This chapter is divided into three sections. Section 1 focuses on fetal defects. Section 2 discusses strictly inherited diseases and familial genetic disease tendencies, while Section 3 focuses on the distinctiveness of diseases of infancy and childhood.

**Section 1: Developmental Abnormalities**

- Embryologic Development
- Congenital Malformations
- Congenital Deformations

**Section 2: Genetic Disorders**

- Mutations
- The broad influence of genetics in disease
  - Disease caused by defective autosomal dominant genes
  - Disease caused by defective autosomal recessive genes
  - Disease caused by defective genes on sex chromosomes
  - Clinical expression of single-gene defects
  - Cytogenetic diseases
- Disease associated with abnormal numbers of sex chromosomes

**Section 3: Pediatric Diseases**

- Perinatal and neonatal disease
  - Intrauterine growth restriction
  - Prematurity
  - Birth injury
  - Fetal and newborn infections
  - Sudden infant death syndrome (SIDS)
  - Hemolytic disease of the newborn (erythroblastosis fetalis)
  - Cystic fibrosis
  - Tumors and tumor-like conditions in children

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**Learning Objectives**

After studying this chapter you should be able to:

1. Distinguish between congenital deformation and malformation, and give an example of each
2. Define teratogen, and give an example of a chemical and an infectious teratogen
3. Distinguish among cytogenetic disease, single-gene (Mendelian or monogenic) disease, and disease resulting from multiple genes (polygenic), and give examples of each
4. Explain the difference between autosomal dominant and recessive genetic behavior
5. Explain how inheritance of genetic defects on the X chromosome is different from gene defects on autosomes
6. Offer several examples of disease caused by single-gene defects
7. Explain how cytogenetic disease differs from other genetic disease, and give an example of a cytogenetic disease
8. Explain the genetic abnormality in Turner syndrome
9. Define prematurity, and briefly discuss the associated risks
10. Explain the difference between prematurity and small for gestational age (SGA)
11. Explain the Apgar score and its usefulness
12. Name the most common category of intrauterine growth restriction, and offer some examples
13. Name the most common type of perinatal infection of the newborn; name and briefly discuss a few common pediatric infections
Section 1: Developmental Abnormalities

• congenital

CONGENITAL MALFORMATIONS
• congenital malformation

CONGENITAL DEFORMATIONS
• congenital deformation

Section 2: Genetic Disorders

• germ cell
• somatic cell
• autosome
• sex chromosome
• monogenic
• cytogenetic

MUTATIONS
• mutation

THE BROAD INFLUENCE OF GENETICS IN DISEASE
• polygenic

DISORDERS OF SINGLE GENES (MONOGENIC DISORDERS)
• allele
• homozygous

• heterozygous
• dominant
• recessive
• Mendelian

CHROMOSOMAL ABNORMALITIES (CYTOGENETIC DISEASES)
• cytogenetic
• karyotype
• Down syndrome
• meiosis

GENETIC DIAGNOSIS
• amniocentesis

Section 3: Pediatric Diseases

PERINATAL AND NEONATAL DISEASE
• premature
• gestational age
• small for gestational age
• intrauterine growth restriction
• respiratory distress syndrome

HEMOLYTIC DISEASE OF THE NEWBORN
• hemolytic disease of the newborn

“Find out the cause of this effect,
Or rather say, the cause of this defect,
For this effect defective comes by cause”
WILLIAM SHAKESPEARE (1564–1616), ENGLISH PLAYWRIGHT, HAMLET (II.i)

Congenital means “present at birth,” although a congenital defect may not reveal itself for many years. Congenital malformations are conditions stemming from intrinsically abnormal embryologic development, which are usually genetic defects. Congenital deformations, on the other hand, are caused by extra-fetal (maternal) mechanical factors that distort the fetus.

MAJOR DETERMINANTS OF DISEASE
• Most congenital defects result from faulty development of the embryo.
• The fetus is especially vulnerable to injury during weeks 3–9 of embryologic development, when fetal organs are forming.
• Some congenital disease results from an inherited genetic defect and may not be apparent at birth.
About 3% of newborns have significant cosmetic or functional defects, and the figure is higher if minor abnormalities are included. Each year about 250,000 infants are born with a serious birth defect; the cause is unknown in most. Chromosome abnormalities account for a minority of newborn birth defects; however, studies reveal that about half of spontaneously aborted fetuses have chromosome abnormalities, indicating that most inborn chromosome defects are lethal. In developed nations, congenital defects are responsible for about half of newborn and childhood deaths; by contrast, in underdeveloped nations, infectious diseases, malnutrition, and other environmental factors are responsible for the great majority of newborn and childhood deaths.

### Embryologic Development

Understanding developmental abnormalities requires understanding the basics of embryologic and fetal development.

The combination of ovum and sperm creates a single-cell conceptus (fertilized ovum), which within a few days divides first into two, then four, then eight primordial cells that are not programmed to develop into a particular tissue or organ. Loss of one of these primitive cells does not cause adverse consequences; however, as more divisions occur, cells differentiate (specialize) and are programmed to develop into particular tissues or organs, such as brain or heart. Loss or damage to cells at this stage can result in spontaneous abortion (Chapter 21) or de-

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**Figure 7-1 Critical stages of embryo development.** Important congenital malformations are most likely to occur in early pregnancy (weeks 3–9), when organs are first developing. Maternal exposures to microbes, usually virus infection, and chemical abuse (drugs and alcohol) are the most common identifiable causes. Serious exposures before or near the time of endometrial implantation usually lead to spontaneous abortion. Exposures to infections, toxins, and other forces have less effect after the 9th week.
developmental abnormality. As is illustrated in Figure 7-1, beginning about two weeks after conception the embryo begins a period of *organogenesis*, during which time it is susceptible to injury that can result in fetal *malformation*.

The embryo forms first as a hollow sphere that grows, stretches, and folds into a series of chambers (the heart and the cerebral ventricles, for example) and tubes (the intestines, bronchi, gland ducts, and spinal canal, for example). Many of these spaces begin originally as grooves, which become tubes as the groove rims grow over and join to form an enclosed space. Some of these spaces do not lead to development of an adult structure but may persist as a congenital malformation. For those spaces that lead to an adult structure, a congenital malformation occurs if the space fails to close normally. Some organs form by dividing from one another, and malformations occur if separation does not occur. Finally, tissues or organs may fail to develop; that is, they may fail to appear or may develop incompletely. Some examples are:

- **Failure of space to close properly.** The vertebral column is a bony tube containing the meninges and spinal cord. If the embryonic neural tube fails to close, the bony vertebral arch remains open posteriorly, usually in the lower back, and the result is *spina bifida* (Fig. 7-2) and related conditions (Chapter 23). Occult spina bifida, or spina bifida occulta (Fig. 7-2B), is common and innocuous. However, in more severe defects (Figure 7-2C, D, and E), the meninges or spinal cord protrude through the defect in the spinal column and are associated with infection and neurologic defects, especially paralysis in the legs and loss of bowel and bladder control. In the severest form of spina bifida, the brain and entire spinal cord fail to form, a condition known as *anencephaly*.

![Figure 7-2 Neural tube defects](image-url)

*Figure 7-2 Neural tube defects.* Cross-section studies of spine. **A.** Normal vertebra and spinal cord. **B.** In occult (minimal) spina bifida (spina bifida occulta) the posterior vertebral arch fails to form. It is usually asymptomatic. **C.** In spina bifida with meningocele, the meninges protrude through the defect. **D.** In spina bifida with myelomeningocele, the meninges and spinal cord protrude through the defect. **E.** In anencephaly, almost all of the brain and spinal cord fail to form.
Adding folic acid supplement to the maternal diet sharply reduces the number of these defects.

- Failure of tissue to divide. Fingers and toes must divide from one another; if division is erroneous, digits may be fused (syndactyly) or may be too numerous (polydactyly).
- Failure of an embryologic structure to disappear normally. The thyroid gland is formed by cells budding from a temporary embryonic duct that arises from the base of the tongue (the thyroglossal duct). If the duct fails to involute normally, it may accumulate fluid to form a thyroglossal duct cyst.
- Failure of tissue or organ to differentiate or grow (agenesis): The drug thalidomide, a sedative no longer prescribed for pregnant women, prevents normal limb development in children of mothers taking the drug.

There are many other congenital malformations in other organs, some of which are discussed below.

**Congenital Malformations**

Congenital malformations are associated with flawed embryologic development. The cause of most congenital malformations is unknown, but it is clear that good nutrition and prenatal care significantly reduce the number of malformed fetuses. Some congenital malformations result from genetic defects (DNA mutations); others from environmental factors. The most common congenital malformations are listed below (approximate birth incidence is in parentheses):

- Hypospadias (~1:300), an abnormal opening of the urethra on the ventral surface of the penis
- Patent ductus arteriosus (~1:600), a persistent open connection between the pulmonary artery and the aorta, which normally closes at birth
- Ventricular septal defect (~1:900), an opening between the left and right ventricles of the heart
- Cleft lip (~1:1,100), a malformation of the upper lip that features a slit extending from the margin of the lip up to the base of the nose
- Spina bifida (~1:2,100), an opening in the posterior (dorsal) arch of one or more of the spinal vertebrae, through which meninges or spinal cord structures may protrude
- Anencephaly (1:3,200), a failure of the brain to develop
- Atrial septal defect (1:5,900), an opening between the right and left atria of the heart, which should close shortly after birth

Deformed fetuses are said to be teratoid (from Greek *teras*, for monster). A **teratogen** is an agent, such as a chemical or virus, capable of inducing congenital fetal malformation. Teratogens include infectious agents, drugs, chemicals, and ionizing radiation. That ionizing radiation can damage fetal or ovarian DNA and induce birth defects became clear as defects soared in the aftermath of the atomic bomb explosions in Hiroshima and Nagasaki, Japan, which ended World War II. There are many chemical teratogens but the most important is alcohol.

Alcohol abuse in pregnancy accounts for the **fetal alcohol syndrome**, consisting of intrauterine fetal growth restriction, central nervous system abnormalities, and distinctive facial characteristics. The full-blown syndrome occurs in about 1 in 1,000 live births in the general population, usually to a mother who is a chronic alcoholic. However, a more common result is less severe maternal alcohol abuse that causes mild childhood mental deficiency and emotional problems.

The most common infectious teratogens are the so-called **TORCH** teratogens:

- Toxoplasmosis
- Rubella
- Cytomegalovirus
- Herpesvirus

Infection occurs in 1–5% of live-born infants in the United States. The greatest damage results if infection occurs during weeks 3–9, the critical period of gestation.

**THE CLINICAL SIDE**

**PREVENTING BIRTH DEFECTS**

The cause of most birth defects is unknown, but birth defects are associated with smoking, alcohol or other drug abuse, poor nutrition, poorly controlled diabetes, and a wide variety of other maternal factors. Pregnant women should not smoke, use drugs, or take any medication without supervision. Alcohol should be avoided. Diabetes, if present, should be tightly controlled.

Because folic acid is important for normal embryologic development in the first few weeks after conception, there is universal agreement that women of childbearing age should take daily multivitamin containing folate before becoming pregnant. Despite dramatic benefit, only about 25% of women do so. Daily consumption of the usual amount of folate (folic acid) in most multivitamin tablets reduces by about 60% the number of infants born with neural tube defects such as spina bifida. In the United States, certain basic food products (enriched flour, for example) have supplemental folic acid added.
when fetal organs are formed. Infection before three weeks induces abortion; later infections produce milder disturbances, including mental impairment. TORCH infections are usually not distinguishable from one another and produce a set of signs and symptoms (the TORCH syndrome). Affected infants exhibit some, but not all, of the following characteristics, which are illustrated in Figure 7-3: microcephaly (small skull), mental retardation, brain calcifications, microphthalmia (small eyeballs), cataracts (opacified lenses), chorioretinitis (inflammation of the retina and iris) and conjunctivitis, congenital heart defects, pneumonia, hepatitis and jaundice, splenomegaly (enlarged spleen), and skin hemorrhages.

Infection by cytomegalovirus or herpesvirus may produce severe fetal damage even as late as the third trimester. Congenital rubella infection can be prevented by maternal vaccination. A vaccine for herpes is gaining acceptance, but there are no vaccines for other TORCH infections.

**Congenital Deformations**

Congenital deformations are caused by maternal mechanical factors that distort the fetus. The two most common deformations are listed below. Approximate birth incidence is in parentheses.

- Clubfoot (−1:400), a twisting inward or outward of the foot so that the sole is not flat to the ground
- Hip dislocation (−1:1,100), a failure of the head of the femur to rest in its socket in the pelvis

Deformations usually arise in the 35th–38th weeks of pregnancy, when the growth of the fetus exceeds the growth of the uterus, filling it to the point that there is not enough amniotic fluid surrounding the fetus to provide cushioning and room for movement. Maternal factors include a malformed uterus owing to large leiomyomas (benign tumors of the uterine wall, Chapter 21), the crowding of multiple pregnancy, and oligohydramnios (decreased amniotic fluid).

**Figure 7-3** TORCH infections. Fetuses infected in the first trimester by Toxoplasma, rubella, cytomegalovirus, herpesvirus, or other microbes have similar clinical findings as those illustrated in this figure.
Insanity is hereditary; you get it from your children.  
SAM LEVENSON (1911-1980), AMERICAN COMEDIAN

Genetic disease, or genetic tendency to develop disease, is transmitted from parent to child by genes in the germ cells of ova or sperm.

Genetically, the normal body has two types of cells: germ cells in the ovary and testis, which produce ova and sperm, and somatic cells, which form all other tissues and organs. Germ cells and somatic cells contain identical sets of chromosomes, but chromosomes in somatic cells are not capable of transmitting genetic defects. For example, smoking damages genes in lung (somatic) cells to cause lung cancer, but the cancer is not transmissible to offspring because it occurs in somatic cells; germ cells are unaffected. Autosomes are those chromosomes that are not sex chromosomes. Sex chromosomes are specialized chromosomes that determine sex, but they also influence other characteristics.

There are two types of sex chromosomes, X and Y. Males have one X and one Y; females have two X chromosomes. Normal somatic and germ cells contain 44 autosomes plus two sex chromosomes (either X and Y, or two Xs). The shorthand notation for normal males is 46,XY; normal females are designated 46,XX. The genetic makeup of a person is called the genotype; the physical traits produced by the genotype are called the phenotype. For example, XX is the genotype for the female phenotype. The relationships and differences between germ and somatic cells and their chromosomes are explained in greater detail later in this chapter in the box titled Basics in Brief 7-1. Figure 7-4 illustrates a normal karyotype.

Figure 7-4 A set of normal chromosomes (karyotype). There are 46 total chromosomes, of which 44 are autosomes (pairs 1-22 in the figure; non-sex chromosomes) and two are sex chromosomes (pair 23 in the figure; two X chromosomes for a female, or one X and one Y for a male). The shorthand for a female is 46,XX and for a male, 46,XY. In each pair one is from the male (blue) and one is from the female (pink parent). Genes are short segments of DNA and are located either on the short (p) arm of the chromosome above the waist or the long (q) arm below it.
set of chromosomes displayed in a manner called a **karyotype**, a photographic display of chromosomes.

All disease is either genetic or environmental or a combination of the two:

- **Genetic** disease is transmitted to a subsequent generation only by genetic defects (mutations) in germ cells, not by genetic defects in somatic cells. Germ cell genetic defects cause **familial** (hereditary) disease.
- On the other hand, some diseases are almost purely **environmental**. Lung cancers, for example, are tumors of somatic cells acquired by inhaling cigarette smoke. The genes in lung cancer cells typically have many genetic and chromosomal abnormalities, but they are not transmissible because the patient's germ cells are not affected.
- Some diseases are a **mixture** of environmental effect and genetic influence. Type 2 (adult onset diabetes, Chapter 17), for example, is associated with obesity (an environmental influence) and a strong familial (hereditary) tendency.

In people with normal **numbers** of chromosomes, traits or diseases that occur because of defects in a **single gene** are called **monogenic** (Table 7-1). Analysis of DNA has led to the identification of thousands of diseases caused by single-gene defects, each of which is characterized by specific and predictable abnormalities. Sickle cell disease and red-green color blindness are examples. **Polygenic** genetic diseases are those conditions associated with the influence of multiple genes.

A third category of genetic disorder is **cytogenetic disease**, caused by extra or absent **whole chromosomes**, or large-scale structural dislocations of chromosome parts, such as pieces of one chromosome that become attached to another. Most cytogenetic disorders occur

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**Table 7-1  Types and Examples of Genetic Disease**

<table>
<thead>
<tr>
<th>Type of Genetic Defect</th>
<th>Chromosomal Abnormality</th>
<th>Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Polygenic</td>
<td>Multiple genes affected; identity unknown</td>
<td>Type II diabetes</td>
</tr>
<tr>
<td>Monogenic (single-gene defect)</td>
<td>Mutation in gene 19 at locus p13</td>
<td>Familial hypercholesterolemia</td>
</tr>
<tr>
<td>Cytogenetic</td>
<td>Extra chromosome 21</td>
<td>Down syndrome</td>
</tr>
</tbody>
</table>

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**HISTORY OF MEDICINE**

**AN ACORN WITH A PURPOSE**

The great Greek thinker Aristotle (384–322 BC) reasoned that oak trees spring from acorns because the acorn contains a “plan” or a “purpose,” that is to say, something within that was meant to be fulfilled, which we now know is DNA. The unraveling of this mystery took two millennia.

That living things were composed of cells was discovered by Englishman Robert Hooke in 1665, as he studied the microscopic structure of the bark of cork trees. Nearly two hundred years passed before another Englishman, Charles Darwin, published *Origin of the Species* in 1859 and opened an era of intense scientific investigation of biologic phenomena. In 1866 Scotsman Robert Brown, of “Brownian motion” fame to legions of high school science students, was studying the microscopic anatomy of orchids when he noticed that every cell contained a nucleus. Shortly thereafter German medical researcher Friedrich Meischer discovered that nuclei contained a new molecule, which he called nuclein. Other investigators discovered that nuclein (DNA) was composed of four simple chemicals, but the scientific establishment resisted the idea that such simple molecules could be responsible for all of life’s complexities.

Then in the 1920s English bacteriologist Fred Griffith discovered that bacteria contained a mysterious substance that could carry behavior from one bacterium to another, and in the 1940s American scientist Oswald Avery discovered that the substance was DNA.

In the early 1950s English scientist Rosalind Franklin discovered that DNA had a corkscrew structure. At the same time, two other English scientists, James Watson and Francis Crick, were trying to build physical models of DNA but could not find one that explained the experimental data. They learned of Franklin’s corkscrew idea and took a critical conceptual step, theorizing that DNA was composed of two *intertwined* corkscrews. The structure they built perfectly explained the experimental data and was widely adopted. Watson and Crick were awarded the Nobel Prize in 1962, by which time Rosalind Franklin had died. Inasmuch as the Nobel Prize can be awarded only to living recipients, Franklin was not honored, a sore point to her many supporters.
spontaneously in the fertilization process. Because they are not related to defective chromosomes in germ cells, they are not inheritable. For example, Klinefelter syndrome, discussed later in this chapter, is caused by an extra X chromosome: the patient, who would otherwise be a normal male (XY), has an extra X, and his genotype is XXY.

**Mutations**

A *mutation* is a permanent change in DNA. The DNA of each gene is composed of long sequences of four nucleotide bases: adenine (A), thymine (T), guanine (G), and cytosine (C). It is convenient to think of DNA as a very long sentence spelled with only four letters: A, T, G, and C. A very short sequence might be . . . GATACGATCCAGT . . . but the entire “sentence” extends thousands of letters in both directions. Sometimes there are typographic mistakes, called mutations. Any force, either chemical or radiologic, that induces DNA mutation is said to be *mutagenic* (causing mutations) or *carcinogenic* (causing cancer). Mutations can occur in germ cells (reproductive cells of the ovary or testis) or somatic cells (all other cells). *Germ cell mutations are transmissible from one generation to the next; somatic cell mutations are not.* For example, mutation of sperm DNA is transmissible, but mutation in the DNA of lung cancer cells is not.

DNA damage can occur in utero. Mutations in embryonic somatic cell genes may produce congenital defects, which are not inheritable. An example is a first trimester maternal rubella virus infection that damages embryonic somatic cell genes and produces severe congenital abnormalities.

Sometimes the germ cell gene defect results from an error in a single point, a *point mutation* (Fig. 7-5). Thus, a sequence that should read CTC becomes CAC. This defect, the substitution of adenine (A) for thymine (T) at a certain point in the gene that controls hemoglobin synthesis, is responsible for sickle cell anemia. In the production of normal hemoglobin A the affected segment of DNA normally codes for glutamic acid. In sickle cell disease this segment of DNA in the gene undergoes a mutation in which thymine (T) is substituted for the adenine (A), which reverses the T/A pair to A/T and produces an abnormal hemoglobin (hemoglobin S) that contains valine instead of glutamic acid at a certain point. Hemoglobin S has physical characteristics that cause it to crystallize and deform red blood cells.

**The Broad Influence of Genetics in Disease**

Most human characteristics (traits) result from effects of multiple genes (they are *polygenic*): hair and eye color, height, weight, intelligence, facial features, and so on. While polygenic influences play a role in many human diseases, they are usually not solely responsible—the environment also plays an important role. Polygenic influence confers vulnerability to disease that becomes evident only with the presence of environmental influences that exceed a certain threshold. For example, a patient may have a familial tendency toward diabetes, but the disease will not occur until the patient’s weight exceeds a certain amount.

Defects involving a single gene are inherited according to strict rules, but the inheritance risk in polygenic disorders can only be estimated and usually equates to an approximate 5–10 percent increase in risk for the disease in question. Lower inheritance risk is associated
with mild disease, higher inheritance risk with more severe disease. Notable examples of inheritable polygenic risk are cleft lip, hypertension, atherosclerosis, adult-onset (type 2) diabetes, gout, mental retardation, and schizophrenia.

When more than one gene influences the development of disease, it is difficult to identify the individual genes responsible. Nevertheless, evidence of their influence can be seen when certain disease tendencies occur in families and the tendency toward disease is passed from one generation to another. Think of inheritable polygenic risk in this way: in affected people, genes create a fertile field for the seeds of environmental injury—if it rains cheeseburgers and French fries a flood of obesity and diabetes may sprout in fertile genetic soil. In other people the genetic soil is less fertile, and a flood of cheeseburgers and fries may not produce obesity or diabetes. There is at least some degree of genetic influence in almost every disease.

**Disease of Single Genes (Monogenic Disorders)**

Of every pair of chromosomes, one is from the father and carries the genetic code for his traits, and one is from the mother and carries the genetic code for her traits. All normal chromosomes from each parent are structurally similar, each carrying a particular gene for a particular trait on a particular chromosome. The matching genes, say for eye color, are called alleles of one another, somewhat like matching earrings, one a gift from the father and one from the mother. The alleles are said to be homozygous if they are identical; that is, if they code for exactly the same trait, say brown eyes. However, if the alleles are not identical, the condition is said to be heterozygous. For example, if one allele codes for brown eyes and its partner codes for blue, the condition is heterozygous.

Either allele may behave in a dominant or in a recessive (submissive) manner. Dominant genes have greater power of expression than do recessive genes. Thus, if a person has one dominant and one recessive gene for the same characteristic, the trait carried by the dominant gene is expressed. If a dominant healthy allele from one parent is paired with a defective recessive allele from the other parent, the dominant trait is expressed, and the patient is healthy but carries the trait. This principle can be observed in the inheritance of normal eye color: the gene for brown eyes is dominant over the gene for blue eyes, which is recessive. If one of the allele pair is brown and the other blue, the brown gene overpowers the recessive blue gene, and the person has brown eyes. The same is true in disease: if the dominant allele is normal and its allele (partner) is mutant, then the recessive mutant (disease-carrying) allele is overpowered, and no disease occurs. A phenotypically normal (physically unaffected) person with a recessive genetic defect is a carrier but does not have the disease.

The inheritance mechanisms for single-gene characteristics are illustrated in Figure 7-6. They were first worked out in the 1860s by Austrian monk Gregor Mendel and are called Mendelian patterns or Mendel’s laws.

As initially described by Mendel, genetic makeup and genetic traits are characterized as follows:

- **Autosomal dominant** (Fig. 7-6A): A trait or disease expressed physically (phenotypically) if only one allele (partner gene) in one autosome of a set of two autosomal chromosomes is present. No identical allele (partner gene) on the companion autosomal chromosome is required. Familial hypercholesterolemia (Chapter 7) is an example.

- **Autosomal recessive** (Fig. 7-6B): A trait or disease expressed physically (phenotypically) only if both alleles (partner genes) are present, one on each chromosome pair. Sickle cell disease (Chapter 11) is an example.

- **Sex-linked recessive**: A trait or disease expressed physically (phenotypically) only if the allele (gene) is present on the X chromosome of a male (XY) or on both X chromosomes of a female (XX). Trait or disease occurs almost exclusively in males (XY) because X and Y share no alleles, that is, there are no partner genes on X for Y and vice versa, and the X allele is expressed because in males there is no normal allele on Y to compensate for the X defect. Females (XX) very rarely may express the trait if, by chance, both copies of X have the same mutant allele. Classic hemophilia (hemophilia A, Chapter 11) is a sex-linked recessive disease. The same rules apply to genes on the Y chromosome, but Y-related defects are rare and are related mainly to sperm production. Certain types of infertility are linked to Y chromosome gene defects.

It is also important to keep in mind that although a particular gene codes a particular trait, that trait may be expressed in various ways, a qualitative characteristic called expressivity. That is to say, the type of disease can somewhat from patient to patient. For example, some patients with cystic fibrosis, discussed later in this chapter, suffer primarily from lung disease; others suffer chiefly from pancreatic and intestinal problems. The
degree of abnormality, the severity of disease, is a quantitative characteristic called *penetrance*. That is, some genes are relatively weak (they have low penetrance), and the resulting disease is less severe than would be a disease resulting from genes with higher penetrance. For example, some patients with cystic fibrosis have severe lung disease, but others may have mild lung disease.

Over 5,000 Mendelian (single-gene) disorders have been identified, and new ones are discovered regularly. They occur in about 0.5% of the population and account for about 1% of hospital admissions. Most humans carry about 6–8 defective genes, almost all of them recessive and therefore are not expressed.

**DISEASE CAUSED BY DEFECTIVE AUTOSOMAL DOMINANT GENES**

An autosomal dominant trait is expressed by a gene located on one of the 44 autosomes. Being autosomal dominant, this trait is dominant over its recessive partner (allele) on the copy of the gene inherited from the other parent.

As is illustrated in Figure 7-6A, the rules of autosomal dominant disease inheritance are:

- The gene is physically expressed if only one copy of it is present in a pair of chromosomes
- An affected parent has a 50% chance of passing the gene to a child

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**Figure 7-6 Patterns of gene inheritance. A.** Autosomal dominant inheritance. The dominant gene is present in one affected, unhealthy (diseased) parent. Half of the children will be affected. **B.** Autosomal recessive inheritance. A recessive gene is present in each healthy, carrier parent. Half of the children will be healthy but carry the gene defect (Hgb SA, sickle cell trait); one fourth will be genetically and clinically normal (Hgb AA); and one fourth will have sickle cell disease (Hgb SS).
Inheritance of the defective gene ensures physical expression of the defect.

Healthy children are not carriers of the defective gene.

Not all mutant genes are inherited from prior generations; some arise as a new mutation in the germ cells of the ovary or testis of a parent and are then passed down the generations as a new defect. For example, about half of all new cases of neurofibromatosis (multiple tumors of nerves, Chapter 23) occur when new mutations arise in chromosome 17 in the germ cells in the ovary or testis of a parent.

**DISEASE CAUSED BY DEFECTIVE AUTOSOMAL RECESSIVE GENES**

An autosomal recessive trait requires two copies of the defective gene: one from the mother and one from the father. Recall the example above regarding eye color: Brown is dominant over blue, and blue eyes result only if a person inherits a recessive blue gene from both parents. One brown-eye gene from either parent guarantees brown eyes.

As is illustrated in Figure 7-6B, the rules of autosomal recessive inheritance are:

- The gene is physically expressed only if both chromosomes of a pair carry a copy of the gene (the homozygous state).
- If a patient carries two copies of the gene, each parent must have had at least one copy each of the gene.
- A parent with two copies of the gene (the abnormal homozygous state) mated with a parent not having the gene (the normal homozygous state) will produce offspring 50% of whom will be carriers of the abnor-
mal gene, but none of the offspring will be physically affected.

- Two parents, each of whom has a single copy of the abnormal gene (the heterozygous state), will produce the following offspring: 25% will be homozygous and physically affected; 50% will carry a single copy of the abnormal gene and will be asymptomatic carriers (the heterozygous state), and 25% will not carry a copy of the gene (the normal homozygous state).

Genes for autosomal recessive disorders are much more common than are those for autosomal dominant ones. However, because they are physically expressed only in the homozygous state (which requires both parents have the recessive gene), it is rare that two people mate who are carrying the same gene; that is, who have the same genotype. Autosomal recessive defects feature relatively uniform clinical signs and symptoms (phenotype) and earlier age at onset. Sickle cell disease (Chapter 11) is an inherited autosomal recessive disorder.

DISEASE CAUSED BY DEFECTIVE GENES ON SEX CHROMOSOMES

Patterns of disease inheritance, expression, and penetrance are different for mutations of the sex (X and Y) chromosomes. The X chromosome and some of the recessive diseases it transmits are illustrated in Figure 7-7. The Y chromosome is much smaller than the X is and contains genes only involving sperm production. Therefore, there are no matching alleles between X and Y chromosomes. Therefore, as is illustrated in Figure 7-8, a recessive defect on the X chromosome is transmitted in Mendelian fashion to half of a mother’s offspring (either male or female), but disease occurs only in sons because sons are XY and the recessive genes on the X chromosome have no normal, matching partner (allele) on the Y to compensate for the defect. Such diseases are said to be X-linked recessive and, with rare exception, occur only in males (XY). The exception occurs when both parents have a recessive defective gene on their X chromosomes, and each therefore must contribute a defective X chromosome to their daughter. An example of X-linked disease is Duchenne muscular dystrophy (Chapter 23), a disease transmitted by mothers to sons only. Daughters become carriers. Females (XX) carry the trait on one of their two X chromosomes but do not have clinical disease, because the normal gene on the partner chromosome compensates for the abnormal gene on the other chromosome. Classic hemophilia (hemophilia A, Chapter 11) is inherited as a sex-linked recessive disease.

CLINICAL EXPRESSION OF SINGLE-GENE DEFECTS

Each gene codes for a single protein (or variations of that protein), which may be one of four types:

- Enzymes and proteins that regulate enzyme activity
- Membrane receptor and transport proteins
- Proteins that regulate cell growth
- Structural, coagulation, and other proteins

Every disease resulting from a single-gene defect falls into one of these categories.

Disease of Enzymes and Proteins Regulating Enzyme Activity

Enzymes are proteins that promote chemical reactions but are not consumed in the reaction. They act on a substance called a substrate and convert it into a product. Therefore, enzyme defects cause either an accumulation of upstream (substrate) raw material or a deficit of an end (downstream) product, much like a dam on a stream results in an accumulation of water upstream and a lack of it downstream.

Gaucher disease is an example of an autosomal recessive disease caused by accumulation of unmetabolized substrate. It results from a defect in the gene that codes for an enzyme that metabolizes glucocerebroside. Unmetabolized glucocerebroside accumulates in macrophages throughout the body, especially in the brain, bone marrow, lymph nodes, and spleen.
Sometimes deficiency of an end product is the cause of disease. Glycogen storage disease is a genetic disease in which the affected enzyme normally converts muscle glycogen into glucose. The defect deprives muscle of glucose and results in severe muscle cramps and necrosis.

Alpha-1 antitrypsin (AAT) deficiency is an autosomal recessive genetic disorder of enzyme regulatory proteins. AAT, a blood protein synthesized by the liver, permeates tissues to protect against excess effect of proteolytic enzymes released by neutrophils recruited to sites of tissue injury and inflammation. Deficiency of AAT is associated with excessive tissue digestion by inflammatory reactions. This is particularly noticeable in the lungs of affected patients, especially smokers. The inflammatory reaction caused by cigarette smoke results in severe autodigestion of alveoli, which in turn results in emphysema.

### Disease of Membrane Receptor and Transport Proteins

Some proteins are designed to attach to other molecules. When they hold the molecule in place, such proteins are called receptors, and when they attach to and move a molecule from one place to another, they are called transport proteins. For example, receptors in the liver capture and hold low-density lipoprotein during the process of excreting cholesterol into bile. Thus, a genetic defect resulting in too few low-density lipopro-
tein receptors would manifest with high levels of blood cholesterol. **Familial hypercholesterolemia** (Fig. 7-9) is a result of such a genetic defect. It is an autosomal-dominant defect of liver receptor proteins for low-density lipoprotein (LDL) and is the most common Mendelian disorder, affecting about one of every 500 people. It assumes special significance because high LDL cholesterol levels in blood are associated with accelerated atherosclerosis. However, most cases of high cholesterol result from bad dietary habits, not genetic defect.

**Cystic fibrosis**, an autosomal recessive disease of receptor proteins, discussed later in this chapter, results from a gene that codes for a defective transport protein that enables transfer of chloride across cell membranes.

**Disease of Growth Control Proteins**

Proto-oncogenes are normal growth control genes that promote cell growth. They are opposed by tumor suppressor genes, which inhibit cell growth. Mutations in these genes are the cause of some malignancies. For example, **neurofibromatosis** (von Recklinghausen disease) is an autosomal dominant disorder of a particular tumor suppressor gene that allows uncontrolled growth of certain cells. Patients with neurofibromatosis have peripheral nerve tumors that may become malignant.

**Disease of Structural, Coagulation, and Other Proteins**

Structural proteins provide support for tissue. For example, fibrillin, a structural protein synthesized by fibroblasts, is an important component of the extracellular matrix. A genetic defect of fibrillin synthesis produces **Marfan syndrome** (Figs. 7-10 and 7-11), an autosomal dominant disease characterized by defects in: 1) the skeleton (very long legs and fingers, a high, arched palate, and hyperextensible joints); 2) the eyes (dislocation of the lens resulting from stretched ligaments), and 3); the cardiovascular system (lax aortic tissue that produces aneurysms and aortic valvular incompetence). Marfan disease is rare, affecting about 1 in 10,000. Because of his tall, lanky habitus, it has been speculated that Abraham Lincoln had Marfan disease; however, most experts think it unlikely.

**Classic hemophilia** (hemophilia A) (Fig. 7-8) is an X-linked recessive disorder of factor VIII, an important blood coagulation protein. Males with hemophilia A lack enough factor VIII for normal clotting.
Cytogenetic Diseases

Cytogenetic disease results from large-scale chromosome abnormalities involving large parts or entire chromosomes and arising in the process of producing ova and sperm from ovarian and testicular germ cells. By contrast, the mutations discussed above involve only a few genes or a tiny fraction of the DNA in a single gene.

Cytogenetic diseases are characterized by: 1) one or more extra chromosomes, 2) a missing chromosome, or 3) structural abnormalities of chromosomes, such as missing parts (deletion), parts that have been moved from one chromosome to another (translocation), or parts that detach and reattach upside down (inversion). Cytogenetic disorders may affect any chromosome.

The basic tool of cytogenetic investigation is the karyotype—a photographic display of chromosomes arranged in matched pairs (one maternal, one paternal) in descending order of length—the largest labeled number 1, the smallest number 22, with the X chromosome.
and Y (tiny) added at the end. By this method extra or missing chromosomes and other abnormalities are identifiable. Figure 7-12 is an example of a karyotype of a female patient with Down syndrome. Additionally, chromosomes also may be stained to reveal patterns of alternating dark and light bands that enable definitive identification of each chromosome and some of its internal detail. About 1 in 200 newborns has some detectable cytogenetic abnormality (although most are innocuous), and it is estimated that 50% of spontaneous first trimester abortions have chromosome abnormalities.

**DISEASE ASSOCIATED WITH ABNORMAL NUMBERS OF AUTOSOMES**

Non-sex chromosomes are autosomes. The loss of an autosome, which leaves the embryo with only one copy of the chromosome instead of the normal pair, is monosomy, a condition that is not compatible with life and results in spontaneous abortion. An extra copy of an autosome, so that the patient has three copies of a partic-

*Figure 7-11 Marfan syndrome.* The sternal scar is from surgical repair of an aortic aneurysm.

*Figure 7-12 The chromosomes in Down syndrome.* A photographic display of chromosomes (karyotype) of a female (XX) patient with Down syndrome reveals three copies of chromosome 21 (trisomy 21) instead of the normal two.
ular chromosome, not two, is trisomy. Most autosomal trisomy results in spontaneous abortion; however, some fetuses survive, especially those with trisomies of chromosomes number 13, 18, or 21, each of which is associated with severe mental and physical problems.

Trisomy 21 (Down syndrome) is the most common cytogenetic disorder in the United States and the single most common cause of mental retardation. Strongly influenced by maternal age, Down syndrome occurs about 1 in every 1,500 births to women under age thirty and about 1 in 25 births to women over 45 years old. A Down syndrome fetus possesses three copies of chromosome 21 (Fig. 7-12), rather than the normal two. The usual cause is a defective ovum that contains two number 21 chromosomes, rather than one; fertilization by sperm adds the third copy.

To understand how an ovum could have an extra 21 chromosome, recall that germ cell division (reduction division) in the ovary (and testis) is different than in other cells. In somatic cell division each of 46 chromosomes divides in half, one half going to one new daughter cell, the other half to the other daughter cell. However, in ovarian and testicular germ cells, chromosomes gather in matched pairs—one whole chromosome goes to one new cell (ovum or sperm), and its twin goes to another cell. This process is known as meiosis, a special type of cell division that occurs only in the gonads and produces ova and sperm with 23 chromosomes each, instead of the 46 in somatic cells. Basics in Brief 7-1 explains meiosis in more detail. Rarely, however, a mistake occurs and both 21 chromosomes go into one new ovum or sperm, and the other ovum or sperm gets none. If such an ovum is fertilized, the sperm brings a copy of 21 to make a total of three. Thus, the conceptus has three copies of chromosome 21, not two. In cytogenetic shorthand the combination for females is 47,XX,+21; in males the combination is expressed 47,XY,+21. Even though the pathogenesis of every case of Down syndrome is not understood, its close association with maternal age suggests that most cases involve an error in ovarian meiosis.

Infants with Down syndrome are mentally retarded and have a flat face with epicanthal folds and abnormalities of the hands and feet, as can be seen in Figures 7-13 and 7-14. They also may have cardiac and intestinal malformations, as well as immune deficiencies and associated infections, and are at an increased risk of leukemia. With correct care many patients live beyond

**BASICS IN BRIEF 7-1**

**MEIOSIS: FROM 46 CHROMOSOMES TO 23 AND BACK AGAIN**

Sperm and ova are different from all other cells because they contain half the number of chromosomes present in all other cells—all other cells contain 46 chromosomes; ova and sperm contain only 23.

Mitosis is the way **autosomes** (chromosomes of somatic—non-germ—cells) divide: each of the 46 chromosomes is duplicated in the two new offspring cells. In mitosis, chromosomes line up at the cell equator, and each chromosome splits into two parts, half going to one daughter cell and half to the other. For example, as skin cells are shed daily and replaced, the new cells are exact copies of the parent cell—each has 46 chromosomes, including the two sex chromosomes. However, in germ cells of the gonads, the process is much different.

Gonadal germ cells, which also contain 46 chromosomes, undergo **meiosis** (or reduction division) to form gametes (ova and sperm) with 23 chromosomes each. In meiosis, chromosomes line up in pairs (for example, both number 21 chromosomes pair up), and one whole chromosome of each pair goes to each new gamete, so that the number of chromosomes in the gamete is half that of the parent germ cell. Each ovum and each sperm, therefore, contain 22 autosomes and one sex chromosome. The new ova have 22 autosomes plus an X sex chromosome; and the new sperm have 22 autosomes, plus an X or a Y sex chromosome. Half of sperm get an X, and the other half get a Y. At conception the total number of chromosomes returns to 46,XX or 46,XY: the ovum contributes 22 autosomes and an X sex chromosome; the sperm contributes 22 autosomes and either an X (and the fertilized egg becomes female) or a Y (and male).

Sometimes, however, meiosis is defective, and both of a pair of chromosomes go into one gamete, which when fertilized has 47 chromosomes; the other gamete does not get one and when fertilized has 45 chromosomes. Fertilization with such defective gametes is the cause of most cytogenetic disorders.
Mental retardation
Slanted eyes
Protruding large and wrinkled tongue
Epicanthal fold
Congenital heart disease
Intestinal defects
Umbilical hernia
Shortened fifth finger
Abnormal creases
Wide gap between first and second toes

**Figure 7-13** Clinical features of Down syndrome.

**Figure 7-14** Facies of Down syndrome. The face is flat, the eyes are wide-set, the bridge of the nose is low, the eyes have epicanthal folds, and the mouth is usually partially open to accommodate an enlarged tongue.
age thirty, but often they develop early Alzheimer disease.

**DISEASE ASSOCIATED WITH ABNORMAL NUMBERS OF SEX CHROMOSOMES**

The most common cause of sex chromosome cytogenetic disease is *faulty meiosis*. In the ovary one ovum gets both of the X chromosomes and the other gets none and is designated O; in the testis one sperm gets both the X and the Y and the other gets none and is designated O. Combinations are depicted in Figure 7-15. If abnormal ovarian meiosis produces an ovum with two X chromosomes and it is fertilized by a normal Y sperm the result is 47,XXY, which is recognized clinically as **Klinefelter syndrome** (Fig. 7-16). A typical patient is tall and effeminate, with long arms and legs, a small penis and atrophic testicles, scant pubic hair, no beard, and female-like hip shape. Many also have enlarged breasts (gynecomastia).

With abnormal meiosis in the testis, one sperm gets both the X and the Y, and the other gets no sex chromosome. If the sperm with no sex chromosome fertilizes a

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**Figure 7-15** *Sex chromosomes in cytogenetic disease.* Some combinations of sex chromosomes are caused by faulty germ cell division (meiosis). On the top left, note that normal ovarian germ cell meiosis produces two ova, each with an X chromosome. At the bottom left note that abnormal ovarian meiosis produces one ovum with two X chromosomes (XX) and one with none (O). Across the top, note on the left that normal testicular germ cell meiosis produces one sperm with an X chromosome and one with a Y chromosome. To the right, note that abnormal testicular meiosis produces one sperm with both the X and Y chromosomes (XY) and one with none (O). The grid displays genetic combinations (genotypes) and clinical syndromes (phenotypes) that result from fertilization of these defective ova and sperm.
normal (X) ovum, the result is 45,X, which is recognized clinically as Turner syndrome (Fig. 7-17). These patients clinically appear to be females who are sexually immature, infertile, have short stature, a wide, webbed neck, a low hairline on the back of the neck, a broad, flat chest with widely separated nipples, scant pubic hair, multiple pigmented skin lesions (nevi, Chapter 24), and no breast development. They do not have menstrual periods, and their ovaries are rudimentary streaks. Congenital cardiac malformations are common.

Other combinations, such as 49, XXXXY, may occur. Mental retardation is common, and severity roughly parallels the number of X chromosomes. The processes involved are beyond the scope of this discussion.

**Genetic Diagnosis**

Prenatal genetic diagnosis is important for many reasons: 1) genetic diseases are transmissible down the generations; 2) they can create lifelong burdens for parents, families, and the affected child, and 3) they consume large amounts of health resources per patient. Diagnosis of genetic disorders usually requires expert advice by a geneticist and laboratory examination of maternal and/or fetal chromosomal material.

Below are some indications for genetic study:
- Mother 35 years or older
- Parents who have a child with known genetic disease
- Other family history of genetic problems

Prior to the arrival of molecular techniques, genetic diagnosis was made by clinical study or by detection of abnormal accumulations of substances in blood, urine, or tissue. Observation of mental retardation in phenylketonuria is an example of the former; detection of hemoglobin S by a sickle cell test on blood is an example of the latter. Now, however, direct examination of DNA is possible.

*Prenatal* genetic diagnosis (Fig. 7-18) should be offered to patients at risk for genetic disease. Fetal cells may be obtained by needle aspiration of the amniotic sac, a procedure called amniocentesis. Fetal cells line the amniotic sac and can be collected from centrifuged sediment and subjected to molecular, genetic, or chemical analysis. Additionally, the placenta is composed of fetal tissue, and by inserting a catheter into the cervix a sample of cells can be aspirated for analysis (chorionic biopsy). After birth, a sample of cord blood can be obtained for the same purpose. These cells can be studied biochemically for evidence of abnormal substances, chromosomes can be studied by karyotype, and the DNA can be analyzed for defects (the accompanying Lab Tools box offers more detail).

*Postnatal* genetic analysis of fetal or parental cells may be indicated when the mother has had multiple spontaneous abortions or a child is born with multiple congenital anomalies, Down syndrome, or other recognizable clinical cytogenetic or genetic disease. Infertile patients also may require genetic diagnosis.
Figure 7-17 Clinical features of Turner syndrome (46,X).

- Low hairline on neck
- Wide, webbed neck
- Heart-shaped face
- Broad, flat chest with widely separated nipples
- Outwardly angled forearms
- Streak ovaries, amenorrhea, infertility
- Coarctation of aorta
- Multiple pigmented nevi

Figure 7-18 Prenatal specimen collection for genetic diagnosis. Techniques to obtain fetal cells for biochemical and genetic study (karyotype or DNA analysis).
Laboratory cytogenetic diagnosis requires construction of a karyotype, as discussed nearby and demonstrated in Figures 7-4 and 7-12.

On the other hand, laboratory investigation of disorders resulting from single-gene (monogenic) defects depends on other techniques. First is polymerase chain reaction (PCR), in which a very small amount of DNA is artificially multiplied into an amount large enough to study, a technique widely used in criminal investigations. Second is restriction fragment length polymorphism (RFLP), a technique of DNA analysis also used in criminal investigations, as well as in genealogy studies and in paternity testing.

Despite its formidable name, the principle of RFLP is simple. Restriction enzymes are known to break DNA at a specific base sequence, wherever it occurs, thus shredding long chains of DNA into a collection of shorter fragments of varying length. For example, a certain enzyme might break DNA at every GAC base sequence; another might break it at every TCA sequence. These enzymes break DNA into fragments of recognizable length, forming a reproducible pattern for any given individual, based on that person’s unique DNA sequences of bases (Chapter 2). The value of RFLP in genetic disease investigation rests on the fact that mutations alter the base sequences. For example, TCA sequences might appear where they had not previously existed and alter the breaking points so that the abnormal DNA has a pattern of fragment lengths different from those of normal DNA.

To understand RFLP, think of people as custom-built houses. RFLP analysis is like taking apart a custom-built house and sorting the lumber into sets according to length. Each house has a distinctive pattern. Identical homes can be disassembled into identical sets of boards time after time, just as DNA—normal or abnormal—can be disassembled into identical restriction fragments each time. However, if a rogue architect changes the plan, causing a mutation, so to speak, in the lengths of boards used to build some areas of the house, the disassembled lumber would reveal the change.

Children are not little adults—not mentally, not physically, not physiologically. Pediatrics is not adult medicine in miniature because:

- Genetic disease is more often a problem in children than adults. For example, sickle cell disease and cystic fibrosis are serious and common diseases that appear first in children.

- Some diseases are unique to childhood. For example, hyaline membrane disease is a condition unique to premature newborns.

- Some diseases take a distinctive form when occurring in children. For example, meningitis in children is usually caused by different microbes than is meningitis in adults.

- Diagnosis often relies on specialized laboratory testing that is not widely available. For example, blood specimens are small and require special skill and equipment to collect, and tests done on children are often not the same as those done on adults.

Perinatal and Neonatal Disease

Important terms in perinatal and neonatal medicine are defined below:

- The perinatal period is the time from the 28th week of pregnancy to the seventh day after birth.
- The neonatal period is the first month after birth.
- Full term pregnancy is 38–40 weeks (after the end of the 37th week).
• **Normal birth weight** is 3,500 grams.
• **Post-term** infants are those born after 42 weeks.
• **Premature** infants are those born before the end of the 37th week; sometimes these infants are called **preterm**.
• **Low birth weight** infants weigh less than 2,500 grams (5.5 lb)

Determining **gestational age** (length of time in the womb) by counting from the first day of the mother’s last menstrual period is a useful technique because women recall it easily. In reality, however, it is about two weeks more than the actual length of gestation because fertilization usually occurs about two weeks after the first day of the last menstrual period.

Duration of gestation, birth weight, and organ maturity go hand-in-hand in normal pregnancy (Fig. 7-19). Most term infants have normal birth weight and have organs that are appropriately mature and ready for life outside the womb. As a rule, infants with low birth weight have shorter gestational age, have less mature organs, and have higher mortality and morbidity than do term infants with normal birth weight and mature organs. However, this is not always the case, and newborn infants are classified according to a system that takes into account both birth weight and gestational age:

• **Small for gestational age (SGA)** infants are those weighing less than predicted for any given gestational age.
• **Appropriate for gestational age (AGA)** infants are those weighing as much as expected at any given gestational age.
• **Large for gestational age (LGA)** infants are those weighing more than expected at any given gestational age.

For example, according to Figure 7-19, an infant born at 32 weeks should weigh near 1,500 grams. An infant born at 32 weeks that weighs 2,500 grams is large for gestational age (LGA) but is very premature. It is sure to have immature organs and is at high risk for complications of prematurity, especially respiratory distress syndrome (discussed below). However, an infant born at 36 weeks and weighing 1,500 gm, though small for gestational age (SGA), is at relatively less risk for complications because its organs are more mature.

![Neonatal mortality risk](image)

**Figure 7-19 Neonatal mortality risk.** Fetal death rate (percent) as a function of birth weight and gestational age. Normal gestation is 38–40 full weeks. Prematurity is gestational age less than 37 full weeks. For example, the mortality is < 1% for term infants that weigh appropriately for gestational age (AGA), but it is about 20% for infants born weighing under 1,500 grams and born at about 30 weeks gestational age.
A very useful tool in newborn care is the Apgar score, named after its originator, pediatric anesthesiologist Virginia Apgar. A numerical assessment of an infant’s condition immediately after birth, it is a useful method for clinical assessment of the vigor of a newborn infant. Points (0, 1, or 2) are assigned for heart rate, respiratory effort, muscle tone, general color, and response to a catheter inserted in the nose. The maximum score is ten. Low scores correlate directly with neonatal illness and death. “The Clinical Side” box above presents the scoring details.

**THE CLINICAL SIDE**

**CLINICAL EVALUATION OF NEWBORN INFANTS: THE APGAR SCORE**
Assessment of newborn infant vigor correlates closely with infant survival. Practices vary, but typically infants are scored at one minute or five minutes after birth. Infants with low scores have higher morbidity and mortality than do infants with higher scores. For example:
- Infants with a five minute score of 0–1 have a 50% mortality rate.
- Mortality is very close to zero for infants scoring 7 or better.

<table>
<thead>
<tr>
<th>The Apgar Scoring System for Newborns</th>
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<tr>
<td>Sign</td>
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<tr>
<td>Heart rate</td>
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<td>Absent</td>
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<td>Respiratory effort</td>
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<td>Response to catheter inserted in nostril</td>
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**INTRAUTERINE GROWTH RESTRICTION**
Newborns weighing less than 2,500 grams (5.5 lb) are low birth weight infants. Most of these are born prematurely (before the end of the 37th week of gestation); however, about one third of low birth weight infants are born at full term and are underweight because of intrauterine growth restriction (IUGR). That is, they are SGA, rather than premature.

Often the cause of IUGR is not known, but maternal factors are the most common identifiable causes—hypertension of pregnancy (toxemia, Chapter 21), malnutrition, drug or alcohol abuse, and heavy cigarette smoking. Fetal alcohol syndrome, a common cause of IUGR, is characterized by a history of maternal alcohol abuse and an SGA infant with a small head (microcephaly), mental retardation, atrial septal defect (Chapter 13), and a characteristic facial appearance.

Placental factors can also cause IUGR. Examples include insufficient placental blood flow, placenta previa (low uterine implantation of the placenta), and premature separation (placental abruption).

Fetal factors include genetic disease, congenital anomalies diseases, and infections (mainly the TORCH group, mentioned above).

**PREMATURITY**
Prematurity is birth before the end of the 37th week of gestation. Most premature infants are of low birth weight, too, but the most critical aspect is length of gestation, because it takes time for organs to mature. About 5–10% of pregnancies produce premature infants. The major causes of prematurity are preterm rupture of the amniotic sac, intrauterine infection, multiple gestation (twin pregnancy), and structural abnormalities of the uterus, cervix, or placenta (such as leiomyomas of the uterine wall), placental hemorrhage, abnormal location of the placental implantation in the wall of the uterus, or a relaxed cervix that opens too early.

Premature infants have immature organs regardless of birth weight and are at substantial risk for brain, liver, and lung disease. Those that are SGA are at even greater risk.
The brain is the least mature of all organs at birth, whether premature or full term. It is especially vulnerable to birth-related hemorrhage as the skull is molded into somewhat of an elongated shape as it passes through the birth canal. Intracranial hemorrhage can occur without skull fracture or bruised or torn brain tissue, and can lead to severe neurologic impairment or death.

The newborn liver is not fully capable of processing bilirubin until about two weeks of age, and almost all healthy newborns experience a normal period of non-toxic physiologic jaundice (Chapter 16) shortly after birth. However, in prematurity the liver is even less capable of handling the normal physiologic load, and bilirubin can rise to toxic levels, resulting in kernicterus, a syndrome of severe brain damage characterized by deposits of bilirubin in the floor of the third ventricle (Fig. 7-20). Thanks to modern prenatal and neonatal care, kernicterus is now very rare in developed nations.

High levels of bilirubin can be treated in two ways. For most infants, phototherapy is sufficient. For a few hours a day the infant is exposed to intense light, which penetrates deep enough into skin to interact with bilirubin in superficial blood vessels and converts bilirubin into a form more easily handled by the infant’s immature liver. In exchange transfusion, necessary for more severe cases, small amounts of infant blood are repeatedly withdrawn and replaced each time with fresh donor blood or plasma that, of course, has little bilirubin in it.

The lungs do not reach full maturity until 6–8 years after birth. In utero they undergo rapid evolution between 28–32 weeks, as type II pneumocytes begin secreting surfactant, a slick, soapy fluid that decreases surface tension of intra-alveolar fluid and decreases the effort required to keep alveoli open and filled with air after birth. Respiratory distress syndrome (RDS) of the newborn (also known as hyaline membrane disease) stems from a lack of surfactant in immature infant lungs (see Case Study 7-1 at the end of this chapter).

Respiratory distress syndrome is a disease of prematurity that affects about 25% of infants born between 32–36 weeks and more than 50% of those born before 28 weeks. The absence of surfactant makes alveoli difficult to keep open, and they collapse, preventing gas exchange. Keeping alveoli open requires intense respiratory effort, and some infants die because they suffocate as their muscles tire. A typical case is a premature, low birth weight infant whose weight is appropriate for gestational age (AGA), and a mother who has diabetes or some other complication of pregnancy. Shortly after delivery, the infant’s breathing becomes difficult, with grunting respirations and sternal and lower rib retraction from the severe effort. Within a few hours after birth, blood oxygen levels fall (hypoxia) and the infant turns blue (cyanosis). Hypoxia causes alveolar and pulmonary vascular damage, and fluid (exudate) accumulates in the alveoli. Protein in the exudate cannot be absorbed, and in time the protein condenses to glue-like consistency that forms a thick membrane (the hyaline membrane, Fig. 7-21) coating alveolar walls, further impairing oxygen transfer. Surviving infants may suffer
hypoxic brain damage. Oxygen and surfactant inhalation may be effective treatments.

Oxygen therapy can be life saving. However, in newborns it must be administered with special care because inhalation of high concentrations of oxygen can result in retinopathy of the newborn (“oxygen blindness”), associated with toxic effect of oxygen on the neonatal retina, or in bronchial dysplasia, associated with a similar toxic effect of oxygen on bronchial mucosa. Oxygen blindness is rare, but bronchial dysplasia occurs in about half of infants weighing less than 1,000 gm who are treated with oxygen. Pathologically it is characterized by bronchial and lung scarring (fibrosis).

**BIRTH INJURY**

About 1 in 5,000 live-born infants is born with an injury directly traceable to the birth process. Considering the contortions and forces of vaginal passage, it is surprising that infants are not injured more often. LGA infants are injured more often than others because greater force is necessary to push the fetus through the birth canal. The most common injuries are, in descending order: fractured clavicle, facial nerve injury with facial paralysis, brachial plexus injury with paralysis of the upper extremity, skull fracture or intracranial injury, and fracture of the humerus. Intracranial hemorrhage is the most severe injury and can produce immediate problems or death; or it may become manifest later as cerebral palsy.

Cerebral palsy (see Chapter 23, Figure 23.11) is a broad clinical term for a non-progressive syndrome of infant brain damage. About 75% of cerebral palsy cases arise from unknown prebirth conditions. About 15% of cases arise from damage suffered after birth: brain or meningeal infections, hyperbilirubinemia, automobile accidents, falls, or child abuse. Cerebral palsy is characterized by varying degrees of motor difficulty including paralysis, uncontrollable movements, and inability to coordinate body movements, which may not be evident at birth but assert themselves as development progresses. Because brain development continues during the first two years of life, cerebral palsy can result from brain damage that occurs in utero or before age two. Neonatal risk factors for cerebral palsy include prematurity, low birth weight, and intrauterine growth retardation (Chapter 7).

**FETAL AND NEWBORN INFECTIONS**

Some maternal infections cross the placenta to infect the fetus, notably the TORCH infections discussed earlier in this chapter. However, most infections are from vaginal bacteria. Sometimes infection is acquired as the fetus passes through the vaginal canal; or bacteria ascend the vaginal canal through the cervix to infect the amniotic fluid (amnionitis), usually late in pregnancy, and particularly if there is an amniotic fluid leak. Infected amniotic fluid is inhaled by the fetus and may cause premature labor and pneumonia or other infections.

Herpesvirus may be a serious fetal threat if a pregnant woman suffers an outbreak of genital herpes at the time of delivery. The threat is so serious that caesarean section may be required in mothers with active genital herpes to avoid exposing the infant to the risk of infection by vaginal delivery.

Necrotizing enterocolitis, a severe inflammatory condition of the gastrointestinal tract, occurs in about 10% of infants weighing <1,500 gm (3.3 lb). The cause is unknown, but infection and poor intestinal blood flow are suspected. The findings are distinctive: intestinal mucosal hemorrhage with bloody diarrhea and shock. Surgical excision of affected bowel is often required. Mortality is high.

**Infections of Children**

The most common pediatric infections are viral; many of them cause acute upper respiratory illnesses featuring fever, cough, and rhinorrhea.

Respiratory syncytial virus (RSV) causes a pediatric syndrome of acute bronchitis, bronchiolitis, and bronchopneumonia.

Measles (rubeola) is a highly contagious respiratory virus best known for the skin rash it produces. In well-nourished, healthy children it is usually not much more than a rite of passage, but in malnourished children it can cause fatal pneumonia, accounting for over one million deaths per year worldwide.

Rubella (German measles, three-day measles) is caused by the rubella virus and presents as sore throat, skin rash, and enlarged lymph nodes. It is much shorter in duration and is a less serious condition than rubeola is. Rubella infection of the fetus, however, can cause especially severe and deforming disease or fetal death (Chapter 7).

Mumps virus causes acute inflammation of the parotid salivary gland (parotitis), and it occasionally causes orchitis (inflammation of the testes), pancreatitis, or encephalitis. It has been virtually eliminated by vaccination.

Infectious mononucleosis is a self-limited (it disappears without treatment), mild syndrome of fever, sore throat, listlessness, lymphocytosis, and splenomegaly, which typically occurs in late adolescence or in college-age youths (Chapter 11). It is caused by the Epstein-
Barr virus (EBV) and almost always is passed in saliva during kissing. Transmission by sexual contact and shared eating and drinking utensils is rare. Diagnosis requires finding distinctive large lymphocytes (atypical lymphocytes) in the peripheral blood and characteristic antibodies (called heterophil antibodies) in blood.

Chickenpox is caused by the varicella-zoster virus, which causes an acute febrile illness characterized by vesicular skin eruptions that may leave unsightly scars.

One of the most common bacterial diseases of children is acute otitis media, discussed in detail in Chapter 25. Streptococcus pneumoniae and Haemophilus influenzae are the most common bacteria involved.

Bronchiolitis, a viral infection of the small airways, is usually caused by the respiratory syncytial virus (RSV). It occurs most often as winter epidemics in infants and children. It presents clinically with low-grade fever, wheezing respiration, and shortness of breath. Secondary bacterial pneumonia may develop, but most cases resolve in 7–10 days with supportive therapy.

Whooping cough is caused by Bordetella pertussis, a Gram-negative bacillus that produces a highly contagious syndrome of intense inflammation in the larynx, trachea, and bronchi, and which can cause fatal asphyxia. Whooping cough gets its name from severe spasms of coughing and the sharp, inspiratory barking sound (stridor, or whoop) that is characteristic of the disease. Whooping cough is usually mild in older children, but may cause death in infants. Vaccination programs have made it uncommon in the United States, but it causes hundreds of thousands of deaths annually in unvaccinated children in developing nations.

Croup is an illness of children, usually age 3 or younger, resulting from influenza A or B virus infection. It can cause inflammation of the larynx, trachea, or bronchi. The most dangerous aspect is laryngitis, which features laryngeal edema that causes a hoarse, brassy, barking cough and a crowing sound (stridor, or whoop) that is characteristic of the disease. Most cases resolve spontaneously, but a neglected case can cause fatal suffocation.

Diphtheria is caused by a gram-positive bacillus, Corynebacterium diphtheriae, which produces a pharyngitis and laryngitis associated with a thick, obstructive inflammatory membrane that can cause death by suffocation. Moreover, the bacillus secretes an exotoxin that can damage the heart, kidney, and brain. Diphtheria now has been almost eliminated in developed nations by effective vaccinations.

Acute bacterial epiglottitis is a disease of school age children caused by H. influenzae and marked by hoarseness and painful swallowing. The epiglottis and nearby pharyngeal tissues are severely inflamed, narrowing the airway and sometimes causing critical airway obstruction.

**Sudden Infant Death Syndrome (SIDS)**

The cause of sudden infant death syndrome (SIDS), sometimes referred to as crib death, is unknown and is best characterized by its epidemiology:

- 90% of victims are under 6 months of age
- Most victims routinely sleep in the prone position
- There is a higher than usual history of prematurity or low birth weight
- Males outnumber females
- Mothers are often less than 20 years old, are unmarried, are smokers or drug abusers, and have low socioeconomic condition
- African-American infants are more often affected than other ethnic groups (genetic? socioeconomic?)

Pathologic findings at autopsy are scant, but a few patients may have minor microscopic abnormalities in structures related to respiratory control: the carotid body, vagus nerve, or part of the brain. A very small number of cases prove to be homicide rather than SIDS, and the index of suspicion rises dramatically with a second case in the same family.

**HEMOLYTIC DISEASE OF THE NEWBORN (ERYTHROBLASTOSIS FETALIS)**

Hemolytic disease of the newborn is anemia resulting from destruction of fetal red blood cells (hemolysis) by maternal antibodies that cross the placenta and enter the fetal circulation. Thanks to modern maternal and neonatal care, it is now very rare in the United States, but it will be discussed in detail because the pathogenetic mechanisms are instructive. In hemolytic disease of the newborn the mother becomes immunized against fetal red blood cells during a pregnancy; then in a subsequent pregnancy the antibodies cross the placenta to attack (hemolyze) red blood cells of the fetus.

Fetal red cells leak into the maternal bloodstream in normal pregnancy, usually without ill effect. However, the red cell membrane contains many proteins, some of which are highly antigenic, and if mother and fetus have certain differences in blood type, the mother may develop antibodies against fetal red cells. One of the most potent antigens is the Rh D antigen (Chapter 8)—often referred to as the “Rh factor”—which is present in the red blood cells of 83% of the United States population.
Although major blood group (A, B, and O) differences between mother and fetus are common, they rarely cause problems. However, Rh D differences can be very serious. If an Rh D-negative mother receives a large dose of Rh D-positive fetal RBCs, she can become immunized against Rh D protein; in other words, the mother becomes primed to produce a flood of antibodies against Rh D fetal RBCs the next time she is pregnant with a fetus having Rh D-positive RBCs.

The ill effect on the fetus is directly proportional to the degree of fetal red-cell destruction. Affected infants are anemic because their red cells are destroyed faster than they can be replaced. Destruction of RBCs releases large amounts of hemoglobin, which is metabolized into more bilirubin than the fetal liver can excrete (Chapter 16). Very high blood bilirubin causes bilirubin deposits in the brainstem, producing a clinical condition known as kernicterus (Fig. 7-20). Severe anemia causes high-output congestive heart failure (Chapter 13), and impairs the liver’s ability to produce albumin, resulting in generalized osmotic edema (Chapter 5). The combination of heart failure and osmotic edema produces severe generalized edema, known as hydrops fetalis (Fig. 7-22). Those most severely affected fetuses may be stillborn or die shortly after birth.

Preventive therapy is very effective and has dramatically reduced the number of cases. ABO and Rh D characteristics of mothers should be determined early in pregnancy. Rh D-negative mothers are given a prophylactic injection of anti-Rh D antibody because there is a high chance that the infant is Rh D positive. A second dose is given immediately after delivery. The injected anti-Rh D antibody attaches to Rh D protein on any Rh D-positive fetal cells in the maternal circulation, masking the fetal Rh D protein from the maternal immune system and preventing maternal production of anti-Rh D antibodies that could cause a problem for a subsequent pregnancy with an Rh D-positive infant.

Cystic Fibrosis

Cystic fibrosis is the most common lethal genetic disease of Caucasians, affecting about 1 in 2,000 live births. The genetic defect affects the transport of chloride (Cl−) across epithelial cell membranes of gland ducts, resulting in decreased chloride in glandular secretions. Because sodium and chloride are transported across the cell membrane together, secretions have decreased sodium (and chloride) and low osmotic pressure and are unable to attract water. The result is very thick mucus that obstructs bronchial and intestinal mucous gland ducts, pancreatic ducts, hepatic bile ducts, and the vas deferens.

Accumulations of this thick mucus in pancreatic ducts prevents digestive enzymes from reaching the GI tract. The result is chronic pancreatitis, gastrointestinal malabsorption (Chapter 15), and malnourishment. Obstruction of hepatic bile ducts causes chronic inflammation and widespread liver scarring (cirrhosis, Chapter 16). Obstruction of the vas deferens causes low sperm count and infertility. Thick mucus from bronchial glands obstructs small bronchi, impairs respiration, and promotes infection (Fig. 7-23). In the fetus or newborn, intestinal mucus may be so thick that it causes intestinal obstruction, which is known as meconium ileus.

In sweat gland ducts the chloride transport defect has the opposite effect: sweat chloride is high, a diagnostic finding characteristic of patients with cystic fibrosis. The Lab Tools box below explains the sweat chloride test and other lab diagnostic tests for cystic fibrosis.

The clinical manifestations of CF vary in severity and in the organs affected. The diagnosis is made early in some patients; in others the disease may not manifest itself for many years. In certain patients intestinal malabsorption symptoms predominate, and patients have large, fatty, smelly stools, malnutrition, and abdominal distention. However, in most patients severe bronchitis and recurrent pneumonia are the biggest problems. Pulmonary infections account for the great majority of CF deaths. Median life expectancy is about 30 years.
Tumors and Tumor-like Conditions in Children

Malignant neoplasms in children are uncommon, but nevertheless they are the second most common cause of death; only fatal accidents are more common. Benign tumors and tumor-like masses are much more common than are malignant ones.

A common and innocuous tumor-like (but non-neoplastic) condition is choristoma. Choristomas are normally formed tissue in an abnormal location. For example, a fairly common choristoma is a patch of embryologically misplaced but otherwise normal pancreas found in the stomach wall. On the other hand, hamartomas are local collections of abnormally formed normal tissue in a normal location. They are best thought of as somewhat of a benign neoplasm and somewhat of a congenital malformation. A good example is bronchial hamartoma. Normal bronchi contain cartilage, epithelium, blood vessels, and lymphoid tissue. A bronchial hamartoma may contain one or all of these tissues, but arranged as a small, nodular mass, not as a normal bronchus. Some experts believe congenital hemangiomas, which are common and may be quite large, are hamartomatous collections of small blood vessels and are not neoplastic.

Acute leukemia is the most common malignant neoplasm of children. Other common tumors include lymphoma (Chapter 11) and tumors of the brain and kidney. As compared to adult malignancies, those in children are more often associated with genetic abnormalities, congenital malformations, and a tendency to spontaneously regress or mature into less malignant tissue. They have a better survival rate, often because they are more responsive to therapy.

Figure 7-23 The lungs in cystic fibrosis. Bronchi are dilated and filled with thick, infected mucus.

Laboratory Testing for Cystic Fibrosis

Patients with cystic fibrosis have high levels of sweat sodium and chloride, the exact opposite of the low sodium and chloride content of thick, water-deprived secretions of bronchial glands and the pancreas that account for most of the clinical symptoms. Patients also have abnormal DNA that can be analyzed for a telltale defect, and high levels blood trypsin, a pancreatic digestive enzyme that “backs up” in the blood because pancreatic ducts are plugged with viscous mucus.

Sweat chloride is the most widely applied laboratory test for cystic fibrosis. Specialized apparatus not often found in adult medical settings is required to collect and analyze sweat in patients suspected of having cystic fibrosis. The test entails applying a weak solution of pilocarpine, a drug that stimulates sweating, to a small area of skin, usually on an extremity, which is then stimulated by a weak electrical current for about five minutes. The skin is then cleaned, and an absorbent patch is applied to the area for 30 minutes. The sweat is weighed and analyzed for chloride concentration. Two specimens should be collected, one from each arm or leg, and the results averaged.

CF patients also have high sweat sodium. Most laboratories now perform both sodium and chloride assays on collected sweat. Abnormally high sweat chloride or sodium levels are very reliable indicators that CF is present.

Sweat collection is very difficult in infants less than six weeks old. In these patients a drop of blood may be collected on paper and analyzed for an abnormally high level of trypsin. A similarly small amount of blood may be subjected to analysis of DNA for the genetic defect of CF.
CASE STUDY 7-1 “I THOUGHT IT WOULD GO AWAY”

Immediately after birth the infant develops respiratory distress with sternal retractions. Administration of pulmonary surfactant fails to improve respiratory status, and respiratory assistance is initiated. Chest radiograph reveals hazy opacification of both lungs. On the next day, seizures occur, and the infant dies. At autopsy the important gross findings include lungs that are heavy and airless, intraventricular brain hemorrhage, and heavy meconium staining of the amniotic sac. (The placenta is available for study because hospital personnel have saved it.) Microscopic study shows widespread acute inflammation in the lungs (acute pneumonia) and the amniotic membranes (acute amnionitis).

DISCUSSION

This woman developed preeclampsia, a syndrome of hypertension, proteinuria, and pedal edema in pregnancy. It can be fatal, especially if not recognized and treated early. The cause is unknown. Delivery of the infant is curative.

This infant was premature by menstrual history and birth weight. Body measurements suggest the gestation was at least 25 weeks; the infant weighed 626 grams, indicating he was also small for gestational age (SGA). Premature labor and SGA are likely attributable to the mother’s heavy smoking, drug use, obesity, and high blood pressure.

The fetal membranes of the placenta were stained green by meconium (meconium is fetal intestinal contents), a sign of fetal distress. These findings were supported by faint, irregular fetal heart sounds on admission and low Apgar scores after birth. Microscopic examination of the membranes revealed acute inflammation, strongly suggesting ascending infection from the vagina, a finding supported by the vaginal exudate and the 48-hour delay between the time when the mother’s water broke and her appearance at the emergency room. The fetal lungs showed bronchopneumonia, indicating the infection spread to the infant, through inhalation of amniotic fluid (a fetus inhales amniotic fluid until birth).

The intraventricular hemorrhage in the brain was consistent with the terminal seizures. Such hemorrhages are associated with prematurity and hypoxia, both of which were present in this infant.

POINTS TO REMEMBER

- Women who do not receive prenatal care tend to have complicated pregnancies, including preeclampsia and premature birth.
- Women who smoke or abuse drugs or alcohol are at increased risk for delivering infants who are sick and premature.
- Premature infants have high rates of illness and death.
1. **Distinguish between congenital deformation and malformation, and give an example of each:**
   Congenital malformations are caused by intrinsic abnormalities of the embryologic developmental process. Deformations, on the other hand, are caused by intrauterine mechanical factors. For example, spina bifida is a malformation; clubfoot is a deformation.

2. **Define teratogen, and give an example of a chemical teratogen and an infectious teratogen:**
   A teratogen is an agent capable of inducing abnormal embryologic development to produce a fetal malformation. The most common teratogens are chemicals and viruses. Of chemicals, the most common teratogen is alcohol abuse by the mother, which produces fetal alcohol syndrome. Of infec-
teratogens, the most common are the so-called TORCH group, of which rubella is one agent.

3. **Distinguish among cytogenetic disease, single-gene (Mendelian or monogenic) disease, and disease resulting from multiple genes (polygenic), and give examples of each:** Cytogenetic disorders result from the absence or duplication of an entire chromosome or to large-scale structural dislocations of parts of a chromosome. Down syndrome (three instead of the normal two copies of chromosome 21) is a cytogenetic disorder. Single-gene (monogenic) disorders result from a defect of one gene and are inherited according to Mendelian principles. Sickle cell disease is an example. Polygenetic influence on the development of disease is associated with multiple genes, not usually identifiable. Type II diabetes mellitus is a disease with clear polygenic (hereditary) influences. Polygenetic influence is much more common than are cytogenetic or single-gene defects.

4. **Explain the difference between autosomal dominant and recessive genetic behavior:** An autosomal dominant genetic characteristic requires only one copy of the gene (from either mother or father) for the characteristic to be physically expressed. An autosomal recessive trait requires two copies of the gene, one from each parent.

5. **Explain how inheritance of genetic defects on the X chromosome is different from gene defects on autosomes:** The principal difference is that a single defective recessive gene is expressed as disease when it occurs on an X chromosome. Recessive genes are not expressed when they occur on autosomes unless both copies of the autosome carry the same defective gene.

6. **Offer several examples of disease caused by single-gene defects:** Gaucher disease, familial hypercholesterolemia, neurofibromatosis (von Recklinghausen disease), Marfan syndrome, hemophilia A (classic hemophilia).

7. **Explain how cytogenetic disease differs from other genetic disease, and give an example of a cytogenetic disease:** A cytogenetic disorder is one in which there is 1) one or more extra chromosomes, 2) a missing chromosome, or 3) large scale structural abnormalities such as missing parts (deletion), parts that have been transposed (translocation) to another chromosome, or parts that detach and reattach upside down (inversion). By contrast, other genetic diseases are caused by abnormalities in single genes. Down syndrome (trisomy 21) is a cytogenetic disease.

8. **Explain the genetic abnormality in Turner syndrome:** With abnormal meiosis in the testis, one sperm get both the X and the Y, and the other gets no sex chromosome. If the sperm with no sex chromosome fertilizes a normal (X) ovum, the result is 45,X, which is recognized clinically as Turner syndrome.

9. **Define prematurity, and briefly discuss the associated risks:** An infant is premature if it is born before 37 full weeks of gestation. Premature infants are especially at risk for respiratory distress syndrome, because their lungs are not mature, and for severe hyperbilirubinemia, which can cause kernicterus, a syndrome of severe brain damage characterized by deposits of bilirubin in the floor of the third ventricle.

10. **Explain the difference between prematurity and small for gestational age (SGA):** Prematurity is a condition in which the newborn infant is born before the end of the 37th full week of pregnancy. SGA is a condition in which the newborn infant weighs less than predicted for any given gestational age.

11. **Explain the Apgar score and its usefulness:** It is a numerical assessment of an infant’s vigor immediately after birth. Points (0, 1, or 2) are awarded for heart rate, respiratory effort, muscle tone, color, and response to a catheter inserted in the nose. The maximum score is ten. Vigorous (high-scoring) infants have low perinatal morbidity and mortality; the opposite is true of low-scoring infants.

12. **Name the most common category of intrauterine growth restriction, and offer examples:** Most causes are maternal and include toxemia of pregnancy, chronic hypertension, malnutrition, drug or alcohol abuse, and heavy cigarette smoking.

13. **Name the most common type of perinatal infection of the newborn; name and briefly discuss a few common pediatric infections:** Most perinatal infections are bacterial and occur as the infant passes through the vaginal canal, or they are caused by ascending infection from the vagina into the amniotic sac. The most common pediatric infections are viral; many of them cause acute upper respiratory illnesses featuring fever, cough, and rhinorrhea. Some examples of viral infections are measles, rubella, chickenpox, bronchiolitis, and croup. Bacterial infections include whooping cough, diphtheria, and epiglottitis.

14. **Briefly list some of the epidemiologic characteristics of sudden infant death syndrome (SIDS):** SIDS occurs disproportionately with age under 6 months, prone sleeping position, prematurity, low birth weight, male sex, unmarried mothers less than 20 years old, smoking, drug abuse, low socioeconomic condition, and African American ethnicity.

15. **Explain the pathogenesis of erythroblastosis fetalis:** It is an immune hemolytic anemia in infants that occurs in Rh D-negative mothers who have developed anti-Rh D antibodies from a prior pregnancy...
with an Rh D-positive infant. Any subsequent pregnancy with an Rh D-positive infant runs the risk that her antibodies will attack the infant’s red blood cells, causing hemolytic anemia in the infant.

16. Explain the nature of the metabolic defect in patients with cystic fibrosis: Cystic fibrosis patients have a defect in the transport of chloride across epithelial cell membranes in ductal glands and in respiratory and gastrointestinal mucus glands. Low chloride in ductal secretions fails to attract sodium; low sodium fails to attract water by osmosis. The result is dehydrated, viscous mucus that obstructs gland ducts and creates a seductive environment for infections.

Typical Test Questions

1. Which one of the following is an example of teratogenesis?
   A. Hyaline membrane disease
   B. Fetal rubella infection at 6 weeks
   C. Acute leukemia
   D. Neonatal pneumonia

2. An autosome is which one of the following?
   A. A somatic cell chromosome
   B. A sex chromosome
   C. A defective gene
   D. A recessive gene

3. The heterozygous state is which one of the following?
   A. Both parents have a gene defect
   B. The patient has one copy of a recessive gene
   C. Half of offspring are affected
   D. Gene expression is high

4. Which of the following is the perinatal period?
   A. The first month after birth
   B. From the 28th week of pregnancy to day 7 of infant life
   C. From conception to delivery
   D. From conception to one month of newborn life.

5. Intrauterine growth restriction is usually caused by which one of the following?
   A. Infection
   B. Fetal factors
   C. Maternal alcohol abuse
   D. Maternal factors

6. True or False? Most term, AGA infants have a brief period of increased blood bilirubin shortly after birth.

7. True or False? Hyaline membrane disease (respiratory distress syndrome) is mainly a disease of prematurity.

8. True or False? Sudden infant death syndrome is usually accompanied by diagnostic changes in brain neurons.

9. True or False? ABO blood group incompatibility is the cause of most hemolytic disease of the newborn.

10. True or False? Intestinal and bronchial gland secretions in cystic fibrosis have low sodium and chloride content.