and chemicals have been declared safe for use during pregnancy because they were not teratogenic in laboratory animals. However, the fact that a drug is not teratogenic for mice or rabbits does not necessarily mean that it is innocuous for humans: thalidomide was found not to be teratogenic in mice and rats but caused complex human malformations when many pregnant women ingested it in their first trimester of pregnancy. Interestingly, long after thalidomide was known to be teratogenic in humans, its teratogenicity in rabbits and monkeys was also demonstrated.

**Errors of Morphogenesis**

Normal intrauterine and postnatal development depends on sequential activation and repression of genes. A fertilized ovum (zygote) has all the genes of an adult organism, but most of them are inactive. As the zygote enters cleavage stages of development, individual genes or sets of genes are specifically activated according to the stage of embryogenesis at which they are needed. Initially, only genes essential for cell replication and growth, cell-cell interaction, and morphogenetic movements are activated. *Abnormal gene activation or structure in early embryonic cells can cause early death.*

The cells that form 2-cell and 4-cell embryos (blastomeres) are developmentally equipotent: each can give rise to an adult organism. Separation of embryonic cells at this stage results in identical twins or quadruplets. Since the blastomeres are equipotent and interchangeable, loss of a single blastomere at this stage of development may occur without serious consequences. On the other hand, if one blastomere contains a lethal genes, the others probably do as well. Activation of such genes invariably leads to the death. Furthermore, if a conceptus is exposed to harmful exogenous influences, the noxious agent exerts the same effect on all blastomeres and also causes death. We conclude that adverse environmental influences on preimplantation-stage embryos exert an all-or-nothing effect: either a conceptus dies or development proceeds uninterrupted, since the interchangeable blastomeres replace the lost. As a rule, exogenous toxins acting on preimplantation-stage embryos do not produce errors of morphogenesis and do not cause malformations (see Fig. 6-2). The most common consequence of toxic exposure at the preimplantation stage is death of the embryo, which often passes unnoticed or is perceived as heavy, albeit delayed, menstrual bleeding.

Injury during the first 8 to 10 days after fertilization usually causes incomplete separation of blastomeres, which leads to conjoined twins (“Siamese twins”) that are joined, e.g., at the head (craniopagus), thorax (thoracopagus), or rump (ischiopagus). With asymmetric conjoined twins one is well-developed and one rudimentary or hypoplastic. The latter is always abnormal and is externally attached to, or internally included in, the body of the better-developed sibling (fetus in fetu). Some congenital teratomas, especially in the sacrococcygeal area, are actually asymmetric monsters.

Most complex developmental abnormalities affecting several organ systems are due to injuries that occur between implantation of the blastocyst and early organogenesis. This period is characterized by rapid cell division, cell differentiation, and formation of so-called developmental fields, in which cells interact and determine each other’s developmental fate. This process leads to irreversible differentiation of groups of cells. Complex morphologic movements form organ primordia (anlage), and organs are then interconnected in functionally active systems. *Formation of primordial organ systems is the stage of embryonic development most susceptible to teratogenesis,* and many major developmental abnormalities are probably due to faulty gene activity or the effects of exogenous toxins (see Fig. 6-2). Disorganized or disrupted morphogenesis may have minor or major consequences at the level of (1) cells and tissues, (2) organs or organ systems, and (3) anatomical regions.

- **Agenesis** is the complete absence of an organ primordium. It may manifest as (1) total lack of an organ, as in unilateral or bilateral renal agenesis; (2) absence of part of an organ, as in agenesis of the corpus callosum of the brain; or (3) lack of tissue or cells within an organ, as in the absence of testicular germ cells in congenital infertility ("Sertoli cell only" syndrome).

- **Aplasia** is the persistence of an organ anlage or rudiment, without the mature organ. Thus, in aplasia of the lung the main bronchus ends blindly in nondescriptive tissue composed of rudimentary ducts and connective tissue.

- **Hypoplasia** means reduced size owing to incomplete development of all or part of an organ. Examples include microphthalmia (small eyes), micrognathia (small jaw), and microcephaly (small brain and head).

- **Dysraphic anomalies** are defects caused by failure of opposed structures to fuse. In spina bifida, the spinal canal does not close completely, and overlying bone and skin do not fuse, leaving a midline defect.

- **Involution failures** denote persistence of embryonic or fetal structures that should have involuted at certain stages of development. A persistent thyroglossal duct is the result of incomplete involution of the tract that connects the base of the tongue with the developing thyroid.

- **Division failures** are caused by incomplete cleavage of embryonic tissues, when that process depends on programmed cell death. Fingers and toes are formed at the distal end of the limb bud through the loss of cells located between the primordia that contain the cartilage. If these cells do not undergo apoptosis, the fingers will be conjoined or incompletely separated (syndactyly).

- **Atresia** reflects incomplete formation of a lumen. Many hollow organs originate as cell strands and cords whose centers are programmed to die, producing a central cavity or lumen. Esophageal atresia is characterized by partial occlusion of the lumen, which was not fully established in embryogenesis.

- **Dysplasia** is caused by abnormal organization of cells into tissues, a situation that results in abnormal histogenesis. (This is different from the use of “dysplasia” to describe pre-cancerous epithelial lesions [see Chapters 1 and 5].) Tuberous sclerosis is a striking example of dysplasia, being characterized by abnormal development of the brain, which contains...
aggregates of normally developed cells arranged into grossly visible “tubers.”

- **Ectopia, or heterotopia,** is an anomaly in which an organ is situated outside its normal anatomic site. Thus, an ectopic heart is not in the thorax. Heterotopic parathyroid glands can be within the thymus in the anterior mediastinum.

- **Dystopia** refers to inadequate migration of an organ that remains where it was during development, rather than migrating to its proper site. For example, the kidneys are first in the pelvis, and then move cephalad out of the pelvis. Dystopic kidneys remain in the pelvis. Dystopic testes are retained in the inguinal canal, and do not descend into the scrotum (cryptorchidism).

Developmental anomalies caused by interference with morphogenesis are often multiple:

- A **polytopic effect** occurs when a noxious stimulus affects several organs that are simultaneously in critical stages of development.

- A **monotropic effect** refers to a single localized anomaly that results in a cascade of pathogenetic events.

- A **developmental sequence anomaly** (anomalad or complex anomaly) is a pattern of defects related to a single anomaly or pathogenetic mechanism: different factors lead to the same consequences through a common pathway. In the Potter complex (Fig. 6-3), pulmonary hypoplasia, external signs of intrauterine fetal compression, and morphologic changes of the amnion are all related to oligohydramnios (a severely reduced amount of amniotic fluid). A fetus in an amniotic sac with insufficient fluid develops the distinctive features of Potter complex irrespective of the cause of oligohydramnios.

A **developmental syndrome** refers to multiple anomalies that are pathogenetically related. The term syndrome implies a single cause for anomalies in diverse organs that have been damaged by the same polytopic effect during a critical developmental period. Many developmental syndromes are related to chromosomal abnormalities or single-gene defects. By contrast, **developmental association, or syntropy,** refers to multiple anomalies that are associated statistically but that do not necessarily share the same pathogenetic mechanisms. Many of the anomalies that now seem unrelated may one day prove to have the same cause. However, until such associations are proved, it is important to bear in mind that not all congenital anomalies in a child with multiple defects are necessarily interrelated. Thus, the birth of a child with multiple anomalies does not prove that the mother was exposed to an exogenous teratogen or that all the diverse anomalies were caused by the same genetic defect. The recognition of specific syndromes, and their distinction from random associations, is essential to assess the risk of recurrence of similar anomalies in subsequent children of the same family.

**FIGURE 6-3. Potter complex.** The fetus normally swallows amniotic fluid and, in turn, excretes urine, thereby maintaining its normal volume of amniotic fluid. In the face of urinary tract disease (e.g., renal agenesis or urinary tract obstruction) or leakage of amniotic fluid, the volume of amniotic fluid decreases, a situation termed **oligohydramnios.** Oligohydramnios results in a number of congenital abnormalities termed **Potter complex,** which includes pulmonary hypoplasia and contractures of the limbs. The amnion has a nodular appearance. In cases of urinary tract obstruction, congenital hydronephrosis is also seen, although this abnormality is not considered part of Potter complex.
After the third month of pregnancy, exposure of the human fetus to teratogenic influences rarely results in major errors of morphogenesis. However, morphologic and, especially, functional consequences may still occur in children exposed to exogenous teratogens during the second and third trimesters. Although organs are already formed by the end of the third month of pregnancy, most still undergo restructuring and maturation as required for extraterine life. Functional maturation proceeds at different rates in different organs: the central nervous system (CNS) requires several years after birth to attain functional maturity until so is still susceptible to adverse exogenous influences for some time after birth.

A deformation is defined as an abnormality of form, shape, or position of a part of the body that is caused by mechanical forces. Most anatomic defects caused by adverse influences in the last two trimesters of pregnancy fall into this category. The responsible forces may be external (e.g., amniotic bands in the uterus) or intrinsic (e.g., fetal hypomobility caused by CNS injury). Thus, a deformity known as equinovarus foot can be due to compression by the uterine wall in oligohydramnios or to spinal cord abnormalities that lead to defective innervation and movement of the foot.

**Clinically Important Malformations Occur in Many Organs and Have Diverse Causes**

**Anencephaly and Other Neural Tube Defects**

Anencephaly is the congenital absence of the cranial vault. The cerebral hemispheres are completely missing or are reduced to small masses at the base of the skull. The disorder is a dysraphic defect of neural tube closure.

The neural tube closes sequentially in a craniocaudal direction, so a defect in this process causes abnormalities of the vertebral column. Spina bifida is incomplete closure of the spinal cord or vertebral column or both. Hernial protrusion of the meninges through a defect in the vertebral column is termed meningocele. Myelomeningocele is the same condition as meningocele, complicated by herniation of the spinal cord itself.

Neural tube defects are discussed in detail in Chapter 28.

**Thalidomide-Induced Malformations**

Limb-reduction deformities, involving any number of extremities, are rare congenital defects of mostly obscure origin that affect 1 in 5000 liveborn infants. They have been known for ages: a Goya depiction of a typical example is in the Louvre Museum in Paris. In the 1960s, a sudden increase in the incidence of limb-reduction deformities in Germany and England was linked to maternal ingestion of a sedative early in pregnancy. Known under the generic name of thalidomide, this derivative of glutamic acid is teratogenic between the 28th and 50th days of pregnancy.

Ten percent of children born to epileptic mothers who were treated with antiepileptic drugs such as hydantoin during pregnancy show characteristic facial features, hypoplasia of nails and digits, and various congenital heart defects. Since this syndrome occurs only two to three times more often in treated epileptics than in untreated ones, it is uncertain whether the defects all reflect adverse effects of the drug. Nevertheless, it appears that fetal susceptibility to this disorder correlates with the fetal level of the microsomal detoxifying enzyme epoxide hydrolase. Presumably, accumulation of poorly detoxified reactive intermediates of hydantoin metabolism promotes teratogenesis.

**Fetal Hydantoin Syndrome**

Fetal alcohol syndrome is caused by maternal consumption of alcoholic beverages during pregnancy. It is a complex of abnormalities including: (1) growth retardation, (2) CNS dysfunction, and (3) characteristic facial dysmorphology. Because not all children adversely affected by maternal alcohol abuse show all these abnormalities, the term fetal alcohol effect is also used.
high rates of alcoholism, such as some tribes of Native Americans, incidence may reach 20 to 150 per 1000. It is thought that abnormalities related to fetal alcohol effect, particularly mild mental deficiency and emotional disorders, are far more common than the full-blown fetal alcohol syndrome.

The minimum amount of alcohol that results in fetal injury is not well established, but children with the entire spectrum of fetal alcohol syndrome are usually born to mothers who are chronic alcoholics. Heavy alcohol consumption during the first trimester of pregnancy is particularly dangerous. The mechanism by which alcohol damages the developing fetus remains unknown despite a large body of research.

PATHOLOGY AND CLINICAL FEATURES: Infants born to alcoholic mothers often show prenatal growth retardation, which continues after birth. These infants also may show microcephaly, epicanthal folds, short palpebral fissures, maxillary hypoplasia, a thin upper lip, a small jaw (micrognathia), and a poorly developed philtrum. Cardiac septal defects may affect up to one third of patients, although these often close spontaneously. Minor abnormalities of joints and limbs may occur.

Fetal alcohol syndrome is the most common cause of acquired mental retardation. One fifth of children with fetal alcohol syndrome have intelligence quotients (IQs) below 70, and 40% are between 70 and 85. Even if their IQ is normal, these children tend to have short memory spans, and to exhibit impulsive behavior and emotional instability (see Chapter 8).

TORCH Complex

The acronym, TORCH, refers to a complex of similar signs and symptoms produced by fetal or neonatal infection with: Toxoplasma (T), rubella (R), cytomegalovirus (C), and herpes simplex virus (H). In the acronym TORCH, the letter “O” represents “others.” The term was coined to alert pediatricians to the fact that fetal and newborn infections by TORCH agents are usually indistinguishable from each other and that assessment should include testing for all TORCH agents, and for some possible others as well (Fig. 6-5). “Other” infections include syphilis, tuberculosis, listeriosis, leptospirosis, varicella-zoster virus infection, and Epstein-Barr virus infection. Human immunodeficiency virus (HIV) and human parvovirus (B19) have been suggested as additions to the list.

Infections with TORCH agents occur in 1% to 5% of all live-born infants in the United States and are major causes of neonatal morbidity and mortality. The severe damage inflicted by these organisms is mostly irreparable, and prevention (if possible) is the only alternative. Unfortunately, titers of serum antibodies against TORCH agents in infants or mothers are usually not diagnostic, and the precise etiology is often unclear.

- **Toxoplasmosis:** Asymptomatic toxoplasmosis is common, and 25% of women in their reproductive years have antibodies to this organism. On the other hand, intrauterine toxoplasma infection occurs in only 0.1% of all pregnancies.

- **Rubella:** Vaccination against rubella in the United States has virtually eliminated congenital rubella. Fewer than 10 cases are reported each year.

- **Cytomegalovirus (CMV):** In the United States, 2/3 of women of childbearing age have antibody to CMV, and up to 2% of newborns are congenitally infected. Most normal infants have maternally derived antibodies, so CMV is diagnosed by urine culture.

- **Herpesvirus:** Intrauterine infection with herpes simplex virus type 2 (HSV-2) is uncommon. The neonatal infection is usually acquired during passage through the birth canal of a mother with active genital herpes. Clinical examination of the mother, the appearance of typical skin lesions in the newborn, and serologic testing and culture for HSV-2 establish the diagnosis. Congenital herpes infection can be prevented by cesarean section of mothers who have active genital lesions.

The specific organisms of the TORCH complex are discussed in detail in Chapter 9.

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PATHOLOGY: The clinical and pathologic findings in the symptomatic newborn vary. Only a minority present with multisystem disease and the entire spectrum of abnormalities (Table 6-1). Growth retardation and abnormalities of the brain, eyes, liver, hematopoietic system, and heart are common.

Lesions of the brain are the most serious pathologic changes in TORCH-infected children. In acute encephalitis, foci of necrosis are initially surrounded by inflammatory cells. Later these lesions calcify, most prominently in congenital toxoplasmosis. Microcephaly, hydrocephalus, and abnormally shaped gyri and sulci (microgyria) are frequent. Radiologically, defects of cerebral matter (porencephaly), missing olfactory bulbs, and other major brain...
defects may be identified. Severe brain damage is reflected in psychomotor retardation, neurologic defects, and seizures.

Ocular defects are prominent in the TORCH complex, particularly with rubella infection, in which over 2/3 of patients have cataracts and microphthalmia. Glaucoma and retinal malformations (coloboma) may occur. Chorioretinitis is common in with rubella, Toxoplasma, and CMV, is usually bilateral and on funduscopy appears as pale, mottled areas surrounded by a pigmented rim. Keratoconjunctivitis is the most common ocular lesion in newborns afflicted with herpes simplex.

Cardiac anomalies occur in many children with the TORCH complex, mostly in congenital rubella. Patent ductus arteriosus and various septal defects are the most common cardiac abnormalities. Pulmonary artery stenosis and complex cardiac anomalies are occasionally seen.

Congenital Syphilis

The organism that causes syphilis, Treponema pallidum, is transmitted to the fetus by a mother who has acquired syphilis during pregnancy. The fetus may possibly develop syphilis if the mother became infected in the 2 years before the pregnancy, although the actual risk cannot be accurately assessed. Congenital syphilis affects about 1 in 2000 liveborn infants in the United States. In pregnant syphilitic women, stillbirth occurs in 1/3, and 2/3 of infants carried to term manifest congenital syphilis.

T. pallidum may invade the fetus at any point in pregnancy. Early infections most likely induce abortions, and grossly visible signs of congenital syphilis appear only in fetuses infected after the 16th week of pregnancy.Spirochetes grow in all fetal tissues, and the clinical presentation is thus variable.

Children with congenital syphilis are normal at first, or show changes like those of the TORCH complex. Early lesions in various organs teem with spirochetes. They show perivascular infiltrates of lymphocytes and plasma cells, and granuloma-like lesions termed gummaws. Many infants are asymptomatic, only to develop the typical stigmata of congenital syphilis in the first few years of life. Late symptoms of congenital syphilis appear many years later and reflect slowly evolving tissue destruction and repair:

- **Rhinitis:** A conspicuous mucopurulent nasal discharge, “snuffles,” is almost always present as an early sign of congenital syphilis. The nasal mucosa is edematous and tends to ulcerate, leading to nosebleeds. Destruction of the nasal bridge eventually results in flattening of the nose, so-called saddle nose.

- **Skin:** A maculopapular rash is common early in congenital syphilis. Palms and soles are usually affected (as in secondary syphilis of adults), although it may involve the entire body or any part. Cracks and fissures (rhagades) occur around the mouth, anus, and vulva. Flat raised plaques (condylomata lata) around the anus and female genitalia may develop early or after a few years.

- **Visceral organs:** A distinctive pneumonitis, characterized by pale hypereosinophilic lungs (pneumonia alba), may develop in the neonatal period. Hepatosplenomegaly, anemia, and lymphadenopathy may also be observed in early congenital syphilis.

- **Teeth:** The buds of incisors and 6th-year molars develop early in postnatal life, the time when congenital syphilis is particularly aggressive. Thus, the permanent incisors may be notched (Hutchinson teeth) and the molars malformed (mulberry molars).

- **Bone:** The most common osseous lesion is an inflammation of the periosteum together with new bone formation (periostitis). This complication is particularly evident in the anterior tibia, resulting in a distinctive outward curving (saber shins).

- **Eye:** A progressive corneal vascularization (interstitial keratitis) is an especially vexing complication of congenital syphilis, occurring as early as 4 years of age and at late as 20 years. The cornea eventually scars and becomes opaque.

- **Nervous system:** The nervous system is commonly involved, with symptoms starting in infancy or after 1 year. Meningitis predominates in early congenital syphilis, leading to convulsions, mild hydrocephalus, and mental retardation. Meningovascular syphilis is a common lesion in later syphilis, which may result in deafness, mental retardation, paraplegia and other manifestations of neurosyphilis. Hutchinson triad refers to the combination of deafness, interstitial keratitis, and notched incisor teeth.

The diagnosis of congenital syphilis is suggested by clinical findings plus a history of maternal infection. Serologic confirmation of syphilis may be difficult in newborns because transplacental transfer of maternal immunoglobulin (Ig)G gives

**TABLE 6-1**

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<thead>
<tr>
<th>Pathologic Findings in the Fetus and Newborn Infected with TORCH Agents</th>
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<tbody>
<tr>
<td><strong>General</strong></td>
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<td><strong>Central nervous system</strong></td>
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<td><strong>Eye</strong></td>
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<td><strong>Liver</strong></td>
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<td><strong>Hematopoietic system</strong></td>
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<td><strong>Skin and mucosae</strong></td>
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<td><strong>Cardiopulmonary system</strong></td>
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<td><strong>Skeleton</strong></td>
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T - Toxoplasma; R - rubella virus; C - cytomegalovirus; H - herpesvirus.
false-positive results. Penicillin is the drug of choice for intrauterine and postnatal syphilis. If penicillin is given during intrauterine life or during the first 2 years of postnatal life, the prognosis is excellent, and most symptoms of early and late congenital syphilis will be prevented.

Chromosomal Abnormalities

Cytogenetics is the study of chromosomes and their abnormalities. The current system of classification is the International System for Human Cytogenetic Nomenclature (ISCN).

The Normal Chromosomal Complement Is 44 Autosomes and 2 Sex Chromosomes

Cytogenetic analysis can be done on any dividing cell but most studies use circulating lymphocytes, which are easily stimulated to undergo mitosis. The dividing cells are treated with colchicine to arrest them in metaphase. Cells are then spread on glass slides to disperse the chromosomes, which are stained to facilitate more precise identification of chromosomes and their distinct bands.

Chromosome Structure

Using a stain such as Giemsa, chromosomes are classified according to their length and the positions of their constrictions, or centromeres. The centromere is the point at which the two identical strands of chromosomal DNA, called sister chromosomes, attach to each other during mitosis. The location of the centromere is used to classify chromosomes as metacentric, submetacentric, or acrocentric. In metacentric chromosomes (1, 3, 19, and 20) the centromere is exactly in the middle. In submetacentric chromosomes (2, 4–12, 16–18, and X), it divides the chromosome into a short arm (p, from French, petit) and a long arm (q, the next letter in the alphabet). Acrocentric chromosomes (13, 14, 15, 21, 22, and Y) display very short arms or stalks and satellites attached to an eccentrically located centromere (Fig. 6-6).

Stains are used to classify chromosomes into seven groups, A to G. Thus, group A contains 2 large metacentric and a large submetacentric chromosome, group B has 2 large submetacentric chromosomes, group C includes 6 submetacentric chromosomes, etc.

Fluorescence In Situ Hybridization (FISH)

FISH uses fluorophore-labeled DNA probes to identify DNA sequences, varying in size from individual genes or small regions of chromosomes (Figs. 6-6 and 6-7). It is also used to identify genetic material lost or gained. Using probes with different fluorophores, one can demonstrate chromosomal translocations. More-recent applications, termed multicolor FISH, or spectral karyotyping, utilize probes that hybridize to whole chromosomes, which facilitates detection of gross chromosomal abnormalities (Figs. 6-6 and 6-7).

Chromosomal Banding

To identify each chromosome individually, special stains delineate specific bands of different staining intensity on each chromosome. The pattern of bands is unique to each chromosome and makes possible to (1) pair two homologous chromosomes, (2) recognize each chromosome, and (3) identify defects on each segment of a chromosome.

Chromosome bands are labeled as follows:

- **G bands:** These segments are highlighted using Giemsa stain (hence “G”).
- **Q bands:** These stain with Giemsa and fluoresce when treated with quinacrine (thus, “Q”).
- **R bands:** On appropriate staining, R bands present as reverse (hence “R”) images of G and Q bands; that is, dark G bands are light R bands and vice versa.
- **C banding:** This is a method for staining centromeres (hence “C”) and other portions of chromosomes containing constitutive heterochromatin. By contrast, facultative heterochromatin forms the inactive X chromosome (Barr body).

• Nucleolar organizing region (NOR) staining: Secondary constrictions (stalks) of chromosomes with satellites are demonstrated by NOR staining.

• T banding: This technique stains the terminal (hence “T”) ends of chromosomes.

Structural Chromosomal Abnormalities May Arise during Somatic Cell Division (Mitosis) or during Gametogenesis (Meiosis)

Changes in chromosome structure that occur in somatic cells during mitosis may: (1) not affect a cell’s basic functions and thus be silent, (2) interfere with one or more key cellular activities and lead to cell death, or (3) change a key cell function (e.g., increase mitotic activity) so as to lead to dysfunction without cell death (see Chapter 5).

The structural chromosomal abnormalities that arise during gametogenesis are important in a different context, because they are transmitted to all somatic cells of the individual’s offspring and may result in heritable diseases.

During normal meiosis, homologous chromosomes (e.g., two chromosomes 1) form pairs, termed bivalents. By a normal process known as crossing-over, parts of these chromosomes are exchanged, thus rearranging the genetic constituents of each chromosome.

By an abnormal process termed translocation, such exchanges may also involve nonhomologous chromosomes (e.g., chromosomes 3 and 21). Two major types of chromosomal translocations are recognized: reciprocal and robertsonian.

Reciprocal Translocations

Reciprocal translocation refers to exchange of acentric chromosomal segments between different (nonhomologous) chromosomes (Fig. 6-8). A reciprocal translocation is balanced if there is no loss of genetic material, so that each chromosomal segment is translocated in its entirety. When such translocations are present in the gametes (sperm or ova), progeny maintain the abnormal chromosomal structure in all somatic cells. Balanced translocations are not generally associated with loss of genes or disruption of vital gene loci, so most carriers of balanced translocations are phenotypically normal. Balanced reciprocal translocations can be inherited for many generations. Reciprocal translocations are particularly well demonstrated by current banding techniques.

Robertsonian Translocations

Robertsonian translocation (centric fusion) involves the centromere of acrocentric chromosomes. When two nonhomologous chromosomes are broken near the centromere, they may exchange two arms to form one large metacentric chromosome and a small chromosomal fragment. The latter lacks a centromere and is usually lost in subsequent divisions. As in reciprocal translocation, robertsonian translocation is balanced if there is no significant loss of genetic material. The carrier is also usually phenotypically normal, but may be infertile. If the carrier is fertile, however, their gametes may produce unbalanced translocations (see Figs. 6-7 and 6-8), in which case the offspring may have congenital malformations.

Chromosomal Deletions

A deletion is loss of a portion of a chromosome and involves either a terminal or an intercalary (middle) segment. Disturbances during meiosis in germ cells or breaks of chromatids during mitosis in somatic cells may result in formation of chromosomal fragments that are not incorporated into any chromosome and are thus lost in subsequent cell divisions.

The shortening of a chromosome because of a deletion may be apparent in routinely stained chromosome preparations. Banding techniques are used to determine whether the arm of the chromosome is shortened because of a deletion of the terminal
Gametic deletion can be associated with either normal or abnormal development. An example of the latter is the cri du chat syndrome, in which the short arm of chromosome 5 is deleted. Deletions may be related to several human cancers, including some hereditary forms of cancer. For example, some familial retinoblastomas are associated with deletions in the long arm of chromosome 13 (see Chapter 5). Wilms tumor aniridia syndrome is associated with deletions in the short arm of chromosome 11.

Chromosomal Inversions

Chromosomal inversion refers to a process in which a chromosome breaks at two points, the affected segment inverts and then reattaches. Pericentric inversions result from breaks on opposite sides of the centromere, whereas paracentric inversions involve breaks on the same arm of the chromosome (see Fig. 6-8). During meiosis, homologous chromosomes that carry a portion or because of a double break in the more central portions. The latter event leads to intercalary deletion and subsequent fusion of adjoining residual fragments.

Gametic deletion can be associated with either normal or abnormal development. An example of the latter is the cri du chat syndrome, in which the short arm of chromosome 5 is deleted. Deletions may be related to several human cancers, including some hereditary forms of cancer. For example, some familial retinoblastomas are associated with deletions in the long arm of chromosome 13 (see Chapter 5). Wilms tumor aniridia syndrome is associated with deletions in the short arm of chromosome 11.
inversions do not exchange segments of chromatids by crossing over as readily as normal chromosomes, because of interference with pairing. Although this is of little consequence for the phenotype of the offspring, it may be important in evolutionary terms, since it may lead to clustering of certain hereditary features.

Ring Chromosomes

Ring chromosomes are formed by a break involving both telomeres of a chromosome, deletion of the acentric fragments and end-to-end fusion of the remaining centric portion of the chromosome (see Fig. 6-8). The consequences depend primarily on the amount of genetic material lost because of the break. The abnormally shaped chromosome may impede normal meiotic division, but in most instances, this chromosomal abnormality is of no consequence.

Isochromosomes

Isochromosomes are formed by faulty centromere division. Normally, centromeres divide in a plane parallel to a chromosome’s long axis, to give two identical hemichromosomes. If a centromere divides in a plane transverse to the long axis, pairs of isochromosomes are formed. One pair corresponds to the short arms attached to the upper portion of the centromere and the other to the long arms attached to the lower segment (see Fig. 6-8).

The most important clinical condition involving isochromosomes is Turner syndrome, in which 15% of those affected have an isochromosome of the X chromosome. Thus, a woman with a normal X chromosome and an isochromosome composed of long arms of the X chromosome is monosomic for all the genes located on the missing short arm (i.e., the other isochromosome, which is lost during the meiotic division). She also has three sets of the genes located on the long arm. The absence of the genes from the short arm accounts for the abnormal development in these persons.

The Causes of Abnormal Chromosome Numbers Are Largely Unknown

A number of terms are important in understanding developmental defects associated with abnormal chromosome numbers.

• Haploid: A single set of each chromosome (23 in humans). Only germ cells have a haploid number (n) of chromosomes.

• Diploid: A double set (2n) of each of the chromosomes (46 in humans). Most somatic cells are diploid.

• Euploid: Any multiple (from n to 8n) of the haploid number of chromosomes. For example, many normal liver cells have twice (4n) the diploid DNA of somatic cells and are, therefore, euploid or, more specifically, tetraploid. If the multiple is greater than 2 (i.e., greater than diploid), the karyotype is polyploid.

• Aneuploid: Karyotypes that are not exact multiples of the haploid number. Many cancer cells are aneuploid, a characteristic often associated with aggressive behavior.

• Monosomy: The absence in a somatic cell of one chromosome of a homologous pair. For example, in Turner syndrome there is a single X chromosome.

• Trisomy: The presence of an extra copy of a normally paired chromosome. For example, Down syndrome is caused by the presence of three chromosomes 21.

Nondisjunction

Nondisjunction is a failure of paired chromosomes or chromatids to separate and move to opposite poles of the spindle at anaphase, during mitosis or meiosis. Numerical chromosomal abnormalities arise primarily from nondisjunction. Nondisjunction leads to aneuploidy if only one pair of chromosomes fails to separate. It results in polyploidy if the entire set does not divide and all the chromosomes are segregated into a single daughter cell. In somatic cells, aneuploidy secondary to nondisjunction leads to one daughter cell that exhibits trisomy (2n + 1) and the other monosomy (2n – 1) for the affected chromosome pair. Aneuploid germ cells have two copies of the same chromosome (n + 1) or lack the affected chromosome entirely (n – 1).

Anaphase lag is a special form of nondisjunction in which a single chromosome or chromatid fails to pair with its homologue during anaphase. It lags behind the others on the spindle and, therefore, is not incorporated into the nucleus of the daughter cell. As a result of anaphase lag and the loss of a single chromosome, one daughter cell is monosomic for the missing chromosome; the other remains euploid.

Pathogenesis of Numerical Aberrations

The causes of chromosomal aberrations are obscure. Putative exogenous factors, such as radiation, viruses, and chemicals, affect the mitotic spindle or DNA synthesis and produce mitotic and meiotic disturbances in experimental animals. However, the role of these factors in causing human chromosomal abnormalities is unknown. Immune factors have been invoked, as there is a correlation between autoantibodies and chromosomal anomalies in families with autoimmune thyroid disorders. Familial occurrence of meiotic failure and chromosomal anomalies provides some evidence that human genes may predispose to faulty cell division. However, these explanations are hypothetical, and only two phenomena are known to be important in genesis of numerical aberrations.

• Nondisjunction during meiosis is more common in persons with structurally abnormal chromosomes. This is probably related to the fact that such chromosomes do not pair or segregate during gametogenesis as readily as do normal ones.

• Maternal age has long been recognized as a major factor in the etiology of certain nondisjunction syndromes, particularly trisomy 21.

Chromosomal Aberrations at Various Stages of Pregnancy

Chromosomal abnormalities identified at birth differ from those found in early spontaneous abortions. At birth, the common chromosomal abnormalities are trisomies 21 (most frequent), 18, 13, and X or Y (47,XXX; 47,XXY; and 47,XYY). Approximately 0.3% of all liveborn infants have a chromosomal abnormality. Among spontaneous abortions, the most common chromosomal abnormalities are 45,X (most frequent), then trisomies 16, 21, and 22. However, trisomy of almost any chromosome can be observed in spontaneous abortions. Up to 35% of spontaneous abortions have a chromosomal abnormality. The reason for these differences is presumably related to survival in utero. Very few fetuses with 45,X survive to term, and trisomy 16 is nearly always lethal in utero; a fetus with trisomy 21 has a better chance of surviving to birth.
Effects of Chromosomal Aberrations

Most major chromosomal abnormalities are incompatible with life. The defects are usually lethal to a developing conceptus, and cause early death and spontaneous abortion. Loss of genetic material (e.g., autosomal monosomies) results in embryos that generally do not survive pregnancy. Monosomy of the X chromosome (45,X) may be compatible with life, although over 95% of such embryos are lost during pregnancy. Absence of an X chromosome (i.e., 45,Y) invariably leads to early abortion.

Autosomal trisomies lead to several developmental abnormalities. Affected fetuses usually die during pregnancy or shortly after birth. Trisomy 21, which defines Down syndrome, is an exception, and people with Down syndrome may survive for years. Trisomy of the X chromosome may result in abnormal development but is not lethal.

Mitotic nondisjunction may involve embryonic cells during early stages of development and result in chromosomal aberrations that are transmitted through some cell lineages but not others. This is called mosaicism: the body contains two or more karyotypically different cell lines. Mosaicism may involve autosomes or sex chromosomes, and the phenotype depends on the chromosome involved and the extent of mosaicism. Autosomal mosaicism is rare, probably because this condition is usually lethal. On the other hand, mosaicism involving sex chromosomes is common and is found in patients with gonadal dysgenesis who present with Turner or Klinefelter syndrome.

Nomenclature of Chromosomal Aberrations

Structural and numerical chromosomal abnormalities are classified by:
1. Total number of chromosomes
2. Designation (number) of affected chromosomes
3. Nature and location of the defect on the chromosome (Table 6-2).

Karyotypes are described sequentially by:
1. Total number of chromosomes
2. Sex chromosome complement
3. Any abnormality.

The short arm of a chromosome is designated p, and the long arm, q. The addition of chromosomal material, whether an entire chromosome or a part of one, is indicated by a plus sign (+) before the number of the affected chromosome. A minus sign (−) denotes loss of part or all of a chromosome. Alternatively, loss (deletion) of part of a chromosome may be designated by del, followed by the location of the deleted material on the affected chromosome. A translocation is written as a t, followed by brackets containing the involved chromosomes. Structural or numerical chromosomal aberrations are seen in 3 to 7 per 1000 liveborn infants, although most are balanced translocations and are asymptomatic.

Numerical Autosomal Aberrations in Liveborn Infants are Virtually All Trisomies

Structural aberrations that may result in clinical disorders include translocations, deletions and chromosomal breakage (Table 6-3).

Trisomy 21 (Down Syndrome)

Trisomy 21 is the most common cause of mental retardation. Furthermore, liveborn infants are only a fraction of all conceptuses with this defect. Two thirds abort spontaneously or die in utero. Life expectancy is also reduced. Advances in treating infections, congenital heart defects, and leukemia—the leading causes of death in patients with Down syndrome—have increased life expectancy.

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**PATHOGENESIS:** There are three mechanisms by which three copies of the genes on chromosome 21 that cause Down syndrome may be present in somatic cells:

- **Nondisjunction** in the first meiotic division of gametogenesis accounts for most (92%–95%) patients with trisomy 21. The extra chromosome 21 is of maternal origin in about 95% of Down syndrome children. Virtually all maternal nondisjunction seems to result from events in the first meiotic division (meiosis I).

- **Translocation** of an extra long arm of chromosome 21 to another acrocentric chromosome causes about 3% of cases of Down syndrome.

- **Mosaicism** for trisomy 21 is caused by nondisjunction during mitosis of a somatic cell early in embryogenesis and accounts for 2% of children born with Down syndrome.
EPIDEMIOLOGY: The incidence of trisomy 21 correlates strongly with increasing maternal age: children of older mothers have much greater risk of having Down syndrome (Fig. 6-10). Up to their mid-30s, women have a constant risk of giving birth to a trisomic child of about 1 per 1000 liveborn infants. Incidence then increases sharply, to 1 in 30 at age 45 years. The risk of a mother having a second child with Down syndrome is 1%, regardless of maternal age, unless the syndrome is associated with translocation of chromosome 21.

Molecular Genetics of Down Syndrome
Chromosome 21 is the smallest human autosome, with less than 2% of all human DNA. It has an acrocentric structure, and all genes of known function (except for ribosomal RNA) are on the long arm (21q). Based on studies of inherited translocations, in which only a portion of chromosome 21 is duplicated, the region on chromosome 21 responsible for the full Down syndrome phenotype is in band 21q22.2, a 4-Mb region of DNA termed the Down syndrome critical region (DSCR). Genes in the DSCR that might be involved in Down syndrome have recently been identified. They encode transcription factors of the nuclear factor of activated T cells (NFAT) family, which are known to influence somatic development.

PATHOGENESIS: The mechanism by which increasing maternal age increases the risk of bearing a child with trisomy 21 is poorly understood. Molecular studies have shown that the maternal age effect is related to maternal nondisjunction events, which implies that the defect lies in meiosis in oocytes. Down syndrome associated with translocation or mosaicism is not related to maternal age.

Down syndrome caused by translocation of an extra portion of chromosome 21 occurs in two situations. Either parent may be a phenotypically normal carrier of a balanced translocation, or a translocation may arise de novo during gametogenesis. These translocations are typically robertsonian, tending to involve only acrocentric chromosomes, with short arms consisting of a satellite and stalk (chromosomes 13, 14, 15, 21, and 22). Translocations between these chromosomes are particularly common since they cluster during meiosis and so are subjected to breakage and recombination more than other chromosomes. The most common translocation in Down syndrome (50%) is fusion of the long arms of chromosomes 21 and 14, t(14q;21q), followed in frequency (40%) by similar fusion involving two chromosomes 21, t(21q;21q).

If the translocation is inherited from a parent, a balanced translocation has been converted to an unbalanced one (see Figure 6-7B). By this scheme, one would expect a one in three chance of Down syndrome among offspring of a carrier of a balanced robertsonian translocation. However, if the mother carries the translocation, the actual incidence is only 10% to 15% and it is less than 5% if the father is the carrier. This reduced incidence probably relates to the early loss of most embryos with trisomy 21.

### TABLE 6–3

<table>
<thead>
<tr>
<th>Syndromes</th>
<th>Features</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Trisomic Syndromes</strong></td>
<td></td>
</tr>
<tr>
<td>Chromosome 21 (Down syndrome 47,XX or XY, +21:1/800)</td>
<td>Epicanthic folds, speckled irides, flat nasal bridge, congenital heart disease, simian crease of palms, Hirschsprung disease, increased risk of leukemia, horseshoe kidney, deformed fingers</td>
</tr>
<tr>
<td>Chromosome 18 (47,XX or XY, +18:1/8000)</td>
<td>Female preponderance, micrognathia, congenital heart disease, polycystic kidneys, polydactyly, simian crease</td>
</tr>
<tr>
<td>Chromosome 13 (47,XX or XY, +13:1/20,000)</td>
<td>Persistent fetal hemoglobin, microcephaly, congenital heart disease, polycystic kidneys, total anomalous venous return</td>
</tr>
<tr>
<td><strong>Deletion Syndromes</strong></td>
<td></td>
</tr>
<tr>
<td>5p - syndrome (Cri du chat 46,XX or XY, 5p –)</td>
<td>Catlike cry, low birth weight, microcephaly, epicanthic folds, congenital heart disease, short hands and feet, simian crease</td>
</tr>
<tr>
<td>11p - syndrome (46,XX or XY, 11p –)</td>
<td>Aniridia, Wilms tumor, gonadoblastoma, male genital ambiguity</td>
</tr>
<tr>
<td>13q - syndrome (46,XX or XY,13q –)</td>
<td>Low birth weight, microcephaly, retinoblastoma, congenital heart disease</td>
</tr>
</tbody>
</table>

All of these syndromes are associated with mental retardation.
PATHOLOGY AND CLINICAL FEATURES: Diagnosis of Down syndrome is ordinarily made at the time of birth by virtue of the infant’s flaccid state and characteristic appearance. The diagnosis is then confirmed by cytogenetic analysis. As the child develops, a typical constellation of abnormalities appears (Fig. 6-11).

- **Mental status:** Children with Down syndrome are invariably mentally retarded. Their IQs decline relentlessly and progressively with age. Mean IQs are 70 below the age of 1 year, declining during the first decade of life to a mean of 30. The major defect seems to be an inability to develop more-advanced cognitive strategies and processes, problems that become more apparent as the child grows older. These children were traditionally described as particularly gentle and affectionate, newer studies have cast serious doubt on the validity of these personality stereotypes.

- **Craniofacial features:** Face and occiput tend to be flat, with a low-bridged nose, reduced interpupillary distance, and oblique palpebral fissures. Epicanthal folds of the eyes impart an Oriental appearance, which accounts for the obsolete term *mongolism.* A speckled appearance of the iris is referred to as *Brushfield spots.* Ears are enlarged and malformed. A prominent tongue, which typically lacks a central fissure, protrudes through an open mouth.

- **Heart:** One third of children with Down syndrome have cardiac malformations. The incidence is even higher in aborted fetuses. Anomalies include atrioventricular canal, ventricular and atrial septal defects, tetralogy of Fallot, and patent ductus arteriosus. Most cardiac defects seem to reflect a problem in formation of the heart’s venous inflow tract.

- **Skeleton:** These children tend to be small, owing to shorter than normal bones of the ribs, pelvis, and extremities. The hands are broad and short and exhibit a “simian crease,” that is, a single transverse crease across the palm. The middle phalanx of the fifth finger is hypoplastic, an abnormality that leads to inward curvature of this digit.

- **Gastrointestinal tract:** Duodenal stenosis or atresia, imperforate anus and Hirschsprung disease (megacolon) occur in 2% to 3% of children with Down syndrome.

- **Reproductive system:** Men with trisomy 21 are invariably sterile, due to arrested spermatogenesis. A few women with Down syndrome have given birth to children, 40% of which had trisomy 21.

- **Immune system:** The immune system in Down syndrome has been the subject of numerous studies, but no clear pattern of defects has emerged. Still, affected children are unusually susceptible to respiratory and other infections.

- **Hematologic disorders:** Persons with Down syndrome are at a particularly high risk of developing leukemia at all ages. The risk of leukemia in Down syndrome children younger than the age of 15 years is about 15-fold greater than normal. In children younger under 3 years, acute nonlymphocytic leukemia predominates. After that, when most of the leukemias in Down syndrome occur, most cases are acute lymphoblastic leukemias. The basis for the high incidence of leukemia is unknown, but leukemic reactions (transient pronounced neutrophilia) are frequent in the newborn with Down syndrome. Interestingly, leukemias that develop in patients who are mosaic for Down syndrome, are invariably trisomic for chromosome 21.

- **Neurologic disorders:** There is no clear pattern of neuropathology associated with Down syndrome, nor are there characteristic changes in the electroencephalogram. Nevertheless, the neurons in trisomy 21 may in fact differ from normal. Virtually all electrical parameters and a number of physiologic ones are altered in cultured neurons from infants with Down syndrome. One of the most intriguing neurologic features of Down syndrome is its association with Alzheimer disease, a relationship that has been appreciated for more than half a
century. The lesions characteristic of Alzheimer disease are universally demonstrable by age 35, including: (1) granulovascular degeneration, (2) neurofibrillary tangles, (3) senile plaques, and (4) loss of neurons (see Chapter 28). The senile plaques and cerebral blood vessels of both Alzheimer disease and Down syndrome always contain an amyloid composed of the same fibrillar protein (β-amyloid protein). The similarity between the neuropathology of Down syndrome and that of Alzheimer disease is also reflected in the appearance of dementia in one-fourth to one-half of older patients with Down syndrome and progressive loss of many intellectual functions that cannot be attributed to mental retardation alone.

- **Life expectancy**: During the first decade of life, the presence or absence of congenital heart disease is the major determinant of survival in Down syndrome. Of those whose hearts are normal, only about 5% die before age 10, while about 25% with heart disease die by then. For those who reach age 10, the estimated age at death is 55, which is 20 years or more lower than that of the general population. Only 10% reach age 70.

**Trisomies of Chromosomes 18, 13 and 22**

**Trisomy 18** is the second most common autosomal syndrome, occurring about once in 8000 live births, an order of magnitude less frequent than Down syndrome. The disorder results in mental retardation and affects females four times as often as males. Virtually all infants with trisomy 18 have congenital heart disease and die in the first 3 months of life.

**Trisomies 13 and 22** are rare and both are associated with mental retardation, congenital heart disease, and other abnormalities. Syndromes associated with trisomies of chromosomes 8 and 9 have also been described.

**Translocation Syndromes**

The prototypical translocation that causes partial trisomy is Down syndrome. Many other partial trisomies are reported, the best documented of which is 9p-trisomy. In this disorder, the short arm of chromosome 9 may be translocated to one of several autosomes. Many kindreds with this syndrome have been described. Carriers of a balanced chromosome 9 translocation are asymptomatic but may pass an unbalanced translocation on to their offspring. The clinical disorder is characterized by mental retardation, microcephaly, and other craniofacial abnormalities. A reciprocal translocation between the long arms of chromosome 18 is usually associated with ring chromosomes. Syndromes associated with 21q– and 22q– are the most common and often resemble Down syndrome.

**Deletions and rearrangements of subtelomeric sequences**: Telomeres are a repetitive sequence (TTAGGG), at the ends of chromosomes. Subtelomeric regions of chromosomes are rich in genes. Deletions and rearrangements of these regions can only be demonstrated by FISH, and are major causes of mild to severe mental retardation and dysmorphic features, and are found in about 5% of such patients.

**Chromosomal Breakage Syndromes**

Several recessive syndromes associated with frequent chromosomal breakage and rearrangements are accompanied by significant risk of leukemia and other cancers. These disorders include xeroderma pigmentosum, Bloom syndrome (congenital telangiectatic erythema with dwarfism), Fanconi anemia (constitutional aplastic pancytopenia), and ataxia telangiectasia. Acquired chromosome breaks and translocations are associated with leukemias and lymphomas, the best documented of which are chronic myelogenous leukemia, t(9;22) and Burkitt lymphoma, mostly t(8;14) (see Chapters 5, 20).

**Numerical Aberrations of Sex Chromosomes Are Much More Common Than Those of Autosomes, Save for Trisomy 21**

The reasons are not entirely clear, but additional sex chromosomes (Fig. 6-12) produce less severe clinical manifestations than do extra autosomes and are less likely to disturb critical stages of development. In the case of additional X chromosomes, the reason that the phenotype tends to be less severely affected is probably related to Lyonization, a normal process in which each cell only has one active X-chromosome (see below).

The contrast between the X and Y chromosomes is striking. Whereas the X chromosome is one of the larger chromosomes, with 6% of all DNA, the Y chromosome is very small. More than 1300 genes have been identified on the X chromosome; the Y chromosome has fewer than 400 genes, one of which is the testis-determining gene (SRY, also known as TDF).

**The Y Chromosome**

In humans, unlike some lower organisms, it appears that genes on the Y chromosome are the key determinants of gender phenotype. Thus, the phenotype of people who are XXY (Klinefelter syndrome; see below) is male, and those who are XO (Turner...
syndrome) are female. The testis-determining gene (SRY, sex-determining region, Y) is an intron-less gene near the end of the short arm of the Y chromosome. The SRY gene encodes a small nuclear protein with a DNA-binding domain. This protein binds another protein (SIP-1) to form a complex that is a transcriptional activator of autosomal genes that control development of a male phenotype. Mutations in this gene lead to XY females, while translocations that introduce this gene into an X chromosome produce XX males.

A small proportion of infertile men with azoospermia or severe oligospermia have small deletions in regions of the Y chromosome. However, the size and location of these deletions are variable and do not correlate with the severity of spermatogenic failure.

The X Chromosome
Males carry only one X chromosome but the same amounts of X chromosome gene products as do females. This seeming discrepancy is explained by the Lyon effect:

- In females, one X chromosome is irreversibly inactivated early in embryogenesis. The inactivated X chromosome is detectable in interphase nuclei as a heterochromatic clump of chromatin attached to the inner nuclear membrane, termed the Barr body. The inactive X chromosome is extensively methylated at gene control regions and transcriptionally repressed. Nevertheless, a significant minority of X-linked genes escape inactivation and continue to be expressed by both X chromosomes. The probability that an X chromosome is rendered inactive seems to correlate with the level of expression of another X-linked gene, XIST, which is expressed only by the inactive partner.
- Either the paternal or maternal X chromosome is inactivated randomly.
- Inactivation of the X chromosome is virtually complete.
- Inactivation of the X chromosome is permanent and transmitted to progeny cells: paternally or maternally derived X chromosomes are propagated clonally. All females are therefore mosaic for paternally and maternally derived X chromosomes. Mosaicism for glucose-6-phosphate dehydrogenase in females was important in demonstrating the monoclonal origin of neoplasms (see Chapter 5).

The issue is not quite so simple, however. If one X chromosome is entirely nonfunctional, persons with XXY (Klinefelter) or XO (Turner) karyotypes should be phenotypically normal. They are not, and the fact that they show phenotypic abnormalities indicates that the inactivated X chromosome still functions, at least in part. Indeed, a part of the short arm of the X chromosome is known to escape X-inactivation. This region, which can pair with a homologous region on the short arm of the Y chromosome and undergo meiotic recombination between the two, is known as the pseudoautosomal region. Genes in this location are present in two functional copies in both males and females. Thus patients with Turner syndrome (45,X) are haploinsufficient for these genes, and those with more than two X chromosomes (e.g., Klinefelter patients) have more than two functional copies. One gene in this region, SHOX, is associated with height, and its haploinsufficiency in Turner syndrome may explain the short stature of Turner patients. Several other genes outside the pseudoautosomal region also escape X inactivation. In both phenotypically male and female children with extra X chromosomes, the degree of mental retardation correlates roughly with the number of X chromosomes.

Klinefelter Syndrome (47,XXY)
In Klinefelter syndrome, or testicular dysgenesis, there are one or more X chromosomes beyond the normal male XY complement. This is the most important clinical condition involving trisomy of sex chromosomes (Fig. 6-13). This syndrome is a prominent cause of male hypogonadism and infertility.
PATHOLOGY: After puberty, the intrinsically abnormal testes do not respond to gonadotropin stimulation and show sequentially regressive alterations. Seminiferous tubules display atrophy, hyalinization, and peritubular fibrosis. Germ cells and Sertoli cells are usually absent and eventually the tubules become dense cords of collagen. Leydig cells are usually increased in number, but their function is impaired, as evidenced by low testosterone levels in the face of elevated luteinizing hormone (LH) levels.

CLINICAL FEATURES: The diagnosis of Klinefelter syndrome is usually made after puberty, because the main manifestations of the disorder during childhood are behavioral and psychiatric. Gross mental retardation is uncommon, although average IQ is probably somewhat reduced. Since the syndrome is so common, it should be suspected in all boys with some mental deficiency or severe behavioral problems. Children with Klinefelter syndrome tend to be tall and thin, with relatively long legs (eunuchoid body habitus). Normal testicular growth and masculinization do not occur at puberty, and testes and penis remain small. Feminine characteristics include a high-pitched voice, gynecomastia, and a female pattern of pubic hair (female escutcheon). Azoospermia results in infertility. All of these changes are due to hypogonadism and a resulting lack of androgens. Serum testosterone is low to normal, but LH and follicle-stimulating hormone are remarkably high, indicating normal pituitary function. High circulating estradiol levels increase the estradiol-to-testosterone ratio, which determines the degree of feminization. Treatment with testosterone will virilize these patients but does not restore fertility.

The XYY Male
Interest in the XYY phenotype (1 per 1000 male newborns) comes from studies in penal institutions suggesting that the prevalence of this karyotype was significantly higher than in the general population. However, the idea that these “supermales” manifest aggressive antisocial behavior because of an extra Y chromosome has not been substantiated in other studies and the topic remains controversial. The only features of the XYY phenotype that are agreed on are tall stature, a tendency toward cystic acne, and some problems in motor and language development. Aneuploidy of the Y chromosome is a consequence of meiotic nondisjunction in the father.

Turner Syndrome
Turner syndrome refers to the spectrum of abnormalities that results from complete or partial X chromosome monosomy in a phenotypic female. It occurs in about 1 liveborn female infant in 5000. In 3/4 of cases, the single X chromosome of Turner syndrome is of maternal origin, suggesting that the meiotic error tends to be paternal. The incidence of the syndrome does not correlate with maternal age, and the risk of producing a second affected female infant is not increased. The 45,X karyotype is actually one of the most common aneuploid abnormalities in human conceptuses, but almost all are aborted spontaneously. In fact, up to 2% of abortuses show this aberration. Since patients with Turner syndrome survive normally after birth, why is the missing X chromosome lethal during fetal development? Perhaps the inactivated X chromosome in normal females (or the Y chromosome in males) protects against early demise of the embryo. It is believed that homologues of Y genes in the pseudoautosomal region of the X chromosome escape inactivation and are critical to the survival of a female conceptus.
Only about half of women with Turner syndrome lack an entire X chromosome (monosomy X). The remainder are mosaics or have structural X chromosome aberrations, such as isochromosome of the long arm, translocations, and deletions. Mosaics with a 45,X/46,XX karyotype (15%) tend to have milder phenotypic manifestations of Turner syndrome and may even be fertile. In about 5% of patients, the mosaic karyotype is 45,X/46,XY, in which case an original male zygote was subsequently modified by a mitotic nondisjunction. Such persons are at a 20% risk of developing a germ cell cancer and should have prophylactic removal of the abnormal gonads.

**Pathology and Clinical Features:** The clinical hallmark of Turner syndrome is sexual infantilism with primary amenorrhea and sterility (Fig. 6-14). In most cases, the disorder is not discovered until the absence of menarche brings the child to medical attention. Virtually all of these women are less than 5 ft (152 cm) tall. Other clinical features include a short, webbed neck (pterygium coli), low posterior hairline, wide carrying angle of the arms (cubitus valgus), broad chest with widely spaced nipples, and hyperconvex fingernails. Half of patients have anomalies on urograms, the most common being horseshoe kidney and malrotation. Many have facial abnormalities, including a small mandible, prominent ears, and epicanthal folds. Defective hearing and vision are common, and as many as 20% are noted to be mentally defective. Pigmented nevi become prominent as the patient ages. For unknown reasons, women with Turner syndrome are at a greater risk for chronic autoimmune thyroiditis and goiter.

Cardiovascular anomalies occur in almost half the patients in Turner syndrome. Coarctation of the aorta is seen in 15%, and a bicuspid aortic valve in as many as a third. Essential hypertension occurs in some patients, and dissecting aneurysm of the aorta is occasionally a cause of death.

The ovaries of women with Turner syndrome show a curious acceleration of normal aging. Ovaries of a normal female fetus initially contain 7 million oocytes each. Fewer than half of these survive to the time of birth. Relentless loss of oocytes continues, so that at menarche only about 5% (400,000) of the original remain, and at menopause a mere 0.1% have survived. Ovaries of fetuses with Turner syndrome contain oocytes at first, but they lose them rapidly, so that none remain by 2 years of age. The ovaries are converted to fibrous streaks, whereas the uterus, fallopian tubes, and vagina develop normally. It may be said that the child with Turner syndrome has undergone menopause long before reaching menarche.

Interestingly, families are known in which several women have premature menopause and show deletions of portions of the long arm of one X chromosome. Such data, together with observations of Turner syndrome, further support the concept that the genes controlling ovarian development and function in the inactivated X chromosome continue to be expressed in the normal female.

Children with Turner syndrome are treated with growth hormone and estrogens and enjoy an excellent prognosis for a normal life, albeit infertile.

**Syndromes in Females with Multiple X Chromosomes**

One extra X chromosome in a phenotypic female (i.e., a 47,XXX karyotype) is the most frequent abnormality of sex chromosomes in women, occurring at about the same rate as Klinefelter syndrome. Most of these women are of normal intelligence, although they may have some difficulty in speech, learning, and emotional responses. Minor physical anomalies are encountered, including epicanthal folds and clinodactyly (inward curvature of the fifth finger). Fertility is the rule, but incidence of congenital defects may be increased in the children of 47,XXX women.

Women with 4 and 5 X chromosomes are reported. Virtually all have been mentally retarded. They superficially resemble women with Down syndrome and do not mature sexually. Women with supernumerary X chromosomes have additional Barr bodies, indicating inactivation of all but one X chromosome. Clearly, some genes on the inactivated X chromosomes continue to be expressed.

**Single Gene Abnormalities Confer Traits That Segregate Sharply Within Families**

The classic laws of mendelian inheritance, named in honor of Gregor Mendel, are:

- A mendelian trait is determined by two copies of the same gene, called alleles, located at the same locus on two homologous chromosomes. In the case of the X and Y chromosomes in males, a trait is determined by just one allele.
- Autosomal genes refer to those located on one of the 22 autosomes.
- Sex-linked traits are encoded by loci on the X chromosome.
- A dominant phenotypic trait requires the presence of only one allele of a homologous gene pair. In other words, the dominant phenotype is present whether the allelic genes are homozygous or heterozygous.
- A recessive phenotypic trait demands that both alleles be identical, that is homozygous.
- Codominance refers to a situation in which both alleles in a heterozygous gene pair are fully expressed (e.g., the AB blood group genes).

Mendelian traits are classified as:

1. Autosomal dominant
2. Autosomal recessive
3. Sex-linked dominant
4. Sex-linked recessive.
Diseases due to sex-linked dominant genes are rare and of little practical significance.

**Mutations**

To make proteins, DNA is transcribed into RNA, which is processed into mRNA, which in turn is translated by ribosomes. Thus, a change in DNA can lead to a corresponding change in the amino acid sequence of a specific protein or interference with its synthesis.

A mutation is a stable heritable change in DNA. The consequences of mutations are highly variable. Some have no functional consequences, whereas others are lethal and cannot be transmitted from one generation to another. Between these extremes is a broad range of mutations that account for the profound genetic polymorphisms of any species. About 1 in 1000 base pairs is polymorphic in the human genome. Indeed, evolution is based on the occurrence over time of nonlethal mutations that alter the ability of a species to adapt to its environment. From the viewpoint of human disease, we focus principally on mutations that alter protein structure or function detectably. The major types of mutations encountered in the study of human genetic disorders (Fig. 6-15) are:

- **Point mutations**: Replacement of one base by another is a point mutation. If it is in the coding region (the part of the gene that is translated into a protein), a point mutation has three possible consequences.
  - In a **synonymous mutation** the new codon with the mutation still codes for the same amino acid. For example, CGA and CGC both code for arginine.
  - A **missense mutation** (three fourths of base changes in the coding region) occurs when the new codon codes for a different amino acid. In sickle cell anemia, an adenine to thymine change in the β-globin gene replaces glutamic acid (GAG) with valine (GUG).
  - A **nonsense mutation** (4%) is one in which a base substitution stops translation. A codon for an amino acid is changed to a termination codon, yielding a truncated protein. For example, UAU codes for tyrosine, but UAA is a stop codon.

- **Frameshift mutations**: Amino acids are encoded by trinucleotide sequences. If the number of nucleotides in a gene is changed by insertion or deletion, and if the number of bases added or deleted is not a multiple of 3, the reading frame of the message is changed. Then, even though the downstream sequence is the same, it will code for a different amino acid sequence and probably a termination signal. Frameshift mutations can also alter transcription, splicing or processing of mRNA.

- **Large deletions**: When a large segment of DNA is deleted, the coding region of a gene may be entirely removed, in which case the protein product is absent. On the other hand, a large deletion may result in the apposition of coding regions of nearby genes, giving rise to a fused gene that codes for a hybrid protein, one in which part or all of one protein is followed by part or all of another.

- **Expansion of unstable trinucleotide repeat sequences**: The human genome contains frequent tandem trinucleotide repeat sequences, some of which are associated with disease. The number of copies of certain repetitive trinucleotide sequences varies among individuals, representing allelic polymorphism of the genes in which they are found. In general, the number of repeats below a particular threshold does not change during mitosis or meiosis, whereas above this threshold, the number of repeats can expand or contract, expansion being far more common. A number of distinct trinucleotide expansions have been identified in human disease (Table 6-4).

**Huntington disease (HD)**: HD is an inherited neurodegenerative disease caused by expansion of a CAG repeat within the coding sequence of the gene, IT15, that codes for the protein huntingtin. In HD, the stable alleles contain 10 to 30 repeats, while persons affected by the disease have 40 to 100 repeats. CAG codes for glutamine, and abnormal expansion of the polyglutamine tract in HD confers a toxic gain-of-function to huntingtin. Although the precise mechanism by which mutant huntingtin causes selective neuronal loss is not understood, there is evidence to suggest that altered protein–protein interactions are responsible. In addition to HD, expanded CAG repeats are involved in a number of other neurodegenerative disorders (see Table 6-4).

**Fragile X syndrome**: This genetic disorder, the most common cause of inherited mental retardation (see below), is due to expansion of a CGG repeat in a noncoding region immediately adjacent to the FMR1 gene on the X chromosome. The expanded CGG repeat somehow silences the FMR1 gene by methylation of its pro-
moter. The abnormal repeat is also associated with an inducible “fragile site” on the X chromosome, which appears in cytogenetic studies as a nonstaining gap or an apparent chromosomal break.

**Myotonic dystrophy (MD):** MD, the most common form of autosomal muscular dystrophy (see Chapter 27), is caused by expansion of a CTG repeat in the 3'-untranslated region of the MD gene. Normal persons have up to 35 CTG repeats, but patients with MD may have up to 2000 repeats. The structure of the protein product of the gene, a protein kinase, is unchanged but it is suspected that other nearby genes are rendered dysfunctional.

**Friedreich ataxia (FA):** FA is an autosomal recessive degenerative disease affecting the CNS and the heart that is associated with expansion of a GAA repeat in the frataxin gene (see Chapter 28), which encodes a mitochondrial protein. Affected persons have 120 to 1700 repeats in the first intron (noncoding) of the frataxin gene.

### Functional Consequences of Mutations

A biochemical pathway represents the sequential actions of a series of enzymes, which are coded for by specific genes. A typical pathway can be represented by the conversion of a substrate (A) through intermediate metabolites (B and C) to the final product (D).

\[
A \rightarrow B \rightarrow C \rightarrow D
\]

A single gene defect can have several consequences:

- **Failure to complete a metabolic pathway:** In this situation, the end-product (D) is not formed because an enzyme that is essential for the completion of a metabolic sequence is missing:

  \[
  A \rightarrow B \rightarrow C \rightarrow D
  \]

An example of the failure to complete a metabolic pathway is **albinism**, a pigment disorder caused by a deficiency of tyrosinase. This enzyme catalyzes the conversion of tyrosine to melanin (through the intermediate formation of dihydroxyphenylalanine (DOPA)). Without tyrosinase, the end-product, melanin, is not formed, and an affected person (an “albino”) has no pigment in all organs that normally contain it, primarily the eyes and skin.

- **Accumulation of unmetabolized substrate:** The enzyme that converts the initial substrate into the first intermediary metabolite may be missing, a situation that results in excessive accumulation of the initial substrate.

  \[
  A \rightarrow B \rightarrow C \rightarrow D
  \]

In phenylketonuria, dietary phenylalanine accumulates because of an inborn deficiency of phenylalanine hydroxylase. The resulting toxic concentration of phenylalanine interferes with postnatal development of the brain and causes severe mental retardation.

- **Storage of an intermediary metabolite:** An intermediary metabolite, which is readily processed into the final product and is normally present only in minute amounts, accumulates in large quantities if the enzyme responsible for its metabolism is deficient.

  \[
  A \rightarrow B \rightarrow C \rightarrow D
  \]

This type of genetic disorder is exemplified by von Gierke disease, a glycogen storage disease that results from a deficiency of glucose-6-phosphatase. The inability to convert glucose-6-phosphate into glucose leads to its alternative conversion to glycogen.

- **Formation of an abnormal end-product:** In this situation, a mutant gene codes for an abnormal protein. Sickle cell anemia results from substitution of valine for glutamic acid in the β globin part of hemoglobin.

### Mutation Hotspots

Certain regions of the genome mutate at a much higher rate than average. The best-characterized hotspot is the dinucleotide pair CG, which is prone to undergo mutation to form TG. The reason is that methylation of cytosine in CG dinucleotides is a common occurrence that is implicated in regulating gene expression. Generally, the methylation product, 5-methylcytosine, represses gene transcription. Importantly, 5-methylcytosine can undergo spontaneous deamination to thymine (Fig. 6-16). If this occurs in a gamete, it can become a fixed, heritable trait in the offspring.

**TABLE 6–4**

<table>
<thead>
<tr>
<th>Disease</th>
<th>Location</th>
<th>Sequence</th>
<th>Normal Length</th>
<th>Premutation</th>
<th>Full Mutation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Huntington disease</td>
<td>4p16.3</td>
<td>CAG</td>
<td>10–30</td>
<td>–</td>
<td>40–100</td>
</tr>
<tr>
<td>Kennedy disease</td>
<td>Xq21</td>
<td>CAG</td>
<td>15–25</td>
<td>–</td>
<td>40–55</td>
</tr>
<tr>
<td>Spinocerebellar ataxia</td>
<td>6p23</td>
<td>CAG</td>
<td>20–35</td>
<td>–</td>
<td>45–80</td>
</tr>
<tr>
<td>Fragile X syndrome</td>
<td>Xq27.3</td>
<td>CGG</td>
<td>5–55</td>
<td>50–200</td>
<td>200–&gt;1000</td>
</tr>
<tr>
<td>Myotonic dystrophy</td>
<td>19q13</td>
<td>CTG</td>
<td>5–35</td>
<td>37–50</td>
<td>50–2000</td>
</tr>
<tr>
<td>Friedreich ataxia</td>
<td>9q13</td>
<td>GAA</td>
<td>7–30</td>
<td>–</td>
<td>120–1700</td>
</tr>
</tbody>
</table>

**FIGURE 6-16.** 5-Methylcytosine is formed from cytosine. Spontaneous deamination of 5-methylcytosine produces thymine.
Autosomal Dominant Disorders Are Expressed in Heterozygotes

A dominant disease occurs when only one defective gene (i.e., mutant allele) is present, whereas its paired allele on the homologous chromosome is normal. The salient features of autosomal dominant traits are (Fig. 6-17):

- Males and females are equally affected, since by definition, the mutant gene resides on one of the 22 autosomal chromosomes. As a consequence, there can be father-to-son transmission (which is absent in X-linked dominant disorders).
- The trait encoded by the mutant gene can be transmitted to successive generations (unless the disease interferes with reproductive capacity).
- Unaffected members of a family do not transmit the trait to their offspring. Unless the disease represents a new mutation, everyone with the disease has an affected parent.
- The proportions of normal and diseased offspring of patients with the disorder are on average equal, because most affected persons are heterozygous, whereas their normal mates do not harbor the defective gene.

New Mutations versus Inherited Mutations

As noted above, an autosomal dominant disease may result from a new mutation rather than transmission from an affected parent. Nevertheless, the offspring of persons with a new dominant mutation are at a 50% risk for the disease. The ratio of new mutations to transmitted ones among persons with dominant autosomal disorders varies with the effect of the disease on reproductive capacity. Greater impairment of reproductive capacity, means a greater proportion will be new mutations. A dominant mutation that leads to complete infertility would have to be a new mutation. If reproductive capacity is only partially impaired, the proportion of new mutations is correspondingly lower. Thus, tuberous sclerosis is an autosomal dominant condition in which mental retardation limits reproductive potential. In this disease, new mutations account for 80% of cases. If a dominant disease has little effect on reproductive activity (e.g., familial hypercholesterolemia), virtually all affected persons will have pedigrees showing classic vertical transmission of the disorder.

![Autosomal Dominant](image)

FIGURE 6-17. Autosomal dominant inheritance. Only symptomatic persons transmit the trait to the next generation, and heterozygotes are symptomatic. Both males and females are affected.

Biochemical Basis of Autosomal Dominant Disorders

There are several major mechanisms by which the presence of one mutant allele and one normal allele is responsible for clinical disease.

- When the gene product is a rate-limiting component of a complex metabolic network (e.g., a receptor or an enzyme), half of the normal amount of gene product may be insufficient to maintain the normal state. This is known as haploinsufficiency. Examples of this mechanism include β-thalassemia and familial hypercholesterolemia caused by defects in the low-density lipoprotein (LDL) uptake receptor by hepatocytes.
- In some diseases, the presence of an extra copy of an allele gives rise to a phenotype. An example of this is Charcot-Marie-Tooth disease, type IA, which is caused by duplication of the peripheral myelin protein-22 gene.
- Constitutive activation of a gene is seen in some familial cancer syndromes. For example, mutations in the RET proto-oncogene are found in families with multiple endocrine neoplasia, type 2. These cause abnormally increased activity of a tyrosine kinase that stimulates cell proliferation.
- Mutations in genes that encode structural proteins (e.g., collagens, cytoskeletal constituents) result in abnormal molecular interactions and disruption of normal morphologic patterns. Such a situation is exemplified by osteogenesis imperfecta and hereditary spherocytosis.

More than 1000 human diseases are inherited as autosomal dominant traits, although most are rare. Examples of human autosomal dominant diseases are given in Table 6-5.

<table>
<thead>
<tr>
<th>Disease</th>
<th>Frequency</th>
<th>Chromosome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Familial hypercholesterolemia</td>
<td>1/500</td>
<td>19p</td>
</tr>
<tr>
<td>von Willebrand disease</td>
<td>1/8000</td>
<td>12p</td>
</tr>
<tr>
<td>Hereditary spherocytosis (major forms)</td>
<td>1/5000</td>
<td>14.8</td>
</tr>
<tr>
<td>Hereditary elliptocytosis (all forms)</td>
<td>1/2500</td>
<td>1,1p,2q,14</td>
</tr>
<tr>
<td>Osteogenesis imperfecta (types I–IV)</td>
<td>1/10,000</td>
<td>17q,7q</td>
</tr>
<tr>
<td>Ehlers-Danlos syndrome, type III</td>
<td>1/5000</td>
<td>?</td>
</tr>
<tr>
<td>Marfan syndrome</td>
<td>1/10,000</td>
<td>15q</td>
</tr>
<tr>
<td>Neurofibromatosis type 1</td>
<td>1/3500</td>
<td>17q</td>
</tr>
<tr>
<td>Huntington chorea</td>
<td>1/15,000</td>
<td>4p</td>
</tr>
<tr>
<td>Retinoblastoma</td>
<td>1/14,000</td>
<td>13q</td>
</tr>
<tr>
<td>Wilms tumor</td>
<td>1/10,000</td>
<td>11p</td>
</tr>
<tr>
<td>Familial adenomatous polyposis</td>
<td>1/10,000</td>
<td>5q</td>
</tr>
<tr>
<td>Acute intermittent porphyria</td>
<td>1/15,000</td>
<td>11q</td>
</tr>
<tr>
<td>Hereditary amyloidosis</td>
<td>1/100,000</td>
<td>18q</td>
</tr>
<tr>
<td>Adult polycystic kidney disease</td>
<td>1/1000</td>
<td>16p</td>
</tr>
</tbody>
</table>
Heritable Diseases of Connective Tissue Are Heterogeneous and Often Inherited As Autosomal Dominant Traits

This discussion is limited to three of the most common and best-studied entities that affect connective tissue: Marfan syndrome, Ehlers-Danlos syndrome, and osteogenesis imperfecta. Even in these well-delineated disorders, clinical symptomatology often overlaps. For instance, some patients exhibit the joint dislocations typical of the Ehlers-Danlos syndrome, but other members of the same family suffer from multiple fractures characteristic of osteogenesis imperfecta. Yet others in the family, with the same genetic defect, may have no symptoms. Thus current classifications based on clinical criteria, will eventually be replaced by references to specific gene defects, as with the hemoglobinopathies.

Marfan Syndrome

Marfan syndrome is an autosomal dominant, inherited disorder of connective tissue characterized by a variety of abnormalities in many organs, including the heart, aorta, skeleton, eyes, and skin. One third of cases represent sporadic mutations. The incidence in the United States is 1 per 10,000.

PATHOGENESIS: The cause of Marfan syndrome is a missense mutation in the gene for fibrillin-1 (FBN1), on the long arm of chromosome 15 (15q21.1). Fibrillin is a family of connective tissue proteins analogous to the collagens, of which there are now about a dozen genetically distinct forms. It is widely distributed in many tissues in the form of a fiber system termed microfibrils. By electron microscopy, microfibrils are threadlike filaments that form larger fibers, which are organized into rods, sheets, and interlaced networks. Microfibrillar fibers are scaffolds for elastin deposition during embryonic development, after which they constitute part of elastic tissues. For example, the deposition of elastin on lamellae of microfibrillar fibers produces the concentric rings of elastin in the aortic wall. By use of immunofluorescent microscopy, abnormal microfibrillar fibers have been visualized in all the tissues affected in Marfan syndrome. Fibrillin-1 is a large, cysteine-rich glycoprotein that forms 10-nm microfibrils in the extracellular matrix of many tissues. Interestingly, the ciliary zonules that suspend the lens of the eye are devoid of elastin but consist almost exclusively of microfibrillar fibers (fibrillin). Dislocation of the lens is a characteristic feature of Marfan syndrome. Deficiencies in the amount and distribution of microfibrillar fibers have been visualized in the skin and fibroblast cultures of patients with Marfan syndrome, which renders the elastic fibers incompetent to resist normal stress.

PATHOLOGY AND CLINICAL FEATURES: People with Marfan syndrome are usually (but not invariably) tall, and the lower body segment (pubis-to-sole) is longer than the upper body segment. A slender habitus, which reflects a paucity of subcutaneous fat, is complemented by long, thin extremities and fingers, which accounts for the term arachnodactyly (spider fingers) (Fig. 6-18). Overall, the affected persons resemble figures in paintings by El Greco.

- Skeletal system: The skull in Marfan syndrome is characteristically long (dolichocephalic), with prominent frontal eminences. Disorders of the ribs are conspicuous and produce pectus excavatum (concave sternum) and pectus carinatum (pigeon breast). The tendons, ligaments and joint capsules are weak, a condition that leads to hyperextensibility of the joints (double-jointedness), dislocations, hernias, and kyphoscoliosis; the last is often severe.

- Cardiovascular system: The most important vascular defect is in the aorta, in which the principal lesion is a wall tunica media. Weakness of the media leads to variable dilation of the ascending aorta and a high incidence of dissecting aneurysms. The dissecting aneurysm, usually of the ascending aorta, may rupture into the pericardial cavity or make its way down the aorta and rupture into the retroperitoneal space. Dilation of the aortic ring results in aortic regurgitation, which may be severe enough to produce angina pectoris and congestive heart failure. The mitral valve may have redundant leaflets and chordae tendineae—leading to mitral valve prolapse syndrome. Cardiovascular disorders are the most common causes of death in Marfan syndrome.

Microscopic examination of the aorta reveals conspicuous fragmentation and loss of elastic fibers, accompanied by an increase in metachromatic mucopolysaccharide. Focally, the defect in the elastic tissue results in discrete pools of amorphous metachromatic material, reminiscent of that seen in Erdheim (idiopathic) cystic medial necrosis of the aorta. Smooth muscle cells are enlarged and lose their orderly circumferential arrangement.

- Eyes: Ocular changes are common in Marfan syndrome and reflect the intrinsic lesion in connective tissue. These include dislocation of the lens (ectopia lentis), severe myopia owing to elongation of the eye and retinal detachment.

Untreated men with Marfan syndrome usually die in their 30s, and untreated women often die in their 40s. However, with antihypertensive therapy and replacement of the aorta with prosthetic grafts, life expectancy approaches normal.

Ehlers-Danlos Syndromes

The Ehlers-Danlos syndromes (EDS) are rare, autosomal dominant, inherited disorders of connective tissue that feature remarkable hyperelasticity and fragility of the skin, joint hypermobility, and often a bleeding diathesis. The disorder is clinically and genetically hete-
Ehlers-Danlos syndrome VI also has major complications, including severe kyphoscoliosis, blindness from retinal hemorrhage, or rupture of the globe and death from aortic rupture. Severe periodontal disease, with loss of teeth by the third decade, characterizes EDS VIII. EDS IX features the development of bladder diverticula during childhood, with a danger of bladder rupture and skeletal deformities.

Many persons who exhibit clinical abnormalities suggesting EDS do not conform to any of the documented types of this disorder. Further genetic and biochemical characterization of such cases is likely to expand the classification of EDS.

**Osteogenesis Imperfecta**

Osteogenesis imperfecta (OI), or brittle bone disease, is a group of inherited disorders in which a generalized abnormality of connective tissue is expressed principally as fragility of bone. OI is inherited in an autosomal dominant pattern, although there are rare cases that are autosomal recessive.

**PATHOLOGY AND CLINICAL FEATURES:**

All types of EDS are characterized by soft, fragile, hyperextensible skin. Patients typically can stretch their skin many centimeters and trivial injuries can lead to serious wounds. Sutures do not hold well, so dehiscence of surgical incisions is common. Hypermobility of the joints allows unusual extension and flexion, e.g., as in the “human pretzel” and other contortionists. EDS IV is the most dangerous variety, owing to a tendency to spontaneous rupture of the large arteries, bowel, and gravid uterus. Death from such complications is common in the third and fourth decades of life.

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**PATHOGENESIS:**

The genetic defects in the 4 types of OI are heterogeneous, but all affect type I collagen synthesis. In 90% of cases, mutations in pro-α1(I) and pro-α2(I) collagen genes mostly cause substitution of other amino acids for the obligate glycine at every third residue.
normalities. Those who are born alive usually die of respiratory failure within the first month of life.

Type III OI is the progressively deforming variant, which is ordinarily detected at birth by the presence of short stature and deformities caused by fractures in utero. Dental defects and hearing loss are common. Unlike other types of OI, type III is often inherited as an autosomal recessive trait.

Type IV OI is similar to type I, except that sclerae are normal and the phenotype is more variable.

Osteogenesis imperfecta is discussed in further detail in Chapter 26.

**Neurofibromatosis**

The neurofibromatoses include two distinct autosomal dominant disorders characterized by the development of multiple neurofibromas, which are benign tumors of peripheral nerves of Schwann cell origin.

*Neurofibromatosis Type I (von Recklinghausen Disease)*

*Neurofibromatosis type I* (NF1) is characterized by (1) disfiguring neurofibromas, (2) areas of dark pigmentation of the skin (café au lait spots), and (3) pigmented lesions of the iris (Lisch nodules). It is one of the more common autosomal dominant disorders, affecting 1 in 3500 persons of all races. The NF1 gene has an unusually high rate of mutation and half of cases are sporadic rather than familial. NF1 was first described in 1882 by von Recklinghausen, but references to this disorder can be found as early as the 13th century.

**PATHOGENESIS:** Germline mutations in the NF1 gene, on the long arm of chromosome 17 (17q11.2), include deletions, missense mutations, and nonsense mutations. The gene product, neurofibromin, belongs to a family of GTPase-activating protein (GAP), which inactivate the ras protein (see Chapter 5). In this sense, NF1 is a classic tumor suppressor. The loss of GAP activity permits uncontrolled ras activation, which presumably predisposes to formation of neurofibromas.

**PATHOLOGY AND CLINICAL FEATURES:** The clinical manifestations of NF1 are highly variable and difficult to explain entirely on the basis of a single gene defect. The typical features of NF1 include:

- **Neurofibromas:** More than 90% of patients with NF1 develop cutaneous and subcutaneous neurofibromas in late childhood or adolescence. These cutaneous tumors, which may total more than 500, appear as soft, pedunculated masses, usually about 1 cm in diameter (Fig. 6-19). However, on occasion they may reach alarming proportions and dominate the physical appearance of a patient, attaining 25 cm in diameter. Subcutaneous neurofibromas present as soft nodules along the course of peripheral nerves. **Plexiform neurofibromas** occur only within the context of NF1 and are diagnostic of that condition. These tumors usually involve the larger peripheral nerves but on occasion may arise from cranial or intraspinal nerves. Plexiform neurofibromas are often large, infiltrative tumors that cause severe disfigurement of the face or an extremity. The microscopic appearance of neurofibromas is discussed in Chapter 28. A major complication of NF1, occurring in 3% to 5% of patients, is the appearance of a neurofibrosarcoma in a neurofibroma, usually a larger one of the plexiform type. NF1 is also associated with an increased incidence of other neurogenic tumors, including meningioma, optic glioma and pheochromocytoma.

- **Café au lait spots:** Although normal persons may exhibit occasional light brown patches on the skin, more than 95% of persons affected by NF1 display six or more such lesions. These are over 5 mm before puberty and greater than 1.5 cm thereafter. Café au lait spots tend to be ovoid, with the longer axis oriented in the direction of a cutaneous nerve. Numerous freckles, particularly in the axilla, are also common.

- **Lisch nodules:** Over 90% of patients with NF1 have pigmented nodules of the iris, which are masses of melanocytes. These lesions are thought to be hamartomas.

- **Skeletal lesions:** A number of bone lesions occur frequently in NF1. These include malformations of the sphenoid bone and thinning of the cortex of the long bones, with bowing and pseudarthrosis of the tibia, bone cysts, and scoliosis.

- **Mental status:** Mild intellectual impairment is frequent in patients with NF1, but severe retardation is not part of the syndrome.

- **Leukemia:** The risk of malignant myeloid disorders in children with NF1 is 200 to 500 times the normal risk. In some patients, both alleles of the NF1 gene are inactivated in leukemic cells.

*Neurofibromatosis Type II (Central Neurofibromatosis)*

*Neurofibromatosis type II* (NF2) refers to a syndrome defined by bilateral tumors of the eighth cranial nerve (acoustic neuromas) and, commonly, by meningiomas and gliomas. The disorder is considerably less common than NF1, occurring in 1 in 50,000 persons. Most patients suffer from bilateral acoustic neuromas, but the condition can be di-
Familial Hypercholesterolemia
Familial hypercholesterolemia is an autosomal dominant disorder characterized by high levels of LDLs in the blood, and deposition of cholesterol in arteries, tendons, and skin. It is one of the most common autosomal dominant disorders, and affecting 1 in 500 adults in the United States in its heterozygous form. Only 1 person in 1 million is homozygous for the disease. Interest in this disease stems from the striking acceleration of atherosclerosis and its complications. (see Chapter 10).

**PATHOGENESIS:** Familial hypercholesterolemia results from abnormalities in the gene that codes for the cell surface receptor that removes LDL from the blood. This gene is on the short arm of chromosome 19. Over 150 different mutations of all kinds in the LDL receptor gene are known.

The LDL receptor is (1) synthesized in the endoplasmic reticulum (ER), (2) transferred to the Golgi complex, (3) transported to the cell surface, and (4) internalized by receptor-mediated endocytosis in coated pits after binding LDL. Genetic defects in each of these steps have been described:

- **Class 1:** This is the most common type of defect and leads to failure of synthesis of nascent LDL-receptor protein in the ER. Most such defects reflect large deletions in the gene (null alleles).
- **Class 2:** These mutations prevent transfer of the nascent receptor from the ER to the Golgi apparatus (transport-defective alleles). Thus, mutant receptor never appears at the cell surface.
- **Class 3:** LDL receptors of class 3 mutations are expressed on the cell surface but are defective in the ligand-binding domain (binding-defective alleles).
- **Class 4:** In this rare class of mutations, LDL binding to the receptor is normal, but the defect prevents receptor clustering in coated pits, thus blocking their internalization by endocytosis (internalization-defective alleles).
- **Class 5:** In this case, internalized LDL–receptor complexes are not discharged from the endosome, and the receptor does not recycle to the plasma membrane (recycling-defective alleles).

Hepatocytes are the main cell type expressing LDL receptor. After LDL bind the receptor, they are internalized and degraded in lysosomes, freeing cholesterol for further metabolism. Lacking LDL receptor function, high levels of LDL circulate, are taken up by tissue macrophages, and accumulate to form occlusive arterial plaques (atheromas) and papules or nodules of lipid-laden macrophages (xanthomas) (see Chapter 10).

**CLINICAL FEATURES:** Heterozygous and homozygous familial hypercholesterolemia are two distinct clinical syndromes, reflecting a clear gene-dosage effect. In heterozygotes, elevated blood cholesterol (mean, 350 mg/dL; normal, < 200 mg/dL) are seen at birth. Tendon xanthomas develop in half the patients before the age of 30, and symptoms of coronary heart disease often occur before age 40. In homozygotes, blood cholesterol content reaches astronomic levels (600 to 1200 mg/dL) and virtually all patients have tendon xanthomas and generalized atherosclerosis in childhood. Untreated homozygotes typically die of myocardial infarction before they reach 30 years of age.

**Autosomal Recessive Disorders Cause Symptoms in People who have Defective Alleles on both Homologous Chromosomes**

Most genetic metabolic diseases exhibit an autosomal recessive mode of inheritance (Fig. 6-20) (Table 6-7). The fact that recessive genes are uncommon and the need for two mutant alleles to produce...
clinical disease determine the key characteristics of autosomal recessive inheritance. Some of the salient features of such disorders are

- The more infrequent the mutant gene in the general population, the lower the chance that unrelated parents carry the trait. Rare autosomal recessive disorders often derive from consanguineous marriages.
- Both parents are usually heterozygous for the trait and are clinically normal.
- Symptoms appear on average in 1 of 4 of their offspring. Half of all offspring are heterozygous for the trait and are asymptomatic. Thus, 2/3 of unaffected offspring are heterozygous carriers.
- As in autosomal dominant disorders, autosomal recessive traits are transmitted equally to males and females.
- Symptomatology of autosomal recessive disorders is ordinarily less variable than with dominant diseases. Recessive traits therefore present more commonly in childhood, while dominant disorders may initially appear in adults.
- The variability in clinical expression of many autosomal recessive diseases is a function of the residual functionality of the affected enzyme. This variability is manifested in (1) different degrees of clinical severity, (2) age at onset, or (3) the existence of acute and chronic forms of the specific disease.

Most mutant genes responsible for autosomal recessive disorders are rare in the general population, because those homozygous for the trait tend to die before reaching reproductive age. Paradoxically, a few lethal autosomal recessive diseases are common. Sickle cell anemia may confer a biological advantage in increasing resistance of heterozygotes to malarial parasitization, and thus compensates for the loss of homozygotes. Almost all males with cystic fibrosis (CF) are sterile because of congenital bilateral absence of the vas deferens, and females have decreased fertility; any enhanced biological fitness of the heterozygote remains obscure.

New mutations for recessive diseases are difficult to identify clinically because resulting heterozygotes are asymptomatic. Nonconsanguineous mating of two such heterozygotes would occur by chance, and many generations later, if at all.

### Biochemical Basis of Autosomal Recessive Disorders

Autosomal recessive disorders are characterized by deficiencies in enzymes rather than in structural proteins. A mutation that inactivates an enzyme does not usually cause an abnormal phenotype in heterozygotes. For instance, since most cellular enzymes operate at substrate concentrations well below saturation, an enzyme deficiency is easily corrected simply by increasing the amount of substrate. Diseases caused by impaired catabolism of dietary substances (e.g., phenylketonuria, galactosemia) or cellular constituents (e.g., Tay-Sachs, Hurler) are autosomal recessive, in heterozygotes, increased substrate concentrations overcome the partial lack of enzyme. By contrast, loss of both alleles in a homozygote results in complete loss of enzyme activity, which situation cannot be corrected by such mechanisms.

### Cystic Fibrosis Is the Most Common Lethal Autosomal Recessive Disorder in the White Population

CF is characterized by (1) chronic pulmonary disease; (2) deficient exocrine pancreatic function; and (3) other complications of inspissated mucus in several organs, including the small intestine, liver, and reproductive tract. The disease results from a defective chloride channel, the cystic fibrosis transmembrane conductance regulator (CFTR).

**Epidemiology:** More than 95% of cases have been reported in whites; the disease is only exceptionally found in blacks and almost never in Asians. About 1 in 25 whites is a heterozygous carrier of the gene and the incidence of the disease is 1 in 2,500 newborns. Within the white population, the incidence of CF varies widely by geographic location. It is highest in the northern European Celtic populations such as Ireland and Scotland, and much lower among southern Europeans.

**Pathogenesis:** The CFTR gene is on the long arm of chromosome 7 (7q31.2). (see Table 6–7) It encodes a protein of 1480 amino acids that is a member of the adenosine triphosphate (ATP)-binding family of membrane transporter proteins. It is a chloride channel in most epithelia, with two membrane-spanning domains, two domains that bind ATP and an “R” domain that contains phosphorylation sites.

CFTR activity is regulated by the balance between kinase and phosphatase activities (i.e., phosphorylation and dephosphorylation). Phosphorylation of the R domain, mostly by cyclic adenosine monophosphate (cAMP)-dependent protein kinase A stimulates chloride channel activity by enhancing ATP binding. Secretion of chloride anions...
by mucus-secreting epithelial cells controls the parallel secretion of fluid and, consequently, the viscosity of the mucus. In normal mucus-secreting epithelia, cAMP activates protein kinase A, which phosphorylates the regulatory domain of CFTR and permits channel opening. The most common mutation in the white population is a deletion of 3 base pairs that deletes a phenylalanine residue (ΔF508). This mutation accounts for 70% of mutations in the white population. The next most common mutation accounts for only 2% of all mutations.

Mutations in the CFTR gene that disturb chloride channel function fall into several functional groupings (Fig. 6-21):

- **Failure of CFTR synthesis:** Mutations that result in premature termination signals interfere with synthesis of the full-length CFTR protein. As a result there is no CFTR-mediated chloride secretion in the involved epithelia.

- **Failure of CFTR transport to the plasma membrane:** Certain mutations prevent proper folding of the nascent protein, so it is then targeted for proteasomal degradation rather than for transport to the plasma membrane (see Chapter 1). The ΔF508 mutation is of this class. However, the role of the ΔF508 mutation in CF varies significantly by geography and ethnicity. In Denmark, it accounts for almost 90% of all CF cases; among Ashkenazi Jews, the figure is only 30%. An analysis of haplotypes suggested that the ΔF508 mutation originated 50,000 years ago in the Middle East, from where it progressively spread throughout the European land mass.

- **Defective ATP binding to CFTR:** Certain mutations allow CFTR proteins to reach the plasma membrane but affect ATP-binding domains, thus interfering with regulation of the channel and decreasing, but not abolishing, chloride secretion.

- **Defective chloride secretion by mutant CFTR:** Mutations in the channel pore inhibit chloride secretion. The relationship between these genotypes (more than 1000 mutations are known) and the clinical severity of CF is complicated and not always consistent. The best correlation seems to be between children with or without pancreatic insufficiency. Severe symptoms are generally found in those with pancreatic insufficiency (85% of all cases of CF), whereas milder cases are associated with preservation of pancreatic function. Class I and class II mutations are generally found among severely affected patients. By contrast, milder forms of CF feature class III and class IV mutations.

All pathologic consequences of CF can be attributed to the abnormally thick mucus, which obstructs lumina of airways, pancreatic, and biliary ducts, and the fetal intestine, and impairs airway mucociliary function. CF was once called mucoviscidosis. Normal CFTR corrects the defect in chloride secretion in cultured cells from CF patients.

**PATHOLOGY:** CF affects many organs that produce exocrine secretions.

**RESPIRATORY TRACT:** Pulmonary disease is responsible for most of the morbidity and mortality associated with CF. The earliest lesion is obstruction of bronchioles by mucus, with secondary infection and inflammation of bronchiolar walls. Recurrent cycles of obstruction and infection result in chronic bronchiolitis and bronchitis, which increase in severity as the disease progresses. Bronchial mucous glands undergo hypertrophy and hyperplasia, and airways are distended by thick and tenacious secretions. Widespread bronchiectasis becomes apparent by age 10 and often earlier. In late stages of the disease, large bronchiectatic cysts and lung abscesses are common. Secondary pulmonary hypertension may complicate the chronic bronchitis.

**PANCREAS:** Most (85%) of patients with CF have a form of chronic pancreatitis, and in long-standing cases, little or no functional exocrine pancreas remains. Inspissated secretions in the
pancreatic ducts produce secondary dilation and cystic change of the distal ducts (Fig. 6-22). Recurrent pancreatitis leads to loss of acinar cells and extensive fibrosis. At autopsy, the pancreas is often simply cystic fibroadipose tissue containing islets of Langerhans.

LIVER: Insipid mucus secretions in the intrahepatic biliary system obstruct the flow of bile in the drainage areas of the affected ducts and lead to focal secondary biliary cirrhosis, which is seen in one fourth of patients at autopsy. Microscopically, the liver shows insipid concretions in bile ducts and ductules, chronic portal inflammation and septal fibrosis. On occasion (2%-5%), the hepatic lesions are sufficiently widespread to lead to the clinical manifestations of biliary cirrhosis.

GASTROINTESTINAL TRACT: Shortly after birth, a normal newborn passes the intestinal contents that have accumulated in utero (meconium). The most important lesion of the gut in CF is small bowel obstruction in the newborn, meconium ileus, which is caused by failure to pass meconium in the immediate postpartum period. This complication occurs in 5% to 10% of newborns with CF and has been attributed to the failure of pancreatic secretions to digest meconium, possibly augmented by the greater viscosity of small bowel secretions.

REPRODUCTIVE TRACT: Almost all boys with CF have atrophy or fibrosis of the reproductive duct system, including the vas deferens, epididymis, and seminal vesicles. The pathogenesis of these lesions relates to obstruction of the lumen by insipid secretions early in life and even in utero. As a result, only 2% to 3% of males become fertile, most demonstrating an absence of spermatozoa in the semen.

Only a minority of women with CF are fertile, and many of them suffer from anovulatory cycles as a result of poor nutrition and chronic infections. Moreover, the cervical mucous plug is abnormally thick and tenacious.

CLINICAL FEATURES: The diagnosis of CF is most reliably made by detecting increased concentrations of electrolytes in the sweat and by genetic studies that demonstrate the disease-causing mutations. The decreased chloride conductance characteristic of CF results in a failure of chloride reabsorption by the cells of the sweat gland ducts and hence to the accumulation of sodium chloride in the sweat (Fig. 6-23). Children with CF have been described as “tasting salty” and may even display salt crystals on their skin after vigorous sweating.

The clinical course of CF is highly variable. At one extreme, death may result from meconium ileus in the neonatal period, whereas some patients have reportedly survived to age 50. Improved medical care and recognition of milder cases of CF have served to extend the average life span which is now about 30 years of age.

The pulmonary symptoms of CF begin with cough, which eventually becomes productive of large amounts of tenacious and purulent sputum. Episodes of infectious bronchitis and bronchopneumonia become progressively more frequent, and eventually shortness of breath develops. Respiratory failure and the cardiac complications of pulmonary hypertension (cor pulmonale) are late sequelae.

The most common organisms that infect the respiratory tract in CF are Staphylococcus and Pseudomonas species. As the disease advances, Pseudomonas may be the only organism cultured from the lung. In fact, the recovery of Pseudomonas species, particularly the mucoid variety, from the lungs of a child with chronic pulmonary disease is virtually diagnostic of CF. Infection with Burkholderia cepacia is associated with cepacia syndrome, a very severe pulmonary infection that is highly resistant to treatment with antibiotics and is commonly fatal.

The failure of pancreatic exocrine secretion leads to malabsorption of fat and protein, an effect that is reflected in bulky, foul-smelling stools (steatorrhea), nutritional deficiencies, and growth retardation.

Postural drainage of the airways, antibiotic therapy, and pancreatic enzyme supplementation are the mainstays of treatment. Molecular prenatal diagnosis of CF is now accurate in 95% of cases.

**Lysosomal Storage Diseases Are Characterized by Accumulation of Unmetabolized Normal Substrates in Lysosomes Because of Deficiencies of Specific Acid Hydrolases**

Lysosomes are membrane-bound collections of hydrolytic enzymes that are used for the controlled intracellular digestion of macromolecules. Lysosomal digestive enzymes are called “acid hydrolases” since their optimal pH is in the acidic range (pH 3.5–5.5). This environment is maintained by an ATP-dependent proton pump in the lysosomal membrane. These enzymes de-
grade virtually all types of biological macromolecules. Extracellular macromolecules that are incorporated by endocytosis or phagocytosis and intracellular constituents that are subjected to autophagy are digested in lysosomes to their basic components. End-products may be transported across the lysosomal membrane into the cytosol, where they are reused in the synthesis of new macromolecules.

Virtually all lysosomal storage diseases result from mutations in genes that encode lysosomal hydrolases. A deficiency in one of the more than 40 acid hydrolases can result in an inability to catabolize the normal macromolecular substrate of that enzyme. As a result, undigested substrate accumulates in and engorges lysosomes, expanding the lysosomal compartment of the cell. The resulting lysosomal distention is often at the expense of other critical cellular components, particularly in the brain and heart, and can lead to a failure of cell function.

Lysosomal storage diseases are classified according to the material retained within the lysosomes. Thus, when the substrates that accumulate are sphingolipids, they are sphingolipidoses. Storage of mucopolysaccharides (glycosaminoglycans) leads to the mucopolysaccharidoses. More than 30 distinct lysosomal storage diseases are known, but we restrict our discussion to the more important examples.

Sphingolipidoses are lysosomal storage diseases characterized by accumulation of lipids derived from the turnover of obsolete cell membranes. Cerebrosides, gangliosides, sphingomyelin, and sulfatides are sphingolipid components of the membranes of a variety of cells. These substances are degraded within lysosomes by complex pathways to sphingosine and fatty acids (Fig. 6-24). Deficiencies of many of the acid hydrolases that mediate specific steps in these pathways lead to accumulation of undigested intermediate substrates in the lysosomes.

**Gaucher Disease**

Gaucher disease is characterized by accumulation of glucosylceramide, primarily in macrophage lysosomes. The disorder was first described in 1882 in a doctoral thesis by Gaucher, but its familial occurrence was not recognized for some 20 years.

**PATHOGENESIS:** The abnormality in Gaucher disease is a deficiency in glucocerebrosidase, a lysosomal acid β-glucosidase. The enzyme deficiency can be traced to a variety of single base mutations in the β-glucosidase gene, on the long arm of chromosome 1 (1q21) (see Table 6-7). Each of the three clinical types of the disease (see below) exhibits heterogeneous mutations in the β-glucosidase gene, although the molecular basis for the phenotypic differences remains to be firmly established.
The glucosylceramide that accumulates in Gaucher cells of the spleen, liver, bone marrow, and lymph nodes derives principally from catabolism of senescent leukocytes. The membranes of these cells are rich in cerebrosides, and when their degradation is blocked by the deficiency of glucocerebrosidase, the intermediate metabolite, glucosylceramide, accumulates. The glucosylceramide of Gaucher cells in the brain is believed to originate from turnover of plasma membrane gangliosides of cells in the CNS.

**PATHOLOGY:** The hallmark of this disorder is the Gaucher cells, which are lipid-laden macrophages characteristically present in the red pulp of the spleen, liver sinuoids, lymph nodes, lungs, and bone marrow, although they may be found in virtually any organ. These cells are derived from resident macrophages in the respective organs, for example, Kupffer cells in the liver and alveolar macrophages in the lung. In the uncommon variants of Gaucher disease with involvement of the CNS, Gaucher cells originate from periventricular cells in Virchow-Robin spaces.

Gaucher cells are large (20–100 μm) with clear cytoplasm and eccentric nuclei (Fig. 6-25). By light microscopy, the cytoplasm has a characteristic fibrillar appearance, which has been likened to “wrinkled tissue paper” and is intensely positive with periodic acid-Schiff (PAS) stain. By electron microscopy, the storage material is found within enlarged lysosomes and appears as parallel layers of tubular structures.

**Enlargement of the spleen is virtually universal in Gaucher disease.** In the adult form of the disorder, splenomegaly may be massive, with spleen weights up to 10 kg. The cut surface of the enlarged spleen is firm and pale and often contains sharply demarcated infarcts. Microscopically, the red pulp shows nodular and diffuse infiltrates of Gaucher cells, and moderate fibrosis.

The liver is usually enlarged by Gaucher cells within sinusoids, but hepatocytes are unaffected. In severe cases, hepatic fibrosis and even cirrhosis may ensue. The extent of bone marrow involvement is variable but leads to radiological abnormalities in 50% to 75% of cases (see Chapter 26).

Gaucher cells may also be found in many other organs, including lymph nodes, lungs, endocrine glands, skin, gastrointestinal tract, and kidneys, although symptoms referable to these organs are uncommon.

When the brain is affected, Gaucher cells are present in Virchow-Robin spaces around blood vessels. In the infantile (neuronopathic) form of Gaucher disease, these cells have also been found in the parenchyma, where they may stimulate gliosis and formation of microglial nodules.

**CLINICAL FEATURES:** Gaucher disease is classified into three distinct forms, based on the age at onset and degree of neurologic involvement:

- **Type 1 (chronic non-neuronopathic):** This variant is the most common of all lysosomal storage diseases and is found principally in adult Ashkenazi Jews, among whom the incidence is 1 in 600 to 1 in 2500. The age at onset is highly variable, some cases being diagnosed in infants and others in persons 70 years old. Similarly, the severity of clinical manifestations varies widely. Most cases are diagnosed as adults and present initially as painless splenomegaly and the complications of hypersplenism (i.e., anemia, leukopenia, and thrombocytopenia). Whereas hepatomegaly is common, clinical liver disease is infrequent. Bone involvement, in the form of pain and pathologic fractures, is the leading cause of disability and may be severe enough to confine the patient to a wheelchair. The life expectancy of most persons with type 1 Gaucher disease is normal. This type of Gaucher disease is now successfully treated by intravenous administration of modified acid glucocerebrosidase, although the extremely high cost limits its use. Marrow transplantation is also effective but is little used because of the risks associated with this therapy. Prenatal diagnosis, based on β-glucosidase activity in amniotic fluid or chorionic villi or on DNA technology, is now routinely available.

- **Type 2 (acute neuronopathic):** Type 2 Gaucher disease is rare and distinctly different from type 1 in the age at onset and clinical presentation. It usually presents by age 3 months with hepatosplenomegaly and has no ethnic predilection. Within a few months, the infant shows neurologic signs, with the classic triad of trismus, strabismus, and backward flexion of the neck. Further neurologic deterioration rapidly follows, and most patients die before the age of 1 year.

- **Type 3 (subacute neuronopathic):** This form is also rare and combines features of type 1 and type 2. Neurologic deterioration presents at an older age than in type 2 and progresses more slowly.

**Tay-Sachs Disease (GM2 Gangliosidosis, Type 1)**

Tay-Sachs disease is the catastrophic infantile variant of a class of lysosomal storage diseases known as the GM2 gangliosidoses, in which this ganglioside is deposited in neurons of the CNS, owing to a failure of lysosomal degradation. The association of a “cherry-red spot” in the retina and profound mental and physical retardation was first pointed out in 1881 by Warren Tay, a British ophthalmologist. Fifteen years later, Bernard Sachs, an American neurologist, described the histologic features of the disorder and coined the term “amaurotic (blind) family idiocy.” Tay-Sachs disease is inherited as an autosomal recessive trait and is predominantly a disorder of Ashkenazi Jews, in whom the carrier rate is 1 in 30,
and the natural incidence of homozygotes is 1 in 4000 live newborns. By contrast, the incidence of Tay-Sachs disease in non-Jewish American populations is less than 1 in 100,000 live births. Screening programs for heterozygotes among Ashkenazi Jews have now reduced the disease incidence by 90%. The other GM2 gangliosidoses are exceedingly rare.

**PATHOGENESIS:** Gangliosides are glycosphingolipids consisting of a ceramide and an oligosaccharide chain that contains N-acetylneuraminic acid (see Fig. 6-24). They are present in the outer leaflet of the plasma membrane of animal cells, particularly in brain neurons.

Lysosomal catabolism of 1 of the 12 known gangliosides in the brain, namely ganglioside GM2, is through the activity of the β-hexosaminidases (A and B), which have α and β subunits and require GM2-activator protein. A deficiency in any of these components results in clinical disease.

Tay-Sachs disease (also known as hexosaminidase α-subunit deficiency) results from about 50 different mutations in the gene on chromosome 15q23-24 that codes for the α subunit of hexosaminidase A, with a resulting defect in the synthesis of this enzyme (see Table 6-7). An insertion of four nucleotides in exon 11 is the most common mutation among Ashkenazi Jews, accounting for over two thirds of the carriers, or about 2% of that population. The β subunits are synthesized normally and associate to form the dimer known as hexosaminidase B, levels of which are normal or even increased in Tay-Sachs disease.

**PATHOLOGY:** GM2 ganglioside accumulates in lysosomes of all organs in Tay-Sachs disease, but it is most prominent in brain neurons and cells of the retina. The size of the brain varies with the length of survival of the affected infant. Early cases are marked by brain atrophy, whereas the brain may be as much as doubled in weight in those who survive beyond a year. Microscopic examination reveals neurons markedly distended with storage material that stains positively for lipids. By electron microscopy, the neurons are stuffed with “membranous cytoplasmic bodies,” composed of concentric whorls of lamellar structures (Fig. 6-26). As the disease progresses, neurons are lost, and many lipid-laden macrophages are conspicuous in the cortical gray matter. Eventually, gliosis becomes prominent and myelin and axons in the white matter are lost. The pathologies of the other forms of GM2 gangliosidoses are similar to those of Tay-Sachs disease, although usually less severe.

**Sandhoff disease** is caused by a mutation in the gene for the β subunit on chromosome 5, and leads to deficiencies of both hexosaminidase A and B.

A third, rare variant is the result of a defect in the synthesis of the GM2-activator protein (chromosome 5) in the face of normal activities of the hexosaminidases.

**CLINICAL FEATURES:** Tay-Sachs disease presents between 6 and 10 months of age and is characterized by progressive weakness, hypotonia, and decreased attentiveness. Progressive motor and mental deterioration, often with generalized seizures, follow rapidly. Vision is seriously impaired. Involvement of retinal ganglion cells is detected by ophthalmoscopy as a cherry-red spot in the macula. This feature reflects the pallor of the affected cells, which enhances the prominence of blood vessels underlying the central fovea. Most children with Tay-Sachs disease die before 4 years of age.

**Niemann-Pick Disease**

Niemann-Pick disease (NPD) refers to lipidoses that are characterized by the lysosomal storage of sphingomyelin in macrophages of many organs, in hepatocytes, and in the brain. These disorders are classified into two categories, termed types A and B. Type A NPD appears in infancy and is characterized by hepatosplenomegaly and progressive neurodegeneration, with death occurring by 3 years of age. Type B NPD is more variable and features principally hepatosplenomegaly and minimal neurologic symptomatology, with survival to adulthood. A particularly high frequency of NPD is observed among Ashkenazi Jews, but the disorder is present in other ethnic groups. Among the former, the incidence of type A NPD is 1 in 40,000 and of type B 1 in 80,000, with a combined heterozygote prevalence of 1 in 100.

![FIGURE 6-26. Tay-Sachs disease.](Image) The cytoplasm of the nerve cell contains lysosomes filled with whorled membranes.
**PATHOLOGY:** The characteristic storage cell in NPD is a foam cell, that is, an enlarged (20–90 μm) macrophage in which the cytoplasm is distended by uniform vacuoles that contain sphingomyelin and cholesterol. By electron microscopy, whorls of concentrically arranged lamellar structures distend the lysosomes.

Foam cells are particularly numerous in the spleen, lymph nodes, and bone marrow but are also found in the liver, lungs, and gastrointestinal tract. The spleen is enlarged, often to massive size, and microscopically, foam cells are diffusely distributed throughout the red pulp. Lymph nodes enlarged by foam cells are seen in many locations. The hematopoietic tissues in the bone marrow may be displaced by aggregates of foam cells. The liver is enlarged by the stored sphingomyelin and cholesterol in lysosomes of both Kupffer cells and hepatocytes.

The brain is the most important organ involved in type A NPD, and neurologic damage is the usual cause of death. At autopsy, the brain is atrophic and in severe cases may be as little as half the normal weight. Neurons are distended by vacuoles containing the same stored lipids found elsewhere in the body. Advanced cases are characterized by a severe loss of neurons and sometimes by demyelination. Foam cells are noted in many locations. Half of children affected by type A disease demonstrate a cherry-red spot in the retina, similar to that seen in Tay-Sachs disease.

**CLINICAL FEATURES:** Type A NPD manifests in early infancy with conspicuous spleen and liver enlargement, and psychomotor retardation. There is a progressive loss of motor and intellectual function, and the child typically dies between the ages of 2 and 3 years. Most type B patients present in childhood with marked hepatosplenomegaly. Pulmonary infiltration with sphingomyelin-laden macrophages eventually leads to compromised respiratory function in many patients with type B disease. However, these patients have little in the way of neurological symptoms and may survive for many years.

**Mucopolysaccharidoses**

The mucopolysaccharidoses (MPS) are an assortment of lysosomal storage diseases characterized by accumulation of glycosaminoglycans (mucopolysaccharides) in many organs. All types of MPS are inherited as autosomal recessive traits, except for Hunter syndrome, which is X-linked recessive. These rare diseases are caused by deficiencies in any one of the 10 lysosomal enzymes that catabolize glycosaminoglycans (Fig. 6-27). Six abnormal phenotypes are described, each varying with the specific enzyme deficiency (Table 6-8).

**PATHOGENESIS:** Glycosaminoglycans (GAGs) are large polymers of repeating disaccharide units containing N-acetylated hexosamine and a hexose or hexuronic acid. Either disaccharide may be sulfated. The accumulated GAGs (dermatan sulfate, heparan sulfate, keratan sulfate, and chondroitin sulfates) in MPS are all derived from cleavage of proteoglycans, which are important extracellular matrix constituents. GAGs are degraded stepwise by removing sugar residues or sulfate groups. Thus, a deficiency in any one of the glycosidases or sulfatases results in the accumulation of undegraded GAGs. A special case is a deficiency of an N-acetyltransferase, which leads to deposition of heparan sulfate in Sanfilippo C disease.
**PATHOLOGY:** Although the severity and location of the lesions in MPS vary with the specific enzyme deficiency, most of these syndromes share certain common features. The undegraded GAGs tend to accumulate in connective tissue cells, mononuclear phagocytes (including Kupffer cells), endothelial cells, neurons and hepatocytes. Affected cells are swollen and clear and stains for metachromasia confirm the presence of GAGs. Electron microscopy shows numerous enlarged lysosomes containing granular or striped material.

The most important lesions involve the CNS, skeleton, and heart, although hepatosplenomegaly and corneal clouding are common.

- **The CNS initially only accumulates GAGs, but as disease advances, there is extensive loss of neurons and increasing gliosis, changes that are reflected in cortical atrophy. Communicating hydrocephalus, owing to meningeal involvement, is common.**

- **Skeletal deformities** result from CAG accumulation in chondrocytes, a process that eventually interferes with normal chondroendochondral ossification. Abnormal foci of osteoid and woven bone are common in the deformed skeleton.

- **Cardiac lesions** are often severe, with thickening and distortion of valves, chordae tendineae, and endocardium. The coronary arteries are frequently narrowed by intimal thickening caused by GAG deposits in smooth muscle cells.

- **Hepatosplenomegaly** is secondary to distention of Kupffer cells and hepatocytes in the liver and accumulation of CAG-filled macrophages in the spleen.

**TABLE 6-8 Mucopolysaccharidoses**

<table>
<thead>
<tr>
<th>Type</th>
<th>Eponym</th>
<th>Location of Gene</th>
<th>Clinical Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>I H</td>
<td>Hurler</td>
<td>4p16.3</td>
<td>Organomegaly, cardiac lesions, dysostosis multiplex, corneal clouding, death in childhood</td>
</tr>
<tr>
<td>I S</td>
<td>Scheie</td>
<td>4p16.3</td>
<td>Stiff joints, corneal clouding, normal intelligence, longevity</td>
</tr>
<tr>
<td>II</td>
<td>Hunter</td>
<td>X</td>
<td>Organomegaly, dysostosis multiplex, mental retardation, death earlier than 15 years of age</td>
</tr>
<tr>
<td>III</td>
<td>Sanfilippo</td>
<td>12q14</td>
<td>Mental retardation</td>
</tr>
<tr>
<td>IV</td>
<td>Morquio</td>
<td>16q24</td>
<td>Skeletal deformities, corneal clouding</td>
</tr>
<tr>
<td>V</td>
<td>Obsolete</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>VI</td>
<td>Maroteaux Lamy</td>
<td>5q13–14</td>
<td>Dysostosis multiplex, corneal clouding, death in second decade</td>
</tr>
<tr>
<td>VII</td>
<td>Sly</td>
<td>7q21.1–22</td>
<td>Hepatosplenomegaly, dysostosis multiplex</td>
</tr>
</tbody>
</table>

**CLINICAL FEATURES:** Hurler syndrome (MPS I H), the most severe clinical form of MPS, remains the prototype of these syndromes. The clinical features of other varieties of MPS are summarized in Table 6-8. The symptoms of Hurler syndrome are apparent between the ages of 6 months and 2 years. These children typically show skeletal deformities, enlarged livers and spleens, a characteristic facies, and joint stiffness. The combination of coarse facial features and dwarfishness is reminiscent of gargoyles that decorate Gothic cathedrals and accounts for the term gargoylism previously appended to this syndrome.

Children with Hurler syndrome suffer developmental delay, hearing loss, corneal clouding, and progressive mental deterioration. Increased intracranial pressure, due to communicating hydrocephalus, can be troublesome. Most patients die from recurrent pulmonary infections and cardiac complications before they reach 10 years.

Detection of heterozygotes is difficult, because of the overlap in enzyme activity of cultured cells with the normal population. Prenatal diagnosis is possible for all the MPS and is routine for Hurler and Hunter syndromes.

**Glycogenoses (Glycogen Storage Diseases):**

The glycogenoses are a group at least 10 distinct inherited disorders characterized by glycogen accumulation, principally in the liver, skeletal muscle, and heart. Each entity reflects a deficiency of one of the specific enzymes involved in glycogen metabolism (Fig. 6-28). With one rare exception (X-linked phosphorylase kinase deficiency), all types of glycogen storage disease are autosomal recessive traits. The glycogenoses are rare, varying in frequency from 1 in 100,000 to 1 in 1 million.

Glycogen is a large glucose polymer (20,000–30,000 glucose units per molecule), that is stored in most cells to provide a ready source of energy during the fasting state. Liver and muscle are particularly rich in glycogen, although its function is different in each organ. The liver stores glycogen not for its own use but rather for rapid supply of glucose to the blood, particularly for the benefit of the brain. By contrast, glycogen in skeletal muscle is used as a local fuel when oxygen or glucose supply falls. Glycogen is synthesized and degraded sequentially by a number of enzymes, a deficiency in any of which leads to accumulation of glycogen.

Although each of the glycogen storage diseases causes glycogen accumulation, the significant organ involvement varies with the specific enzyme defect. Some mainly affect the liver, whereas others principally cause cardiac or skeletal muscle dysfunction. Importantly, the symptoms of a glycogenosis can reflect either accumulation of glycogen itself (Pompe disease, Andersen disease) or the lack of the glucose that is normally derived from glycogen degradation (von Gierke disease, McArdle disease). We discuss only several representative examples of the known glycogenoses.

**von GIERKE DISEASE (TYPE IA GLYCOGENOSIS):** von Gierke disease is a result of a deficiency in glucose-6-phosphatase and is characterized by accumulation of glycogen in the liver. Symptoms reflect the inability of the liver to convert glycogen to glucose, a defect that results in hepatomegaly and hypoglycemia. The
disorder is usually evident in infancy or early childhood. Growth is commonly stunted, but with treatment, the prognosis for normal mental development and longevity are generally good.

**POMPE DISEASE (TYPE II GLYCOGENOSIS):** Pompe disease is a lysosomal storage disease that involves virtually all organs and results in death from heart failure before the age of 2. The juvenile and adult variants are less common and have a better prognosis. Normally, a small proportion of cytoplasmic glycogen is degraded within lysosomes after an autophagic sequence. Type II glycogenosis is caused by a deficiency in the lysosomal enzyme acid α-glucosidase (17q23), which leads to inexorable accumulation of undegraded glycogen in lysosomes of many different cells. Interestingly, patients do not suffer from hypoglycemia, because the major metabolic pathways of glycogen synthesis and degradation in the cytoplasm are intact.

**ANDERSEN DISEASE (TYPE IV GLYCOGENOSIS):** Andersen disease is a very rare condition in which an abnormal form of glycogen, termed *amylopectin*, is deposited principally in the liver but also in the heart, muscles, and nervous system. Children with type IV glycogenosis typically die between the ages of 2 and 4 years from cirrhosis of the liver. The disorder results from a deficiency in the branching enzyme (amylログラクトントランスフェラーゼ) (3p12) that creates the branch points in normal glycogen molecules. The absence of brancher enzyme leads to formation and accumulation of an insoluble and toxic form of glycogen that is normally not present in animal cells and resembles plant starch. Liver transplantation cures Andersen disease. Remarkably, the deposits of amylopectin in the heart and other extrahepatic tissues are greatly reduced following liver transplantation, although the mechanism for this effect is obscure.

**MCARDLE DISEASE (TYPE V GLYCOGENOSIS):** McAndile disease is characterized by accumulation of glycogen in skeletal muscles, due to a deficiency of muscle phosphorylase (11q13), the enzyme that releases glucose-1-phosphate from glycogen. Symptoms usually appear in adolescence or early adulthood and consist of muscle cramps and spasms during exercise and sometimes my-

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**CHAPTER 6: DEVELOPMENTAL AND GENETIC DISEASES**

**FIGURE 6-28. Sequential catabolism of glycogen and the enzymes that are deficient in various glycogenoses.** Glycogen is a long-chain branched polymer of glucose residues, which are connected by α-1,4 linkages, except at branch points, where an α-1,6 linkage is present. Phosphorylase hydrolyzes α-1,4 linkages to a point three glucose residues distal to an α-1,6-linked sugar. These three glucose residues are transferred to the chain linked by α-1,4 bonds, by the bifunctional debrancher enzyme amylo-1,6-glucosidase. Subsequently the same enzyme removes the α-1,6-linked sugar at the original branch point. This creates a linear α-1,4 chain, which is degraded by phosphorylase to glucose-1-phosphate. Following the conversion to glucose-6-phosphate, glucose is released by the action of glucose-6-phosphatase. A small proportion of glycogen is totally degraded within lysosomes by acid α-glucosidase. Red x’s-metabolic block.
ocytolysis and resulting myoglobinuria. Avoidance of exercise prevents the symptoms.

**Cystinosis**

Cystinosis is a lysosomal storage disease characterized by accumulation of crystalline cystine in lysosomes because of the absence of cystinosin, a transmembrane cystine transporter. The gene that is affected by this mutation is at chromosome 17p13. Cystinosis occurs in 1 per 100,000 to 200,000 live births. It is characterized by renal Fanconi syndrome (polydipsia, excretion of large amounts of dilute urine, dehydration, electrolyte imbalances, growth retardation, and rickets) beginning between 6 and 12 months of age. Untreated, cystinosis progresses to renal failure, often before adolescence. Abnormalities in pulmonary and brain function are common in older patients. Cystine crystals are present in almost all cells and organs. Renal transplantation can be used to treat the renal failure seen in cystinosis. The use of cysteamine to decrease lysosomal cystine greatly slows progression of the disease and has improved survival.

**Inborn Errors of Amino Acid Metabolism Manifest with Variably Severe Symptomatology**

Heritable disorders involving the metabolism of many amino acids have been described (Table 6-9). Some are lethal in early childhood; others are asymptomatic biochemical defects that have no clinical significance. Some of these are treated in chapters dealing with specific organs. Here we restrict our discussion to the examples provided by defects in the metabolism of phenylalanine and tyrosine (Fig. 6-29).

**Phenylketonuria**

Phenylketonuria (PKU, hyperphenylalaninemia) is an autosomal recessive deficiency of the hepatic enzyme phenylalanine hydroxylase. The disorder is characterized by high levels of circulating phenylalanine, leading to progressive mental deterioration in the first few years of life. The overall incidence of PKU is 1 per 10,000 in white and Asian populations, but it varies widely across different geographic areas. Its frequency is highest (1 in 5000) in Ireland and western Scotland and among Yemenite Jews.

**PATHOGENESIS:** Phenylalanine is an essential amino acid derived exclusively from the diet. It is oxidized in the liver to tyrosine by phenylalanine hydroxylase (PAH). Deficiency in PAH results in both hyperphenylalaninemia and formation of phenylketones from transamination of phenylalanine. Phenylpyruvic acid and its derivatives are excreted in the urine, but phenylalanine itself, rather than its metabolites, causes the neurologic damage central to this disease. Thus, the term hyperphenylalaninemia is actually a more appropriate designation than PKU.

A variety of point mutations in the PAH gene, on the long arm of chromosome 12 (12q22-24.1), are responsible for the deficiency in PAH in most patients of European origin. By contrast, PKU among Yemenite Jews reflects a single deletion in the PAH gene. An analysis of family histories of the Yemenite Jewish community has traced the origin of this defect to a common ancestor from Sanà, Yemen, before the 18th century. A different PAH gene deletion causes the disease in the affected Scottish population.

**FIGURE 6-29.** Diseases caused by disturbances of phenylalanine and tyrosine metabolism.
The mechanism of the neurotoxicity associated with hyperphenylalaninemia during infancy has not been precisely established, but several processes have been implicated: (1) competitive interference with amino acid transport systems in the brain, (2) inhibition of the synthesis of neurotransmitters, and (3) disturbance of other metabolic processes. These effects presumably lead to inadequate development of neurons and defective synthesis of myelin.

The lack in PAH activity is not always absolute: hyperphenylalaninemia milder than in classic PKU is described. In such cases, phenylpyruvic acid is not excreted in the urine. Patients with <1% of the normal activity of PAH generally have a PKU phenotype, whereas those with more than 5% are considered to exhibit non-PKU hyperphenylalaninemia, do not suffer neurologic damage, and develop normally. It is presumed that non-PKU hyperphenylalaninemia is caused by mutations different from those in classic PKU.

Malignant hyperphenylalaninemia occurs in a few (<5%) infants with hyperphenylalaninemia. In this condition, dietary restriction of phenylalanine does not arrest neurologic deterioration. These patients have a deficiency in tetrahydrobiopterin (BH₄), a cofactor required for hydroxylation of phenylalanine by PAH. In some instances, this defect results from a failure to regenerate BH₄ owing to an inherited lack of dihydropteridine reductase (DHPR), the enzyme that reduces dihydrobiopterin (BH₂) to the tetrahydro form (BH₄). The mutant DHPR gene is on the short arm of chromosome 4, and so is distinct from the PAH gene. Alternatively, in some cases synthesis of BH₄ is impaired. Although infants with malignant hyperphenylalaninemia are initially indistinguishable phenotypically from those with classic PKU, BH₄ deficiency also interferes with synthesis of the neurotransmitters dopamine (tyrosine hydroxylase-dependent) and serotonin (tryptophan hydroxylase-dependent). Thus, the mechanism underlying brain damage in malignant hyperphenylalaninemia likely involves more than a simple elevation in the levels of phenylalanine.

**CLINICAL FEATURES:** Phenylketonuria illustrates the interaction between “nature and nurture” in the pathogenesis of disease. The disorder is based on a genetic defect, but its expression depends on the provision of a dietary constituent. The affected infant appears normal at birth, but mental retardation is evident within a few months. By the age of 12 months, the untreated infant has lost about 50 IQ points, which means that a child with normal intelligence has been reduced to an imbecile who requires institutionalization. Infants with PKU tend to have fair skin, blond hair, and blue eyes, because PKU patients suffer some harm when phenylalanine is reintroduced into the diet. Thus, how long phenylalanine restriction should be maintained is not certain.

In developed countries, the clinical phenotype of classical PKU is now more of historical interest than of significant public health concern. About 10 million newborns worldwide are screened annually for hyperphenylalaninemia by a simple blood test, and most of the estimated 1000 new cases are promptly treated.

The success of newborn screening programs in detecting PKU, and the prompt institution of a low-phenylalanine diet allows many PKU homozygotes to live a normal life and to reproduce. Expectant mothers who are homozygous for PKU (maternal PKU) must consume a low-phenylalanine diet during pregnancy if the fetus is to avoid complications associated with maternal hyperphenylalaninemia. Infants exposed to high levels of phenylalanine in utero show microcephaly, mental and growth retardation, and cardiac anomalies. In other words, high levels of phenylalanine are teratogenic.

**Tyrosinemia**

Hereditary tyrosinemia (hepatorenal tyrosinemia, tyrosinemia type I) is a rare (1 in 100,000) autosomal recessive inborn error of tyrosine catabolism that manifests as acute liver disease in early infancy or as a more chronic disease of the liver, kidneys, and brain in children. Elevated levels of tyrosine and its metabolites are found in the blood. Both forms of the disease are caused by a deficiency of fumarylacetoacetate hydrolase (15q23-25), the last enzyme in the catabolic pathway that converts tyrosine to fumarate and acetoacetate. In the acute form there is no enzyme activity, whereas children with chronic disease have variable residual activity. Cell injury in hereditary tyrosinemia is attributed to abnormal toxic metabolites, succinylacetone, and succinylacetocatate. Acute tyrosinemia manifests in the first few months of life as hepatomegaly, edema, failure to thrive, and a cabbagelike odor. Within a few months, infants die of hepatic failure.

Chronic tyrosinemia is characterized by cirrhosis of the liver, renal tubular dysfunction (Fanconi syndrome), and neurologic abnormalities. Hepatocellular carcinoma supervenes in more than a third of patients. Most children die before the age of 10 years. Liver transplantation corrects the hepatic metabolic abnormalities and prevents the neurologic crises. Combined liver–kidney transplants have also been done to treat chronic tyrosinemia. Prenatal diagnosis is accomplished by demonstrating succinylacetone in amniotic fluid or fumarylacetocatate hydrolyase deficiency in cells obtained by amniocentesis or chorionic villus sampling.

**Alkaptonuria (Ochronosis)**

Alkaptonuria is a rare autosomal recessive deficiency of hepatic and renal homogentisic acid oxidase. It features excretion of homogentisic acid in the urine, generalized pigmentation and arthritis. The enzyme deficiency prevents catabolism of homogentisic acid, an intermediate gene product in phenylalanine and tyrosine metabolism. Alkaptonuria is of greater historical significance than of clinical importance. Studies almost a century ago by Garrod and others described the inheritance of alkaptonuria and were among the first to define the concept of hereditary inborn errors of metabolism.

Patients with alkaptonuria excrete urine that darkens rapidly on standing, due to formation of a pigment on the nonenzymatic oxidation of homogentisic acid (Fig. 6-30). In longstanding alkaptonuria, a similar pigment is deposited in numerous tissues, particularly the sclera, cartilage in many areas (ribs, larynx, trachea), tendons, and synovial membranes. Although the pigment appears bluish black on gross examination, it is brown under the
arthropathy coined by Virchow. A degenerative and frequently disabling longevity of affected persons.

volvement of many organs, alkaptonuria does not reduce the pigment deposition, but this has not been proved. Despite the in-

of alkaptonuria. It is tempting to ascribe the joint disease to the

at the surface, owing to the oxidation of homogentisic acid. After 2 hours

the left, which has been standing for 15 minutes, shows some darkening

FIGURE 6-30. Urine from a patient with alkaptonuria. The specimen on

microscope, accounting for the term ochronosis (color of ocher) coined by Virchow. A degenerative and frequently disabling arthropathy ("ochronotic arthritis") often develops after years of alkaptonuria. It is tempting to ascribe the joint disease to the pigment deposition, but this has not been proved. Despite the involvement of many organs, alkaptonuria does not reduce the longevity of affected persons.

Albinism

Albinism refers to a heterogeneous group of at least 10 inherited disorders in which absent or reduced biosynthesis of melanin causes hypopigmentation. This condition is found throughout the animal kingdom (from insects to humans). The most common type is oculocutaneous albinism (OCA), a family of closely related diseases that (with a single rare exception) represent autosomal recessive traits (see Table 6-7). OCA is characterized by a deficiency or complete absence of melanin pigment in the skin, hair follicles, and eyes. The frequency of OCA in whites is 1 per 18,000 in the United States and is 1 in 10,000 in Ireland. American blacks have the same high frequency of OCA as the Irish.

Two major forms of OCA are distinguished by the presence or absence of tyrosinase, the first enzyme in the biosynthetic pathway that converts tyrosine to melanin (see Fig. 6-29).

Tyrosinase-positive OCA is the most common type of albinism in whites and blacks. Patients typically begin life with complete albinism, but with age, a small amount of clinically detectable pigment accumulates. A defect in the P gene (15q11.2-13) prevents melanin synthesis. The P gene has been postulated to code for a tyrosine-transport protein.

Tyrosinase-negative OCA is the second most common type of albinism and is characterized by complete absence of tyrosinase (11q14-21) and melanin: melanocytes are present but contain unpigmented melanosomes. Affected people have snow-white hair, pale pink skin, blue irides, and prominent red pupils, owing to an absence of retinal pigment. They typically have severe ophthalmic problems, including photophobia, strabismus, nystagmus, and decreased visual acuity.

The skin of all types of albinos is strikingly sensitive to sunlight. Exposed skin areas require strong sunscreen lotions. These patients are at a greatly increased risk for squamous cell carcinomas of sun-exposed skin. In fact, among a group of more than 500 albinos in equatorial Africa, not one survived beyond the age of 40 years, nearly all having succumbed to cancer. Interestingly, albinos seem to have a lower than normal frequency of malignant melanoma.

An X-Linked Disorder Features an Abnormal Gene on the X Chromosome

Expression of an X-linked disorder (Fig. 6-31) is different in males and females. Females, having two X chromosomes, may be homozygous or heterozygous for a given trait. It follows that clinical expression of the trait in a female is variable, depending on whether it is dominant or recessive. By contrast, males have only one X chromosome and are said to be hemizygous for the same trait. Thus, regardless of whether the trait is dominant or recessive, it is invariably expressed in the male.

A cardinal attribute of all X-linked inheritance, is lack of transmission from father to son: a symptomatic father donates only a normal Y chromosome to his male offspring. By contrast, he always donates his abnormal X chromosome to his daughters, who are therefore obligate carriers of the trait. As a consequence, the disease classically skips a generation in the male, the female carrier transmitting it to grandsons of the original symptomatic male.

X-Linked Dominant Traits

X-linked dominance refers to expression of a trait only in the female, since the hemizygous state in the male precludes a distinction between dominant and recessive inheritance (Fig. 6-32).
The distinctive features of X-linked dominant disorders are:

- Females are affected twice as frequently as males.
- A heterozygous woman transmits the disorder to half her children, whether male or female.
- A man with a dominant X-linked disorder transmits the disease only to his daughters.
- Clinical expression of the disease tends to be less severe and more variable in heterozygous females than in hemizygous males.

Only a few X-linked dominant disorders are described, among which are familial hypophosphatemic rickets and ornithine transcarbamylase deficiency. In such diseases, variations in the phenotype of the trait in the female may be explained, at least in part, by the Lyon effect (i.e., inactivation of one X chromosome). This random inactivation results in mosaicism for the mutant allele, leading to inconstant expression of the trait.

**X-Linked Recessive Traits**

Most X-linked traits are recessive; that is, heterozygous females do not have clinical disease (Fig. 6-33). The characteristics of this mode of inheritance are:

- Sons of women who are carriers have a 50% chance of inheriting the disease; daughters are not symptomatic. However, 50% of daughters will also be carriers.
- All daughters of affected men are asymptomatic carriers, but the sons of these men do not have the trait and cannot transmit it to their children.
- Symptomatic homozygous females can result from the rare mating of an affected man and an asymptomatic, heterozygous woman. Alternatively, Lyonization may preferentially inactivate the normal X chromosome, which in extreme cases may lead to a heterozygous female expressing an X-linked recessive trait.
- The trait tends to occur in maternal uncles and in male cousins descended from the mother’s sisters.

Table 6-10 presents a list of representative X-linked recessive disorders.

**X-Linked Muscular Dystrophies (Duchenne and Becker Muscular Dystrophies)**

The muscular dystrophies are devastating muscle diseases. Most are X-linked, although a few are autosomal recessive. The X-linked muscular dystrophies are among the most frequent human genetic diseases, occurring in 1 per 3500 boys, an incidence approaching that of CF. Duchenne muscular dystrophy (DMD), the most common variant, is a fatal progressive degeneration of muscle that appears before the age of 4 years. Becker muscular dystrophy (BMD) is allelic with DMD but is less common and milder.

Muscular dystrophy is discussed in Chapter 27.

**Hemophilia A (Factor VIII Deficiency)**

Hemophilia A is an X-linked recessive disorder of blood clotting that results in spontaneous bleeding, particularly into joints, muscles, and internal organs. The disease is discussed in Chapter 20.

**Fragile X Syndrome**

Fragile X syndrome is the most common form of inherited mental retardation and is caused by expansion of a CGG repeat at the Xq27 fragile site. It is second only to Down syndrome as an identifiable cause of mental retardation. The disease affects 1 in 1250 males and 1 in 2500 females.
CLINICAL FEATURES: A male newborn with fragile X syndrome appears normal, but during childhood, typical features appear, including increased head circumference, facial coarsening, joint hyperextensibility, enlarged appetite, and macroorchidism. Some children may have autism spectrum disorders, learning disabilities, and attention deficit hyperactivity disorder (ADHD).

PATHOGENESIS: The well-known fact that more males than females are institutionalized for mental retardation was traditionally ascribed to societal factors. However, it was recognized in the early 1970s that X-linked inheritance of mental retardation accounted for most of this excess of males. Whereas fully 20% of all cases of heritable mental retardation are X-linked disorders, one-fifth of these are associated with a single genetic defect, namely, an inducible fragile site on the X chromosome (Xq27).

A fragile site represents a specific locus, or band, on a chromosome that breaks easily. It is usually detected in cytogenetic preparations as a nonstaining gap or constriction (Fig. 6-34). Importantly, under the routine conditions of preparing cells for karyotypic analysis, most fragile sites are not detected. However, when the same cells in culture are treated so as to impair DNA synthesis (e.g., with methotrexate, flouxuridine), fragile sites are revealed. At least 11, and possibly as many as 50, fragile sites occur in the genomes of most persons, both on autosomes and on the X chromosome. However, the locus at Xq27 is associated with mental retardation and other clinical findings that characterize fragile X syndrome. As discussed, the fragile site at Xq27 is a distinct kind of mutation characterized by amplification of a CGG repeat.

Within fragile X families, the probability of being affected is related to position in the pedigree; that is, later generations are more likely than earlier ones to be affected (Sherman paradox or genetic anticipation). This fact relates to progressive triplet repeat expansion. Chromosomes with more than about 52 repeats can increase the number of repeats—so-called expansion. Small expansions, which tend to be asymptomatic, can enlarge, particularly during meiosis in females, leading to larger expansions in successive generations. These are known as premutations. Expansions with more than 200 repeats are associated with mental retardation and represent full mutations. Expansion of a premutation to a full mutation during gametogenesis only occurs in females. Thus, daughters of men with premutations (carriers) are never clinically symptomatic, whereas the sisters of the transmitting males occasionally produce affected daughters. However, the daughters of carrier males always harbor the premutation. The frequency of conversion of a premutation to a full mutation in such women (i.e., the probability that their sons will have fragile X syndrome) varies with the length of the expanded tract. Premutations with more than 90 repeats are almost always converted to full mutations. As fragile X syndrome is recessive, most daughters of carrier males transmit mental retardation to 50% of their sons. These considerations explain the greater risk of the disorder in succeeding generations of fragile X families (Fig. 6-35).

FIGURE 6-34. Fragile X chromosome.

FIGURE 6-35. Inheritance pattern of fragile X syndrome. The number of copies of the trinucleotide repeat (CGG) is shown below selected members in this pedigree. Expansion occurs primarily during meiosis in females. When the number of repeats exceeds ~200, the clinical syndrome is manifested. Individuals shaded orange carry a premutation and are asymptomatic.
people die in early adulthood from complications of their vascular sufficiency, then cerebral, renal, and cardiac infarcts. Affected tissue is increasingly compromised, leading to progressive vascular involvement of Fabry disease. The functionally affected microvasculature of a tumor, angiokeratoma, is a characteristic cutaneous manifestation. Brain, heart, skin, kidneys, and other organs. A particular type of enzyme, α-galactosidase A, show promise in arresting the disease.

Fabry Disease
Fabry disease is a deficiency of lysosomal α-galactosidase A. This X-linked syndrome leads to accumulation of globotriaosylceramide and other glycosphingolipids in the endothelium of the brain, heart, skin, kidneys, and other organs. A particular type of tumor, angioendothelioma, is a characteristic cutaneous manifestation of Fabry disease. The functionally affected microvasculature is increasingly compromised, leading to progressive vascular insufficiency, then cerebral, renal, and cardiac infarcts. Affected people die in early adulthood from complications of their vascular disease. Recent treatments using recombinant α-D-galactosidase A show promise in arresting the disease.

Mitochondrial Diseases
Mitochondrial proteins are encoded by both nuclear and mitochondrial genes. Most mitochondrial respiratory chain proteins are encoded by nuclear genes, although several are products of the mitochondrial genome. A few rare, autosomal recessive (mendelian) disorders that represent defects in nuclear encoded mitochondrial proteins have been described. However, most inherited defects in mitochondrial function result from mutations in the mitochondrial genome. A few rare, autosomal recessive (mendelian) disorders that represent defects in nuclear encoded proteins have been described. However, most inherited defects in mitochondrial function result from mutations in the mitochondrial genome. A few rare, autosomal recessive (mendelian) disorders that represent defects in nuclear encoded mitochondrial proteins have been described. However, most inherited defects in mitochondrial function result from mutations in the mitochondrial genome.

Genetic Imprinting
Genetic imprinting refers to the observation that the phenotype associated with some genes differs, depending on whether the allele is inherited from the mother or the father. In the case of imprinted genes, either the maternal or paternal allele is maintained in an inactive state. This normal physiologic process results from methylation of DNA cytosine residues in regulatory elements in the imprinted allele. The nonimprinted allele provides the biological function for that locus. If the nonimprinted allele is disrupted through mutation, the imprinted allele remains inactivated: it cannot compensate for the missing function. Imprinting occurs in meiosis during gametogenesis, and the pattern of imprinting is maintained to variable degrees in different tissues. It is reset during meiosis in the next generation, so the selection of a given allele for imprinting can vary from one generation to the next.

In the extreme case, experimental embryos that obtain both sets of chromosomes exclusively from either the mother or the father never survive to term. A less severe manifestation of genetic imprinting is seen in uniparental disomy, in which both members of a single chromosome pair are inherited from the same parent. The pair of chromosomes may be copies of one parental chromosome (uniparental isodisomy) or may be the same pair found in one parent (uniparental heterodisomy). Uniparental disomy is rare, but has been implicated in unexpected patterns of inheritance of genetic traits. For instance, a child with uniparental isodisomy may manifest a recessive disease if only one parent carries the trait, as has been observed in a few cases of cystic fibrosis and hemophilia A. Loss of a chromosome from a trisomy or duplication of a chromosome in the case of a monosomy can lead to uniparental disomy. Interestingly, as many as 1% of viable pregnancies carry uniparental disomy for at least one chromosome.

Genetic imprinting is well illustrated by certain hereditary diseases whose phenotype is determined by the parental source of the mutant allele. Deletion of the 15q11-13 locus results in Prader-Willi syndrome when the affected chromosome is inherited maternally and in Angelman syndrome when it is of
paternal origin. The phenotypes of these disorders are remarkably different. Prader-Willi syndrome features hypotonia, obesity, hypogonadism, mental retardation, and a specific facies. By contrast, Angelman syndrome patients are hyperactive, display inappropriate laughter, have a facies different from that of Prader-Willi syndrome, and suffer from seizures. Prader-Willi syndrome develops because the maternal locus is imprinted (silenced), and the same region on the paternal chromosome is deleted. The converse obtains in Angelman syndrome: the paternal gene is imprinted and the maternal locus is inactivated by mutation, e.g., deletion. This pattern is similar to loss of heterozygosity in tumor-suppressor genes by aberrant methylation in some cases of cancer (see Chapter 5). The gene responsible for Angelman syndrome appears to be UBE3A. The gene(s) responsible for Prader-Willi syndrome have not been definitively identified.

Genetic imprinting is implicated in a number of other situations relevant to human disease. For example, in some childhood cancers, including Wilms tumor, osteosarcoma, bilateral retinoblastoma, and embryonal rhabdomyosarcoma, the maternal allele of a putative tumor-suppressor gene is lost and the remaining allele is on a chromosome of paternal origin. In the case of familial glomus tumor, an adult neoplasm, both males and females may carry the trait, but it is transmitted only through the male. Thus, the responsible gene is active only when it is located on the paternal autosome. Finally, as noted above, the premutation of fragile X syndrome is expanded to the full mutation only during female gametogenesis, implying that the trinucleotide repeat is treated differently on passage through the female than in the male.

### Multifactorial Inheritance

Multifactorial inheritance describes a process by which a disease results from the effects of a number of abnormal genes and environmental factors. Most normal human traits reflect such complexities, and are not inherited as simple dominant nor as recessive mendelian attributes. For example, multifactorial inheritance determines height, skin color, and body habitus. Similarly, most of the common chronic disorders of adults—diabetes, atherosclerosis, and many forms of cancer and arthritis and hypertension—represent multifactorial genetic diseases and are well known to “run in families.” The inheritance of many birth defects is also multifactorial (e.g., cleft lip and palate, pyloric stenosis, and congenital heart disease) (Table 6-11).

<table>
<thead>
<tr>
<th>TABLE 6–11</th>
<th>Representative Diseases Associated with Multifactorial Inheritance</th>
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<tbody>
<tr>
<td><strong>Adults</strong></td>
<td><strong>Children</strong></td>
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<tr>
<td>Hypertension</td>
<td>Pyloric stenosis</td>
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<tr>
<td>Atherosclerosis</td>
<td>Cleft lip and palate</td>
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<tr>
<td>Diabetes, type II</td>
<td>Congenital heart disease</td>
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<tr>
<td>Allergic diathesis</td>
<td>Meningomyelocele</td>
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<tr>
<td>Psoriasis</td>
<td>Anencephaly</td>
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<tr>
<td>Schizophrenia</td>
<td>Hypospadias</td>
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<tr>
<td>Ankylosing spondylitis</td>
<td>Congenital hip dislocation</td>
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<tr>
<td>Gout</td>
<td>Hirschprung disease</td>
</tr>
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The concept of multifactorial inheritance is based on the notion that multiple genes interact with each other and with environmental factors to produce disease in an individual patient. Such inheritance leads to familial aggregation that does not obey simple mendelian rules. Thus, inheritance of polygenic diseases is studied by population genetics, rather than by analysis of individual families.

The number of involved genes for any polygenic disease is not known. Thus, it is not possible to ascertain accurately the risk of a particular disorder in an individual case. The probability of disease can only be predicted from the numbers of relatives affected, the severity of their disease and statistical projections based on population analyses. Whereas monogenic inheritance implies a specific risk of disease (e.g., 25% or 50%), the probability of symptoms in first-degree relatives of a person affected with a polygenic disease is usually about 5% to 10%.

The biological basis of polygenic inheritance rests on the evidence that more than one fourth of all genetic loci in normal humans contain polymorphic alleles. Such genetic heterogeneity provides a background for wide variability in susceptibility to many diseases, which is compounded by the many interactions with environmental factors.

- **Expression of symptoms is proportional to the number of mutant genes.** Close relatives of an affected person have more mutant genes than the population at large and a greater chance of expressing the disease. The probability of expressing the same number of mutant genes is highest in identical twins.
- **Environmental factors influence expression of the trait.** Thus, concordance for the disease may occur in only one third of monozygotic twins.
- **The risk in first-degree relatives (parents, siblings, children) is the same (5%–10%).** The probability of disease is much lower in second-degree relatives.
- **The probability of a trait’s expression in later offspring is influenced by its expression in earlier siblings.** If one or more children are born with a multifactorial defect, the chance of its recurrence in later offspring is doubled. For simple mendelian traits, in contrast, the probability is independent of the number of affected siblings.
- **The more severe a defect, the greater the risk of transmitting it to offspring.** Patients with more-severe polygenic defects presumably have more mutant genes and their children thus have a greater chance of inheriting the abnormal genes than the offspring of less severely affected persons.
- **Some abnormalities characterized by multifactorial inheritance show a sex predilection.** For example, pyloric stenosis is more common in males, while congenital dislocation of the hip is more common in females. Such differential susceptibility is believed to represent a difference in the threshold for expression of mutant genes in the two sexes. For example, if the number of mutant genes required for pyloric stenosis in males is A, it may require 4A in the female. Then, a woman who had pyloric stenosis as an infant has more mutant genes to transmit to her children than does a similarly afflicted man. Indeed, the son of such a woman actually has a 25% chance of being born with pyloric stenosis, compared with a 4% risk for the son of an affected man. As a general rule, if there is an altered sex ratio in the incidence of a polygenic defect, a member of the less commonly affected sex has a much greater probability of transmitting the defect.
by national professional organizations for several years. This will not have this disease.

available in some centers to ensure that an implanted embryo utilization combined with preimplantation genetic diagnosis is available. In vitro fertilization combined with preimplantation genetic diagnosis to determine the genetic status of the fetus. In vitro fertilization with each pregnancy. These couples can be offered prenatal diagnosis to identify couples in which both members are heterozygous carriers. The objective is to include in a so-called “Ashkenazi screen.” The objective is to identify couples in which both members are heterozygous carriers and who thus have a 25% risk of having an affected offspring with each pregnancy. These couples can be offered prenatal diagnosis to determine the genetic status of the fetus. In vitro fertilization combined with preimplantation genetic diagnosis is available in some centers to ensure that an implanted embryo will not have this disease.

Prenatal screening for carriers of CF has been recommended by national professional organizations for several years. This represents the first large-scale adoption of testing for carriers of genetic diseases. Guidelines recommend that screening for CF be offered to all white and Ashkenazi Jewish women because of the relatively high frequency of CF in these groups. A panel of 25 CF mutations has been chosen for this DNA-based testing. If a woman is a carrier of a CF mutation, then her partner should be tested to see if the couple is at risk of having an affected offspring. Because of the distribution of CF mutations, the recommended panel will detect only about 80% of known CF mutations in whites, but over 97% among Ashkenazi Jews. Among other ethnic groups, detection rates are lower.

Prenatal Diagnosis of Genetic Disorders

Amniocentesis and chorionic villus biopsy are the most important methods for diagnosis of a developmental or genetic disorder. Both procedures are safe, reliable, and easily performed. The indications for chorionic villus biopsy or amniocentesis are:

- Age 35 years old and over: The risk of having a child with Down syndrome is about 1 in 300 for a 40-year-old woman, compared with 1 in 1200 at age 25. The risk rises even higher with advanced maternal age.
- Previous chromosomal abnormality: The overall risk of recurrence of Down syndrome in a succeeding child of a woman who has already borne an infant with trisomy 21 is 1%.
- Translocation carrier: Estimates of risks to the offspring of translocation carriers vary from 3% to 15%. Carriers of balanced translocations are at increased risk for producing children with unbalanced karyotypes and resulting phenotypic abnormalities.
- History of familial inborn error of metabolism: Recessive inborn errors of metabolism have a 25% risk for each child if each parent is heterozygous for the trait. Prenatal diagnosis can identify disorders for which a biochemical diagnosis can be made.
- Identified heterozygotes: Carrier detection programs, such as Tay-Sachs Disease Prevention Program, identify couples in which both spouses are carriers of the same recessive gene. Each pregnancy in such couples has a 25% risk of an affected child and prenatal diagnosis can be made routinely.
- Family history of X-linked disorders: Fetal sex determination, using amniotic cells, can be offered to women known to be carriers of X-linked disorders. The diagnosis of some of these conditions can be established biochemically by amniotic fluid analysis.

New molecular techniques for carrier detection and early prenatal diagnosis are of ever-increasing utility. Gene-specific DNA probes have been developed for many genetic diseases, including hemophilia A and B, the hemoglobinopathies, phenylketonuria, and α1-antitrypsin deficiency. Most heterozygous carriers for Duchenne and Becker muscular dystrophies, Huntington chorea, and CF can be identified by such techniques.

Diseases of Infancy and Childhood

The period from birth to puberty has been traditionally subdivided into several stages.

- Neonatal age (the first 4 weeks)
- Infancy (the first year)
• Early childhood (1 to 4 years)
• Late childhood (5 to 14 years)

Each of these periods has its own distinct anatomical, physiologic, and immunologic characteristics, which determine the nature and form of various pathologic processes. Morbidity and mortality rates in the neonatal period differ considerably from those in infancy and childhood. Infants and children are not simply “small adults,” and they may be afflicted by diseases unique to their particular age group.

Prematurity and Intrauterine Growth Retardation

Human pregnancy normally lasts 40 ± 2 weeks, and most newborns weigh 3300 ± 600 g. The World Health Organization defines prematurity as a gestational age of less than 37 weeks (timed from the first day of the last menstrual period). Traditionally prematurity was defined as a birth weight below 2500 g, regardless of gestational age. However, it is now appreciated that full-term infants may weigh under 2500 g because of intrauterine growth retardation rather than prematurity. Thus, low-birth-weight infants (<2500 g) are termed (1) appropriate for gestational age (AGA) or (2) small for gestational age (SGA).

In the United States, the frequency of low-birth-weight infants is less than 6% among whites. Two thirds of these infants are premature (AGA). By contrast, when the frequency of low-birth-weight infants exceeds 10%, as it does for blacks (>12%), most of these newborns suffer from intrauterine growth retardation and are considered SGA.

About 1% of all infants born in the United States weigh less than 1500 g and are classified as very-low-birth-weight infants. Such babies account for half of neonatal deaths, and their survival is determined by their birth weight. If premature newborns are cared for in neonatal intensive care units, 90% of infants over 750 g survive. Between 500 g and 750 g, 45% survive, of whom more than half develop normally.

• Etiology: The factors that predispose to premature birth of an infant (AGA) are (1) maternal illness, (2) uterine incompetence, (3) fetal disorders, and (4) placental abnormalities. When the life of a fetus is threatened by such conditions, it may be necessary to induce premature delivery to save the infant. In a substantial proportion of AGA infants, the cause of premature birth is unknown. Intrauterine growth retardation and the resulting birth of SGA infants are associated with disorders that (1) impair maternal health and nutrition, (2) interfere with placental circulation or function, or (3) disturb the growth or development of the fetus.

CLINICAL FEATURES: There is a substantial overlap between the complications of prematurity itself (AGA) and intrauterine growth retardation (SGA). However, certain general principles apply. Prematurity is often associated with severe respiratory distress, metabolic disturbances (e.g., hyperbilirubinemia, hypoglycemia, hypocalcemia), circulatory problems (anemia, hypothermia, hypotension), and bacterial sepsis. By contrast, SGA infants are a much more heterogeneous group, including many infants with congenital anomalies and infections acquired in utero. Even when these causes of intrauterine growth retardation are excluded, neonatal complications in SGA infants reflect gestational age more than birth weight. In addition to the many problems associated with prematurity, SGA infants often suffer from perinatal asphyxias, meconium aspiration, necrotizing enterocolitis, pulmonary hemorrhage, and disorders related to birth defects or inherited metabolic diseases.

Organ Immaturity is a Cause of Neonatal Problems

The maturity of the newborn can be defined in both anatomic and physiologic terms. Maturing organs in infants born prematurely differ from those in term infants, although complete maturation of many organs may require days (lungs) to years (brain) after birth.

LUNGS: Pulmonary immaturity is a common and immediate threat to the viability of low-birth-weight infants. The lining cells of the fetal alveoli do not differentiate into type I and type II pneumocytes until late in pregnancy. Amniotic fluid fills the fetal alveoli and drains from the lungs at birth. Sometimes immature infants show sluggish respiratory movement that does not fully expel the amniotic fluid from the lungs. Respiratory embarrassment may ensue, a syndrome called amniotic fluid aspiration, but that actually represents retained amniotic fluid. Air passages contain desquamated squamous cells (squames) and lanugo hair from the fetal skin and protein-rich amniotic fluid (Fig. 6-37).

The ability of the alveoli to remain expanded during the respiratory cycle, i.e., not to collapse when the individual exhales, is largely due to pulmonary surfactant, which reduces intraalveolar surface tension. Surfactant is produced by type II pneumocytes, and is a complex mixture of several phospholipids, 75% phosphatidylcholine (lecithin), and 10% phosphatidylglycerol. The

![FIGURE 6-37. Retention of amniotic fluid in the lung of a premature newborn. The incompletely expanded lung contains squames (arrows), consisting of squamous epithelial cells shed into the amniotic fluid from the fetal skin.](image-url)
The pathogenesis of RDS of the newborn is intimately linked to a deficiency of surfactant (Fig. 6-39). When a newborn starts breathing, type II cells release their surfactant stores. The biophysical role of surfactant is to reduce surface tension, i.e., to decrease the affinity of alveolar surfaces for each other. This allows alveoli to remain open when the baby exhales and reduces resistance to reinflating the lungs with the second breath. If surfactant function is inadequate, as it is in many premature infants with immature lungs, alveoli collapse when the baby exhales and resist expansion when the child tries to take its second breath. The energy required for the second breath must then overcome the cell-cell affinity within the alveoli and inspiration therefore requires considerable effort and damages the alveolar lining. The injured alveoli leak plasma into airspaces. Plasma constituents, including fibrinogen and albumin, bind surfactant and impair its function, thus further exacerbating the respiratory insufficiency. Many alveoli are perfused with blood, but not ventilated by air, which leads to hypoxia and acidosis and further compromise in the ability of type II pneumocytes to produce surfactant. Moreover, hypoxia produces pulmonary arterial vasoconstriction, thereby increasing right-to-left shunting through the ductus arteriosus and foramen

**TABLE 6–12**

<table>
<thead>
<tr>
<th>Apgar Score*</th>
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<tr>
<td>Sign</td>
</tr>
<tr>
<td>Heart rate</td>
</tr>
<tr>
<td>Respiratory effort</td>
</tr>
<tr>
<td>Muscle tone</td>
</tr>
<tr>
<td>Response to catheter in nostril</td>
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*Sixty seconds after the completion of birth, these five objective signs are evaluated, and each is given a score of 0, 1, or 2. A maximum score of 10 is assigned to infants in the best possible condition.

Neonatal Respiratory Distress Syndrome (RDS) is due to Deficiency of Surfactant

Neonatal RDS is the leading cause of morbidity and mortality among premature infants. It accounts for half of all neonatal deaths in the United States. Its incidence varies inversely with gestational age and birth weight. Thus, more than half of newborns younger than 28 weeks gestational age have RDS, whereas only one fifth of infants between 32 and 36 weeks do. In addition to prematurity, other risk factors for RDS include (1) neonatal asphyxia, (2) maternal diabetes, (3) delivery by cesarean section, (4) precipitous delivery, and (5) twin pregnancies.

### Neonatal Respiratory Distress Syndrome (RDS)

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### The Apgar Score

Clinical assessments of neonatal maturity in general are usually performed 1 minute and 5 minutes after delivery, and certain parameters are scored according to the criteria recommended by Virginia Apgar (Table 6-12). In general, the higher the Apgar score, the better the clinical condition of the infant. The score taken at 1 minute is an index of asphyxia and of the need for assisted ventilation. The 5-minute score is a more accurate indication of impending death or the likelihood of persistent neurologic damage. For example, in newborns weighing less than 2000 g who have a 5-minute Apgar score of 9 or 10, the mortality during the first month is less than 5%; it is almost 80% when the Apgar score is reduced to 3 or less.

![FIGURE 6-38. Changes in amniotic fluid composition during pregnancy.](image)
PATHOLOGY: On gross examination, the lungs are dark red and airless. Alveoli are collapsed. Alveolar ducts and respiratory bronchioles are dilated and contain cellular debris, proteinaceous edema fluid and erythrocytes. The alveolar ducts are lined by conspicuous, eosinophilic, fibrin-rich, amorphous structures, called hyaline membranes, hence the original term for neonatal RDS, hyaline membrane disease (Fig. 6-40). Walls of collapsed alveoli are thick, capillaries are congested and lymphatics are filled with proteinaceous material.

CLINICAL FEATURES: Most newborns destined to develop RDS appear normal at birth and have high Apgar scores. The first symptom, usually appearing within an hour of birth, is increased respiratory effort, with forceful intercostal retraction and the use of accessory neck muscles. Respiratory rate increases to more than 100 breaths per minute, and the baby becomes cyanotic. Chest radiographs show a characteristic “ground-glass” granularity and in terminal stages the fluid-filled alveoli appear as complete “white out” of the lungs. In severe cases, the infant becomes progressively obtunded and flaccid. Long periods of apnea ensue and the infant
eventually dies of asphyxia. Despite advances in neonatal intensive care, the overall mortality of RDS is about 15%, and one third of infants born before 30 weeks of gestational age die of this disorder. In milder cases, the disorder peaks within 3 days, after which gradual improvement takes place.

The major complications of RDS relate to anoxia and acidosis and include:

- **Intraventricular cerebral hemorrhage**: The periventricular germinal matrix in the newborn brain is particularly vulnerable to hemorrhage because the dilated, thin-walled veins in this area rupture easily (Fig. 6-41). The pathogenesis of this complication is not fully understood but is believed to reflect anoxic injury to the periventricular capillaries, venous sludging and thrombosis and impaired vascular autoregulation.

- **Persistent patent ductus arteriosus**: In almost 1/3 of newborns who survive RDS, the ductus arteriosus remains patent. With recovery from the pulmonary disease, pulmonary arterial pressure declines, and the higher pressure in the aorta reverses the direction of blood flow in the ductus, thereby creating a persistent left-to-right shunt. Congestive heart failure may ensue and necessitate correction of the patent ductus.

- **Necrotizing enterocolitis**: This intestinal complication of RDS is the most common acquired gastrointestinal emergency in newborns. It is thought to be related to ischemia of the intestinal mucosa, which leads to bacterial colonization, usually with *Clostridium difficile*. The lesions vary from those of typical pseudomembranous enterocolitis to gangrene and perforation of the bowel.

- **Bronchopulmonary dysplasia (BPD)**: BPD is a late complication of RDS usually in infants who weigh less than 1500 g and were maintained on a positive-pressure respirator with high oxygen tensions. It is thought that the disorder results from oxygen toxicity superimposed on RDS. In such patients, respiratory distress persists after the third or fourth day and is reflected in hypoxia, acidosis, oxygen dependency, and the onset of right-sided heart failure. Radiographs of the lungs show a change from almost complete opacification to a spongiform appearance, with small lucent areas alternating with denser foci. The bronchiolar epithelium is hyperplastic, with squamous metaplasia in the bronchi and bronchioles. There are atelectasis, interstitial edema, and thickening of alveolar basement membranes. BPD is a chronic disease; affected infants may continue to require oxygen supplementation into their second or third years of life. Some studies also suggest that a degree of respiratory impairment may persist, even into adolescence and beyond.

Advances in treatment of neonatal RDS have dramatically improved the prognosis for preterm infants. Antenatal glucocorticoids are often administered to women experiencing preterm labor to accelerate pulmonary maturation. Surfactant preparations, the most effective of which are derived from natural surfactants, have greatly increased survival. Improvements in ventilatory support have, as well, been instrumental in the improved survival of these infants.

**Erythroblastosis Fetalis Is a Hemolytic Disease Caused by Maternal Antibodies Against Fetal Erythrocytes**

The disorder was first recognized by Hippocrates but was not fully understood until 1940, when the Rh (Rhesus) antigen on erythrocytes was identified. More than 60 antigens on red blood cell membranes can elicit antibody responses, but only antibodies against Rh D antigen and the ABO system cause a significant incidence of hemolytic disease.

**Rh Incompatibility**

The distribution of Rh antigens among ethnic groups varies. In American whites, 15% are Rh-negative (Rh D−), whereas only 8% of blacks are Rh D−. Japanese, Chinese, and Native American Indian populations contain essentially no Rh D− persons. By contrast, in the Basque population, among whom the mutation that causes the Rh D− phenotype may have arisen, the prevalence of Rh D− persons is 35%.

**PATHOGENESIS**: The Rh blood group system consists of some 25 components, of which only the alleles cde/CDE need be considered in this discussion. Among infants with erythroblastosis fetalis caused by Rh incompatibility, 90% are due to antibodies against D, the remaining cases involving C or E. Rh-positive fetal erythrocytes (>1 mL) enter the circulation of an Rh-negative mother at the time of delivery, eliciting antibodies in her to the D antigen (Fig. 6-42). Because the quantity of fetal blood necessary to sensitize the mother is introduced into her circulation only at the time of delivery, erythroblastosis fetalis does not ordinarily affect the first baby. However, when a sensitized mother again carries an Rh-positive fetus, much smaller quantities of fetal D antigen elicit an increase in antibody titer. In contrast to IgM, IgG antibodies are small enough to cross the placenta and thus produce hemolysis in the fetus. This cycle is exaggerated in multiparous women and the severity of erythroblastosis tends to increase progressively with each succeeding pregnancy.
FIGURE 6-42. Pathogenesis of erythroblastosis fetalis due to maternal–fetal Rh incompatibility. Immunization of the Rh-negative mother with Rh-positive erythrocytes in the first pregnancy leads to the formation of anti-Rh antibodies of the immunoglobulin (Ig)G type. These antibodies cross the placenta and damage the Rh-positive fetus in subsequent pregnancies.

Since 15% of white women are Rh D−, and since they have an 85% chance of marrying an Rh D+ man, 13% of all marriages are theoretically at risk for maternal–fetal Rh incompatibility. The actual incidence of erythroblastosis fetalis is, however, much lower. This apparent discrepancy is explained by several factors: (1) More than half of Rh-positive men are heterozygous (D/d), and thus only half of their offspring express the D antigen. (2) Only half of all pregnancies have large enough fetal-to-maternal transfusions to sensitize the mother. (3) Even in those Rh-negative women who are exposed to significant amounts of fetal Rh-positive blood, many do not mount a substantial immune response. Even after multiple pregnancies, only 5% of Rh-negative women are ever delivered of infants with erythroblastosis fetalis.
• **Hydrops fetalis** occurs in the most extreme form of the disease, in which case severe maceration is evident on delivery. Numerous erythroblasts are demonstrable in visceral organs that are not extensively autolyzed.

• **Kernicterus,** also termed bilirubin encephalopathy, is defined as a neurologic condition associated with severe jaundice and characterized by bile staining of the brain, particularly of the basal ganglia, pontine nuclei, and dentate nuclei in the cerebellum. Although brain damage in jaundiced newborns was first mentioned in the 13th century, the association of kernicterus with high levels of unconjugated bilirubin was not appreciated until 1952. Kernicterus (from the German, Kern, nucleus) is essentially confined to newborns with severe unconjugated hyperbilirubinemia, usually related to erythroblastosis. The bilirubin derived from the destruction of erythrocytes and the catabolism of the released heme is not easily conjugated by the immature liver, which is deficient in glucuronyl transferase.

The development of kernicterus is directly related to the level of unconjugated bilirubin and is rare in term infants when serum bilirubin levels are below 20 mg/dL. Premature infants are more vulnerable to hyperbilirubinemia and may develop kernicterus at levels as low as 12 mg/dL. Bilirubin is thought to injure the cells of the brain by interfering with mitochondrial function. Severe kernicterus leads initially to loss of the startle reflex and athetoid movements, which in 75% progresses to lethargy and death. Most surviving infants have severe choreoathetosis and mental retardation; a minority have varying degrees of intellectual and motor retardation.

**PREVENTION AND TREATMENT:** Exchange transfusions may keep the maximum serum bilirubin at an acceptable level. However, phototherapy, which converts the toxic unconjugated bilirubin into isomers that are nontoxic and excreted in the urine, has greatly reduced the need for exchange transfusions. The incidence of erythroblastosis fetalis secondary to Rh incompatibility has been greatly reduced (to <1% of women at risk) by the use of human anti-D globulin (RhGAM) within 72 hours of delivery. The quantity of RhGAM administered to the mother suffices to neutralize 10 mL of antigenic fetal cells that may have entered the maternal circulation during delivery.

**ABO Incompatibility**

The availability of RhGAM for Rh-negative mothers has drastically decreased the incidence of Rh-incompatible erythroblastosis. Today ABO incompatibility is the main cause of hemolytic disease of the newborn. Although 25% of pregnancies result in ABO incompatibility between mother and offspring, hemolytic disease develops in only 10% of such children, usually infants with blood type A. The low antigenicity of the ABO factors in the fetus accounts for the mildness of ABO hemolytic disease. Natural anti-A and anti-B antibodies are IgM, which does not cross the placenta. However, certain incomplete antibodies to A antigen may be IgG, which does cross the placenta, so ABO isoimmune disease may be seen in firstborn infants. However, most cases of hemolytic anemia from ABO incompatibility are seen after a previous incompatible pregnancy.

Most infants with ABO incompatibility have mild disease, jaundice being the only clinical feature. The complications of erythroblastosis associated with Rh incompatibility are unusual with ABO disease. Nevertheless, kernicterus has occasionally been reported.

**Birth Injury Spans the Spectrum from Mechanical Trauma to Anoxic Damage**

Some birth injuries relate to poor obstetric manipulation, whereas many are unavoidable sequela of routine delivery. Birth injuries occur in about 5 per 1000 live births. Factors that predispose to birth injury include cephalopelvic disproportion, dystocia (difficult labor), prematurity, and breech presentation.

**Cranial Injury**

• **Caput succedaneum** refers to edema of the scalp caused by trauma to the head incurred during the passage through the birth canal. The swelling rapidly disappears and is more a source of parental anxiety than of clinical concern.

• **Cephalohematoma** is defined as a subperiosteal hemorrhage that is confined to a single cranial bone and becomes apparent within the first few hours after birth. It may or may not be associated with a linear fracture of the underlying bone.
Most cephalohematomas resolve without complication and require no treatment.

- **Skull fractures** during birth result from the impact of the head on the pelvic bones or pressure from obstetric forceps. Linear fractures, the most common variety, are asymptomatic and do not require any treatment. Depressed fractures are usually caused by trauma from forceps. Although many depressed fractures do not initially produce symptoms, they usually require mechanical elevation because of the risk of underlying cranial trauma from persistent pressure. In contrast to most fractures, those of the occipital bone often extend through the underlying venous sinuses and produce fatal hemorrhage.

- **Intracranial hemorrhage** is one of the most dangerous birth injuries and may be traumatic, secondary to asphyxia, or a result of an underlying bleeding diathesis. Traumatic intracranial hemorrhage occurs in the setting of (1) significant cephalopelvic disproportion, (2) precipitous delivery, (3) breech presentation, (4) prolonged labor, or (5) the inappropriate use of forceps. These traumas can result in **subdural or subarachnoid hemorrhage**, which are commonly secondary to lacerations of the falx cerebi or tentorium cerebelli that involve the vein of Galen or the venous sinuses. As noted above, anoxic injury from asphyxia, particularly in the premature infant, is often associated with intraventricular hemorrhage.

The prognosis for newborns with intracranial hemorrhage depends on its extent. Massive hemorrhage is often rapidly fatal. A surviving infant may recover completely or may have long-term impairment, usually in the form of cerebral palsy or hydrocephalus. However, many cases of cerebral palsy have been shown by ultrasound studies to relate to brain damage acquired 2 weeks or more prior to birth rather than from birth trauma.

**Peripheral Nerve Injury**

Brachial palsy, with varying degrees of paralysis of the upper extremity, is caused by excessive traction on the head and neck or shoulders during delivery. The injury may be permanent if the nerves are severed. Function may return within a few months if the palsy results from edema and hemorrhage.

**Phrenic nerve paralysis** and associated paralysis of a hemidiaphragm may be associated with brachial palsy and result in breathing difficulties. The condition generally resolves spontaneously within a few months.

**Facial nerve palsy** usually presents as a unilateral flaccid paralysis of the face caused by injury to the seventh cranial nerve during labor or delivery, especially with forceps. When severe, the entire affected side of the face is paralyzed and even the eyelid cannot be closed. The prognosis again depends on whether the nerve was lacerated or simply injured by pressure.

**Fractures**

The clavicle is more vulnerable to fracture during delivery than any other bone and may be associated with fracture of the *humerus*. Immobilization of the arm and shoulder usually provides for complete healing. Fractures of other long bones and the nose occasionally occur during birth but heal easily.

**Rupture of the Liver**

The only internal organ other than the brain that is injured with any frequency during labor and delivery is the liver. This organ is injured by mechanical pressure during difficult or premature births. Rupture of the liver may lead to the formation of a hematoma large enough to cause a palpable abdominal mass and anemia; surgical repair of the laceration may be required.

### Sudden Infant Death Syndrome Does Not Have a Known Cause

The sudden infant death syndrome (SIDS), also known as “crib death,” is defined as “the sudden death of an infant or young child which is unexpected by history and in which a thorough postmortem examination fails to demonstrate an adequate cause of death.” Although the diagnosis of SIDS is arrived at solely by excluding other specific causes of sudden death, this catastrophe is nevertheless considered a distinct clinicopathologic entity. SIDS actually was first described in the American colonies in 1686, but modern attention to the disorder dates only a few decades.

Typically, the victim of SIDS is an apparently healthy young infant who has been asleep without any hint of impending calamity. Clinically, the infant does not awaken from an otherwise normal sleep period. Postmortem examination does not identify a cause of death, such as pneumonia, food aspiration, sepsis, or cerebral hemorrhage. This tragic sequence has aroused great public concern, because it must be separated from homicide, which has been demonstrated in a number of cases to be the true cause of mysterious death in children.

**EPIDEMIOLOGY:** After the neonatal period, SIDS is the leading cause of death in the first year of life, accounting for more than one third of all deaths in this period. Incidence in the United States is 2 per 1000 live births. Most (90%) cases occur before 6 months of age. Most deaths from SIDS are during the winter months, but no association between particular respiratory infections and infant death has been established. Most deaths occur at night or during periods associated with sleep. The reported death rates for SIDS have declined dramatically. This has been attributed to “Back to Sleep” campaigns that encourage parents to place infants on their backs for sleeping.

The risk factors for SIDS have been difficult to ascertain and are based principally on retrospective studies. The strongest **maternal risk factors** appear to be:

- Low socioeconomic status (poor education, unmarried mother, poor prenatal care)
- Black race
- Age younger than 20 years at first pregnancy
- Cigarette smoking during and following pregnancy
- Use of illicit drugs during pregnancy
- Increased parity

The **risk factors for the infant** are controversial. The consensus includes:

- Low birth weight
- Prematurity
- An illness, often gastrointestinal, within the last 2 weeks before death
- Subsequent siblings of SIDS victims
- Survivors of an apparent life-threatening event, defined as an episode characterized by some combination of apnea, color change, marked alteration in muscle tone, and choking or
PATHOLOGY: At autopsy, several morphologic alterations are described in victims of SIDS, but their relevance to the etiology and pathogenesis of this disorder remains unclear. Chronic hypoxia brainstem gliosis, medial hypertrophy of small pulmonary arteries, persistence of extramedullary hematopoiesis in the liver, retention of periadrenal brown fat, and right ventricular hypertrophy may suggest a degree of chronic hypoxia. However, except for brainstem gliosis, none of these changes occurs with any regularity. Petechiae on the surfaces of the lungs, heart, pleura, and thymus, which have been reported in most infants dying of SIDS, are probably terminal events and have been attributed to negative intrathoracic pressure produced by respiratory efforts.

Neoplasms of Infancy and Childhood

Malignant tumors between the ages of 1 and 15 years are distinctly uncommon, but cancer remains the leading cause of death from disease in this age group. In children, 10% of all deaths are due to malignancies, and only accidental trauma kills a larger number. Unlike adults, in whom most cancers are of epithelial origin (e.g., carcinomas of the lung, breast, and gastrointestinal tract), most malignant tumors in children arise from hematopoietic, nervous, and soft tissues (Fig. 6-44). Another feature that distinguishes childhood tumors from those of adults is the fact that many of the former are part of developmental complexes. Examples include Wilms tumor associated with aniridia, genitourinary malformations, and mental retardation (WAGR complex);
Physiology of the body associated with Wilms tumor, hepatoblastoma, and adrenal carcinoma; and tuberous sclerosis in association with renal tumors and rhabdomyomas of the heart. Some neoplasms are apparent at birth and are obviously developmental tumors that have evolved in utero. In addition, abnormally developed organs, persistent organ primordia, and displaced organ rests are all vulnerable to neoplastic transformation.

The individual cancers of childhood, including disorders such as the leukemias, neuroblastoma, Wilms tumor, various sarcomas, and germ cell neoplasms, are discussed in detail in the chapters dealing with the respective organs. The basic principles of neoplasia and carcinogenesis, including those applicable to pediatric cancers, are discussed in Chapter 5.

Benign Tumors and Tumorlike Conditions Encompass a Wide Range of Abnormalities

HAMARTOMAS: These lesions represent focal, benign overgrowths of one or more of the mature cellular elements of a normal tissue, often with one element predominating. Although the cells of a hamartoma are often arranged in a highly irregular fashion, the distinction between this developmental abnormality and a true benign neoplasm is often conjectural.

CHORISTOMAS: Also called heterotopias, choristomas are similar to hamartomas but are minute or microscopic aggregates of normal tissue components in aberrant locations. Choristomas are represented by rests of pancreatic tissue in the wall of the gastrointestinal tract or of adrenal tissue in the renal cortex.

HEMANGIOMAS: These lesions, of varying size and in diverse locations, are the most frequently encountered tumors in childhood. Whether hemangiomas are true neoplasms or hamartomas is unclear, although half are present at birth and most regress with age. Large, rapidly growing hemangiomas occasionally can be serious lesions, especially when they occur on the head or neck. A port wine stain is a congenital capillary hemangioma that involves the skin of the face and scalp and is often large enough to be disfiguring, imparting a dark purple color to the affected area. Unlike many small hemangiomas, they persist for life and are not easily treated.

LYMPHANGIOMAS: Also termed cystic hygromas, lymphangiomas are poorly demarcated swellings that are usually present at birth and thereafter rapidly increase in size. Most lymphangiomas occur on the head and neck, but the floor of the mouth, mediastinum, and buttocks are not uncommon sites. The classification of these tumors is imprecise; some researchers consider them developmental malformations or hamartomas and others call them neoplasms. Lymphangiomas appear as unilocular or multilocular cysts with thin, transparent walls and straw-colored fluid. Microscopically, myriad dilated lymphatic channels are separated by fibrous septa. Unlike hemangiomas, these lesions do not regress spontaneously and should be resected.

SACROCOCCYGEAL TERATOMAS: Although rare, these germ cell neoplasms are the most common solid tumors in the newborn, with an incidence of 1 in 40,000 live births. At least 75% of sacrococcygeal teratomas occur in girls, and a substantial number have been encountered in twins. The tumors are usually noticed at birth as a mass in the region of the sacrum and buttocks. They are commonly large, lobulated masses, often as large as the infant’s head. One half of tumors grow externally and may be connected to the body by a small stalk. Some have both external and intrapelvic components, whereas a few grow entirely in the pelvis. Microscopically, sacrococcygeal teratomas are composed of numerous tissues, particularly of neural origin. Most (90%) sacrococcygeal teratomas detected before the age of 2 months are benign, but up to half of those diagnosed later in life are malignant. Associated congenital anomalies of the vertebral, genitourinary system and anorectum are common. The lesion should be resected promptly.

Cancers in the Pediatric Age Group Are Uncommon

The incidence of childhood malignancies is 1.3 per 10,000 per year in children under the age of 15 years. The mortality clearly varies with the intrinsic behavior of the tumor and the response to therapy, but as an overall figure, the death rate for childhood cancer is only about one-third the incidence. Almost half of all malignant diseases in patients under 15 years of age are acute leukemias and lymphomas. Leukemias alone, particularly acute lymphoblastic leukemia, account for one third of all cases of childhood cancer. Most of the other malignant neoplasms are neuroblastomas, brain tumors, Wilms tumors, retinoblastomas, bone cancers, and various soft tissue sarcomas.

The genetic influences in the development of childhood tumors have been particularly well studied in the case of retinoblastoma, Wilms tumor and osteosarcoma. The issues relating to the interaction of inherited mutations and environmental influences in the pathogenesis of malignant tumors in both children and adults are discussed in Chapter 5.