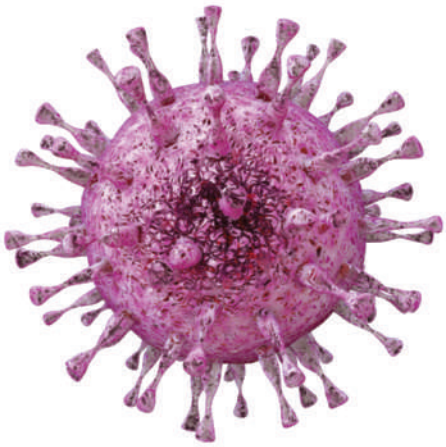

PORTH'S Essentials of Pathophysiology

FIFTH EDITION

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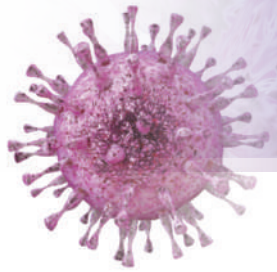
To my husband, Stephen Sr., and children—Richie, Robby,
Stephen Jr., and Rachel—who always inspire me.
To those pursuing or continuing a love for healthcare,
with a special thanks for your dedication, compassion, and selflessness.



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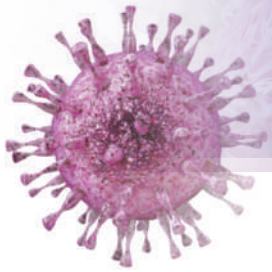

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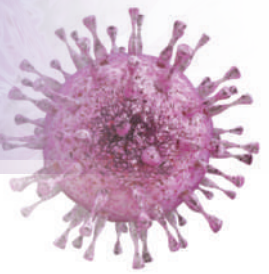


Preface

This book was written with the intent of presenting the subject matter of pathophysiology as the foundation for all future studies in the health sciences. The text provides necessary content for the beginning student to build upon while also serving those furthering their education by reinforcing the link between comprehending complex disease process and clinical decision-making. This text will serve as a reference long after the coursework is completed.

This edition considers the many technologic advances allowing health care providers to diagnose earlier and with more accuracy. A diverse array of contributors for *Porth's Pathophysiology*, 10th Edition (from which this *Essentials* book is derived)was selected based on subject expertise.

This text focuses on the scientific basis upon which the practice components of the health professions are based. The evidence-based information provides data for best practices, ultimately improving health care outcomes.

A holistic conceptual framework uses body systems as an organizing structure and demonstrates how the systems are interrelated. Selection of content was based on common causes of morbidity and mortality across the life span, and recent advances in the fields of genetics, epigenetics, immunology, microbiology, and molecular biology are included. Content is presented in a manner that is logical and understandable for students. One goal of the new edition is to provide critical information needed to understand complex health alterations while delivering the content in a reader-friendly format. The chapters are arranged so that fundamental concepts such as cellular adaptation, inflammation and repair, genetic control of cell function and inheritance, and immunologic processes appear in the early chapters before the specific discussions of particular disease states.

Strengths of the text include the expanded chapters on health and disease; nutrition; sleep and sleep disorders; and thought, emotion, and mood disorders. Advances in health care are presented through the inclusion of international studies, World Health Organization guidelines, updated standards, and the health variants of diverse populations.

Organization

Many of the units have an introductory chapter that contains essential information about the structure and function of the body systems that are being discussed in the unit. Each such chapter provides the foundation for understanding the pathophysiology content presented in the subsequent chapters. The chapter outline that appears at the beginning of each chapter provides an overall view of the chapter content and organization.

Features of This Book

This book includes the following special features to help you master the essential content.

Objectives

Objectives appear at the beginning of each chapter to provide a focus for your study. After you have finished each of these areas of content, you may want to go back and make sure that you have met each of the objectives.

Learning Objectives

After completing this chapter, the learner will be able to meet the following objectives:

1. Contrast disorders due to multifactorial inheritance with those caused by single-gene inheritance.
2. Cite the most susceptible period of intrauterine life for development of defects because of teratogenic agents.
3. State the cautions that should be observed when considering use of drugs during pregnancy, including the possible effects of alcohol abuse, vitamin A derivatives, and folic acid deficiency on fetal development.
4. Describe the process of genetic assessment.
5. Describe screening methods used for prenatal diagnosis including specificity and risks.

Key Terms and Glossary

To enable you to better use and understand the vocabulary of your profession, throughout the text you will encounter key terms in bold purple. This is a signal that a word and the ideas associated with it are important to learn. In addition, a glossary is provided to help you expand your vocabulary and improve your comprehension of what you are reading. The glossary contains concise definitions of the key terms. If you are unsure of the meaning of a term you encounter in your reading, check the glossary in the back of the book before proceeding.

Lysosomes play an important role in the normal metabolism of certain substances in the body. In some inherited diseases known as **lysosomal storage disorders**, a specific lysosomal enzyme is absent or inactive, preventing digestion of certain cellular substances and allowing them to build up in cells.[6] There are approximately 50 lysosomal storage disorders, each caused by a lack of activity of one or more lysosomal enzymes, and each disorder is rare.

Boxes

Boxes are used throughout the text to summarize and highlight key information.

"Key Points" Boxes

One of the ways to approach learning is to focus on the major ideas or concepts. Because health care is an applied science, it is imperative that rather than trying to memorize a list of related and unrelated bits of information, you understand the content and relate it to cases you encounter. Health care providers must apply these concepts in the clinical setting, which requires an understanding of the underlying etiology, histology, symptoms, risk factors, and hallmark features of a particular disease. As you have probably already discovered, it is impossible to memorize everything that is in a particular section or chapter of the book. It has been said that pathophysiology is a new language for many students. So not only does your brain have to figure out where to store all the information, it must also be able to retrieve the information when you need it. This is best accomplished by understanding rather than memorizing information. Most important of all, memorized lists of content can seldom, if ever, be applied directly to an actual clinical situation. The "Key Points" boxes guide you in identifying the major ideas or concepts that form the foundation for truly understanding the major areas of content. When you understand the concepts in the "Key Points" boxes, you will have a framework for remembering and using the facts given in the text.

KEY POINTS

Cellular Adaptations

- Cells are able to adapt to increased work demands or threats to survival by changing their size (atrophy and hypertrophy), number (hyperplasia), and form (metaplasia).
- Normal cellular adaptation occurs in response to an appropriate stimulus and ceases once the need for adaptation has ceased.

"Summary Concepts" Boxes

The "Summary Concepts" boxes at the end of each main section provide a review and a reinforcement of the important content that has been covered. Use the summaries to ensure that you have covered and understood what you have read.

SUMMARY CONCEPTS

Neonates are protected against antigens in early life as a result of passive transfer of maternal IgG antibodies through the placenta and IgA antibodies in colostrum and breast milk. Many changes occur with aging, but the exact mechanisms are not completely understood. However, the elderly population is more prone to infection and autoimmune disorders secondary to altered response in both innate and adaptive immune function.

"Understanding" Boxes

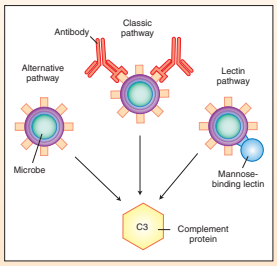
"Understanding" boxes focus on the physiologic processes and phenomena that form the basis for understanding disorders presented in the text. This feature breaks a process or phenomenon down into its component parts and presents it in a sequential manner, providing an insight into the many opportunities for disease processes to disrupt the sequence.

UNDERSTANDING → The Complement System

The complement system provides one of the major effector mechanisms of both humoral and innate immunity. The system consists of a group of proteins (complement proteins C1 through C9) that are normally present in the plasma in an inactive form. Activation of the complement system is a highly regulated process, involving the sequential breakdown of the complement proteins to generate a cascade of cleavage products capable of proteolytic enzyme activity. This allows for tremendous amplification because each enzyme molecule activated by one step can generate multiple activated enzyme molecules at the next step. Complement activation is inhibited by proteins that are present on normal host cells; thus, its actions are limited to microbes and other antigens that lack these inhibitory proteins.

The reactions of the complement system can be divided into three phases: **(1)** the initial activation phase, **(2)** the early-step inflammatory responses, and **(3)** the late-step membrane attack responses.

1 **Initial Activation Phase** There are three pathways for recognizing microbes and activating the complement system: (1) the alternative pathway, which is activated on microbial cell surfaces in the absence of antibody and is a component of innate immunity; (2) the classical pathway, which is activated by certain types of antibodies bound to antigen and is part of humoral immunity; and (3) the lectin pathway, which is activated by a plasma lectin that binds to mannose on microbes and activates the classical system pathway in the absence of antibody.



Tables and Charts

Tables and charts are designed to present complex information in a format that makes it more meaningful and facilitates recall of the information. Tables, which have two or more columns, are often used for the purpose of comparing or contrasting information. Charts, which have one column, are used to summarize information.

TABLE 20-1 Common Disorders Affecting the Vestibular System

Type of Disorder	Pathology
Acoustic neuroma	A noncancerous growth or tumor on the vestibulocochlear nerve
Benign paroxysmal positional vertigo	Disorder of otoliths
Ménière disease	Dislodgement of otoliths that participate in the receptor function of the vestibular system
Motion sickness	Repeated stimulation of the vestibular system such as during car, air, and boat travel
Labyrinthitis	Acute viral or bacterial infection of the vestibular pathways
Vestibular migraine	Dizziness or vertigo occurs with or without headache; related to the neurotransmitter serotonin

Illustrations and Photos

The detailed, full-color illustrations will help you to build your own mental image of the content that is being presented. Each drawing has been developed to fully support and build upon the ideas in the text. Some illustrations are used to help you picture the complex interactions of the multiple phenomena that are involved in the development of a particular disease; others can help you to visualize normal function or understand the mechanisms that enable the disease processes to exert their effects. In addition, photographs provide a realistic view of selected pathologic processes and lesions.

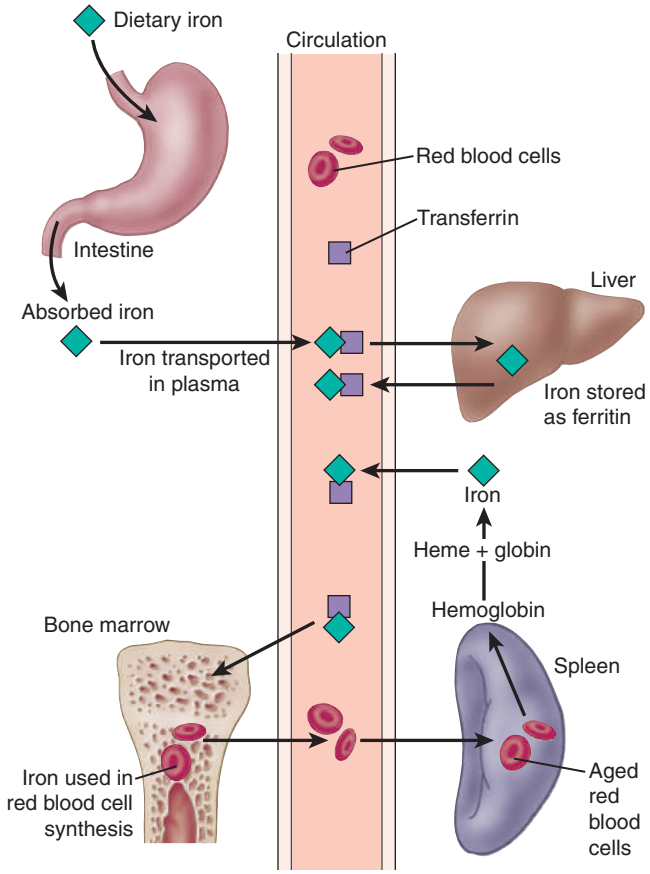


FIGURE 23-3. Diagrammatic representation of the iron cycle, including its absorption from the gastrointestinal tract, transport in the circulation, storage in the liver, recycling from aged red cells destroyed in the spleen, and use in the bone marrow synthesis of red blood cells.

Concept Mastery Alerts

Concept Mastery Alerts clarify fundamental nursing concepts to improve the reader's understanding of potentially confusing topics, as identified by Misconception Alerts in Lippincott's Adaptive Learning Powered by prepU.

Concept Mastery Alert

Smoking is an independent risk factor for the development of coronary artery disease and should be avoided, but it has not been identified as a direct cause of hypertension.

Interactive Learning Resources

Interactive learning tools available online enrich learning and are identified with icons in the text.

- **Concepts in Action Animations** bring physiologic and pathophysiologic concepts to life, explaining concepts that are difficult to understand.
- **Interactive Tutorials** include graphics and animations and provide interactive review exercises.

Review Exercises

The Review Exercises at the end of each chapter are designed to help you integrate and synthesize material and to help you verify your understanding of the material presented. If you are unable to answer a question, reread the relevant section in the chapter. (Answers are available for instructors at http://thepoint.lww.com/PorthEssentials5e.)

Review Exercises

1. A 32-year-old woman with diabetes is found to have a positive result on a urine dipstick test for microalbuminuria. A subsequent 24-hour urine specimen reveals an albumin excretion of 50 mg (an albumin excretion >30 mg/day is abnormal).
   - **A.** Use the structures of the glomerulus in Figure 32-5 to provide a possible explanation for this finding. Why specifically test for the albumin rather than the globulins or other plasma proteins?
   - **B.** Strict control of blood sugars and treatment of hypertension have been shown to decrease the progression of kidney disease in person with diabetes. Explain the physiologic rationale for these two types of treatments.
2. A 54-year-old man, seen by his physician for an elevated blood pressure, was found to have a serum creatinine of 2.5 and BUN of 30. He complains that he has been urinating more frequently than usual, and his first morning urine specimen reveals dilute urine with a specific gravity of 1.010.
   - **A.** Explain the elevation of serum creatinine in terms of renal function.
   - **B.** Explain the inability of people with early renal failure to produce concentrated urine as evidenced by the frequency of urination and the low specific gravity of his first morning urine specimen.

Appendix

The appendix "Lab Values" provides rapid access to normal values for many laboratory tests, as well as a description of the prefixes, symbols, and factors (*e.g.*, micro, μ, 10^{-6}) used for describing these values. Knowledge of normal values can help you to put abnormal values in context.

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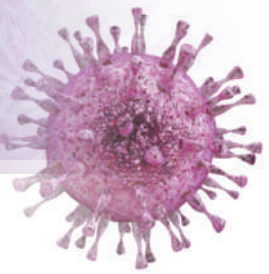

Acknowledgments

The expertise of the contributors for *Porth's Pathophysiology*, 10th Edition (from which this *Essentials* book is derived) keeps the book at the forefront of advances in science and medicine. Their attention to detail and desire to share current, relevant, and essential information with learners are primary strengths of the text. For the fifth edition, several chapters were merged to improve flow of content, and chapters that include new discoveries were added. Thanks also to Dr. Rupa Lalchandani Tuan for her time and talent in helping to ensure the accuracy of the information and assisting in condensing it to reflect only essential content needed to understand disease processes.

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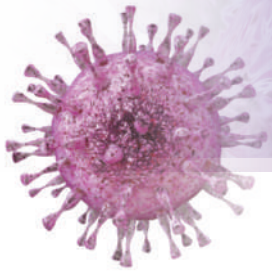
Lastly, I want to thank my family for their inspiration during this difficult time of transition in my life. I also want to thank all the professors who have kept in touch with me throughout this project, cheering me forward to produce a text that is understandable yet concise and that meets the learning needs of today's health care professional.



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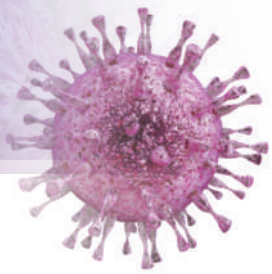

CHAPTER 5

Genetic and Congenital Disorders

Learning Objectives

After completing this chapter, the learner will be able to meet the following objectives:

1. Contrast disorders due to multifactorial inheritance with those caused by single-gene inheritance.
2. Cite the most susceptible period of intrauterine life for development of defects because of teratogenic agents.
3. State the cautions that should be observed when considering use of drugs during pregnancy, including the possible effects of alcohol abuse, vitamin A derivatives, and folic acid deficiency on fetal development.
4. Describe the process of genetic assessment.
5. Describe screening methods used for prenatal diagnosis including specificity and risks.

Congenital defects, sometimes called birth defects, are abnormalities of a body structure, function, or metabolism that are present at birth. They affect more than 185,000 infants discharged from the hospital in the United States each year and are the leading cause of infant death.[1] Congenital defects may be caused by genetic factors or environmental factors that are active during embryonic or fetal development. Although congenital defects caused by genetic factors are present at birth, they may not make their appearance until later in life. This chapter provides an overview of genetic and congenital disorders and is divided into three parts:

1. Genetic and chromosomal disorders
2. Disorders due to environmental agents
3. Diagnosis and counseling

Genetic and Chromosomal Disorders

Most genetic disorders are caused by changes in the deoxyribonucleic acid (DNA) sequence that alters the synthesis of a single gene product. Other genetic disorders are a result of chromosomal aberrations such as deletion or duplication errors, or are due to an abnormal number of chromosomes.

The genes on each chromosome are arranged in strict order, with each gene occupying a specific location or *locus*. The two members of a gene pair, one inherited from the mother and the other from the father, are called *alleles*. If the members of a gene pair are identical (*i.e.*, code the exact same gene product), the person is homozygous, and if the two members are different, the person is heterozygous. The genetic composition of a person is called a genotype, whereas the phenotype is the observable expression of a genotype in terms of physical or biochemical traits. If the trait is phenotypically seen in the heterozygote, the allele is said to be *dominant*. If it is phenotypically seen only in the homozygote, the allele is *recessive*. Many genes have more than one normal allele (alternate forms) at the same locus. This is called a *polymorphism*. Although most traits follow a dominant or recessive pattern, it is possible for both alleles of a gene pair to be phenotypically seen in the heterozygote, a condition called *codominance*. Blood group inheritance (*e.g.*, AO, BO, AB) is an example of both codominance and polymorphism.

A gene *mutation* is a biochemical event such as nucleotide change, deletion, or insertion that produces a new allele for a particular gene. A single mutant gene may be expressed in many different parts of the body. Marfan syndrome, for example, is a single gene defect in a connective tissue protein that has widespread effects involving skeletal, eye, and cardiovascular structures. The disorder may be inherited as a family trait or arise as a sporadic case because of a new mutation.

Single-Gene Disorders

Single-gene disorders are caused by a defective or mutant allele at a single gene locus and follow mendelian patterns of inheritance. Single-gene disorders are characterized by their patterns of transmission, which usually are obtained through a family genetic history. The patterns of inheritance depend on whether the phenotype is dominant or recessive and whether the gene of concern is located on an autosomal or sex chromosome. In addition to disorders caused by mutations of genes located on the chromosomes within the nucleus, another (but more rare) class of disorders involves the mitochondrial genome and shows a maternal pattern of inheritance.

Virtually all single-gene disorders lead to the formation of an abnormal protein or the decreased production of a gene product. These changes can result in many different types of systemic alterations. Table 5-1 lists some of the common single-gene disorders and their manifestations.

Autosomal Dominant Disorders

In autosomal dominant disorders, a single mutant allele from an affected parent is transmitted to an offspring regardless of sex. The affected parent has a 50% chance of transmitting the disorder to each offspring (Fig. 5-1). The unaffected relatives of the parent or unaffected siblings of the offspring do not transmit the disorder. In many conditions, the age of onset is delayed, and the signs and symptoms of the disorder do not appear until later in life.

Autosomal dominant disorders also may manifest as a new mutation. Many autosomal dominant mutations are accompanied by reduced reproductive capacity; therefore, the defect is not repeated in future generations. If an autosomal defect is accompanied by a total inability to reproduce, essentially all new cases of the

TABLE 5-1 Some Disorders of Mendelian or Single-Gene Inheritance and Their Significance

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

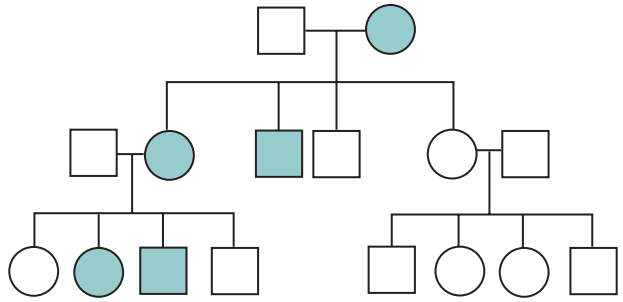

FIGURE 5-1. Simple pedigree for inheritance of an autosomal dominant trait. *Squares* represent males, *circles* represent females. The *shaded symbols* represent an affected parent with a mutant gene. An affected parent with an autosomal dominant trait has a 50% chance of passing the mutant gene on to each child regardless of sex.

disorder will be due to new mutations. If the defect does not affect reproductive capacity, it is more likely to be inherited from a parent.

Although there is a 50% chance of inheriting a dominant genetic disorder from an affected parent, there can be wide variation in **gene penetrance** and expression. When a person inherits a dominant mutant gene but fails to exhibit the associated phenotype, the trait is described as having *reduced penetrance*. The person who has a mutant gene but does not express it is an important exception to the rule that unaffected persons do not transmit an autosomal dominant trait. These people can transmit the gene to their descendants and so produce a "skipped generation" in their family history. Autosomal dominant disorders also can display *variable expressivity*, meaning that they can be expressed differently in people who carry the mutant gene. Polydactyly or supernumerary digits, for example, may be expressed in either the fingers or the toes.[2] Other disorders of autosomal inheritance, Marfan syndrome and neurofibromatosis (NF), are described here.

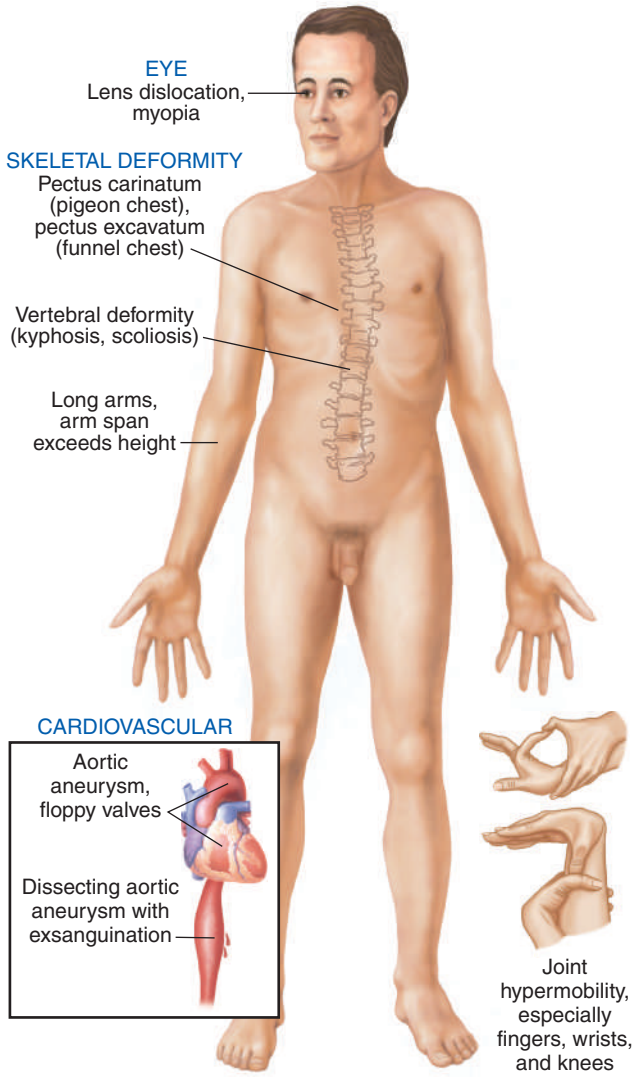

FIGURE 5-2. Clinical features of Marfan syndrome.

Marfan Syndrome

Marfan syndrome is an autosomal dominant disorder of the connective tissue. The basic biochemical abnormality in Marfan syndrome affects *fibrillin I*, a major component of microfibrils found in the extracellular matrix.[3] Fibrillin I is coded by the *FBNI* gene, which maps to chromosome 15q21. The prevalence of Marfan syndrome is estimated to be 1 per 5000. Approximately 70% to 80% of cases are familial and the remainder are sporadic, arising from new mutations in the germ cells of the parents.[3]

Marfan syndrome affects several organ systems, including the eyes; the cardiovascular system; and the skeletal system (bones and joints).[3] There is a wide range of variation in the phenotype for the disorder. The skeletal deformities include a long, thin body with exceptionally long extremities and long, tapering fingers, sometimes called *arachnodactyly* or *spider fingers*; hyperextensible joints; and a variety of spinal deformities, including **kyphosis** and scoliosis (Fig. 5-2). Chest deformities, pectus excavatum (*i.e.*, deeply depressed sternum) or pigeon chest deformity, often are present and may require surgery. The most common eye disorder is bilateral dislocation of the lens because of weakness of the suspensory ligaments. Myopia and predisposition to retinal detachment also are common. However, the most life-threatening aspects of the disorder are the cardiovascular defects, which include mitral valve **prolapse**, progressive dilation of the aortic valve ring, and weakness of the aorta and other arteries. Dissection and rupture of the aorta may lead to premature death.

The diagnosis of Marfan syndrome is based on major and minor diagnostic criteria that include skeletal, cardiovascular, and ocular deformities. There is currently no cure for Marfan syndrome. Treatment plans include regular assessment of the at-risk systems.

Neurofibromatosis

NF is a condition that causes tumors to develop from the Schwann cells of the neurologic system.[4] There are at least two genetically and clinically distinct forms of the disorder:

1. Type 1 NF (NF-1), also known as *von Recklinghausen disease*.

2. Type 2 bilateral acoustic NF (NF-2).[4,5]

Both of these disorders result from a genetic defect in a tumor suppressor gene that regulates cell differentiation and growth. The gene for NF-1 has been mapped to the long arm of chromosome 17 and the gene for NF-2 to chromosome 22.[4,6]

Type 1 NF is a common disorder, characterized by **cutaneous** and subcutaneous neurofibromas that develop in late childhood or adolescence.[4] The cutaneous neurofibromas, which vary in number from a few to many hundreds, manifest as soft, **pedunculated** lesions that project from the skin. They are the most common type of lesion, often are not apparent until puberty, and are present in greatest density over the trunk (Fig. 5-3). The subcutaneous lesions grow just below the skin. They are firm and round and may be painful. Plexiform neurofibromas involve the larger peripheral nerves. They tend to form large tumors that cause severe disfigurement of the face, overgrowth of an extremity, or skeletal deformities such as scoliosis. Pigmented nodules of the iris (Lisch nodules), which are specific for NF-1, usually are present after 6 years of age.[7] They do not present any clinical problem but are useful in establishing a diagnosis.

A second major component of NF-1 is the presence of large (usually ≥15 mm in diameter), flat cutaneous pigmentations, known as *café au lait spots*. They are usually a uniform light brown in whites and darker brown in people of color, with sharply demarcated edges. Although small single lesions may be found in normal children, larger lesions or six or more spots greater than 1.5 cm in diameter suggest NF-1.[8] The skin pigmentations become more evident with age as the melanosomes in the epidermal cells accumulate melanin.

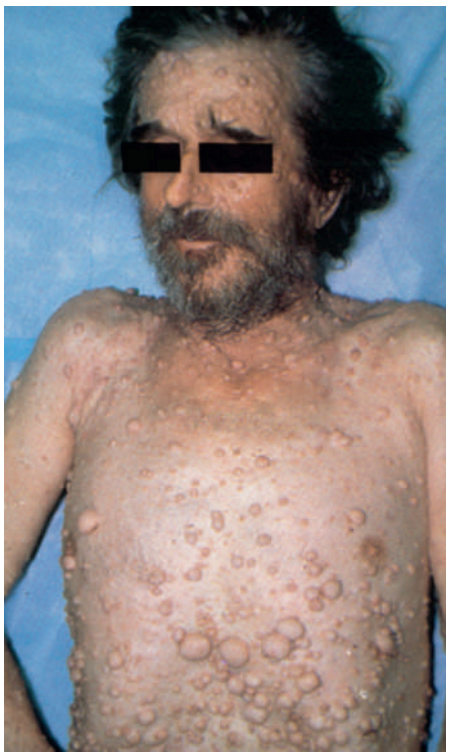

FIGURE 5-3. Neurofibromatosis type 1. Multiple cutaneous neurofibromas are noted on the face and trunk. (From Strayer D. S., Rubin E. (Eds.) (2015). *Rubin's pathology: Clinicopathologic foundations of medicine* (7th ed., Fig. 6-20C, p. 269). Philadelphia, PA: Lippincott Williams & Wilkins.)

Children with NF-1 are also susceptible to neurologic complications including an increased incidence of learning disabilities, attention deficit disorders, abnormalities of speech, and complex partial and generalized tonic–clonic seizures. Malignant neoplasms are also a significant problem in people with NF-1. One of the major complications of NF-1, occurring in 3% to 5% of people, is the appearance of a neurofibrosarcoma.[4] NF-1 is also associated with increased incidence of other neurogenic tumors, including meningiomas, optic gliomas, and pheochromocytomas.

Type 2 NF is characterized by tumors of the acoustic nerve. Most often, the disorder is asymptomatic through the first 15 years of life. This type of NF occurs less frequently, at a rate of 1 in 50,000 people. The most frequent symptoms are headaches, hearing loss, and **tinnitus**. There may be associated intracranial and spinal meningiomas.

Autosomal Recessive Disorders

Autosomal recessive disorders are manifested only when both members of the gene pair are affected (homozygous). In this case, both parents may be unaffected but are carriers of the defective gene. Autosomal recessive disorders affect both sexes. The occurrence risks in each pregnancy are one in four for an affected child, two in four for a carrier child, and one in four for a normal (noncarrier, unaffected), homozygous child (Fig. 5-4). *Consanguineous mating* (mating of two related people), or inbreeding, increases the chance that two people who mate will be carriers of an autosomal recessive disorder.

With autosomal recessive disorders, the age of onset is frequently early in life. In addition, the symptomatology tends to be more uniform than with autosomal dominant disorders. Autosomal disorders are characteristically caused by loss-of-function mutations, many of which impair or eliminate the function of an enzyme. In the case of a heterozygous carrier, the presence of a mutant gene usually does not produce symptoms because equal amounts of normal and defective enzymes are synthesized. This "margin of safety" ensures that cells with half their usual amount of enzyme function normally. By contrast, the inactivation of both alleles in a homozygote results in complete loss of enzyme activity. Autosomal recessive disorders include almost all inborn errors of metabolism. Enzyme disorders that impair catabolic pathways result in an accumulation of dietary substances (*e.g.*, phenylketonuria [PKU]) or cellular constituents (*e.g.*, lysosomal storage diseases). Other disorders result from a defect in the enzyme-mediated synthesis of an essential protein (*e.g.*, the cystic fibrosis transmembrane conductance regulator in cystic fibrosis). Two examples of autosomal recessive disorders that are not covered elsewhere in this book are PKU and Tay–Sachs disease.

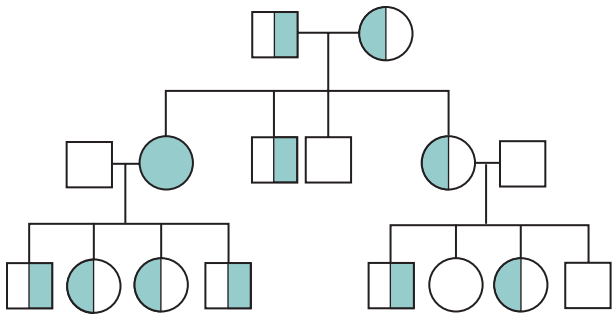

FIGURE 5-4. Sample pedigree for inheritance of an autosomal recessive trait. *Squares* represent males, *circles* represent females. When the symbols are *half shaded*, then that parent is a carrier of an autosomal recessive trait. When both parents are carriers, on each conception, there is a 25% chance of having an affected child (*full-shaded circle* or *square*), a 50% chance of a carrier child, and a 25% chance of a nonaffected or noncarrier child, regardless of sex.

Phenylketonuria

PKU is a rare autosomal recessive metabolic disorder that affects approximately 1 in every 10,000 to 15,000 infants in the United States. The disorder is caused by a deficiency of the liver enzyme phenylalanine hydroxylase, which allows toxic levels of the amino acid, phenylalanine, to accumulate in tissues and the blood.[9] If untreated, the disorder results in mental retardation, microcephaly, delayed speech, and other signs of impaired neurologic development.

Because the symptoms of PKU develop gradually and are difficult to assess, all infants are screened for abnormal levels of serum phenylalanine.[5] Infants with the disorder are treated with a special diet that restricts phenylalanine intake to prevent mental retardation as well as other neurodegenerative effects. Infants with elevated phenylalanine levels should begin treatment by 7 to 10 days of age, indicating the need for early diagnosis.[9]

Tay–Sachs Disease

Tay–Sachs disease is a variant of a class of lysosomal storage diseases, known as the *gangliosidoses*, in which there is failure to break down the GM2 gangliosides of cell membranes.[10] Tay–Sachs disease is inherited as an autosomal recessive trait and occurs 10 times more frequently in offspring of Eastern European (Ashkenazi) Jews as compared to the general population, although targeted carrier screening efforts have shown success in reducing rates for this population.[11]

The GM2 ganglioside accumulates in the lysosomes of all organs in Tay–Sachs disease, but is most prominent in the brain neurons and retina.[10] Microscopic examination reveals neurons ballooned with cytoplasmic vacuoles, each of which constitutes a markedly distended lysosome filled with gangliosides.[10] In time, there is progressive destruction of neurons, including in the cerebellum, basal ganglia, brainstem, spinal cord, and autonomic nervous system. Involvement of the retina is detected by ophthalmoscopy as a cherry-red spot on the **macula**.[10]

Infants with Tay–Sachs disease appear normal at birth but begin to manifest progressive weakness, muscle flaccidity, and decreased responsiveness at approximately 6 to 10 months of age.[10] This is followed by rapid deterioration of motor and mental function, often with development of generalized seizures. Retinal involvement leads to visual impairment and eventual blindness. Death usually occurs before 4 to 5 years of age.[10] Analysis of the blood serum for the lysosomal enzyme, hexosaminidase A, which is deficient in Tay–Sachs disease, allows for accurate identification of genetic carriers for the disease.[11]

X-Linked Recessive Disorders

Sex-linked disorders are almost always associated with the X chromosome, and the inheritance pattern is predominantly recessive. Remember that the sex chromosomes for human females are XX and human males are XY. Because of the presence of a normal X, female heterozygotes (carriers) rarely experience the effects of a recessive defective gene, whereas all males who receive the gene are typically affected as they only have the mutant copy.

The common pattern of inheritance in a family is one in which an unaffected mother is a carrier of the mutant allele. She is not affected herself because she has one normal X that is dominant over the mutant recessive X. Because she will contribute one of these two X chromosomes to each of her offspring, she has a 50% chance of transmitting the mutant gene to her sons (who only have one X and will be affected), and her daughters have a 50% chance of being carriers of the mutant gene (who have two X chromosomes and so will not be affected because of the presence of a normal X) (Fig. 5-5).

When the affected son procreates, he only has his mutant X or a normal Y to pass on to the next generation. In order to have a daughter, the father donates his only X chromosome, which combines with one of the mother's two X chromosomes, resulting in a XX child. Because his X is mutated, he transmits the mutant gene to 100% of his daughters, who then become carriers. Because the genes of the Y chromosome are unaffected, the affected male does not transmit the defect to any of his sons, and they will not be carriers or transmit the disorder to their children.

Although rare, females can be affected with an X-linked recessive disorder. In order for this to happen, an affected male would need to have a child with a carrier female. In this case, 50% of the sons would be affected, and 50% of the daughters would be affected. The remaining daughters would be carriers like their mother. X-linked recessive disorders include color blindness, glucose-6-phosphate dehydrogenase deficiency, hemophilia A, and X-linked **agammaglobulinemia**.

X-Linked Dominant Disorders

X-linked dominant disorders are not as common as X-linked recessive disorders affecting both males and females that inherit a copy of the mutated X chromosome.

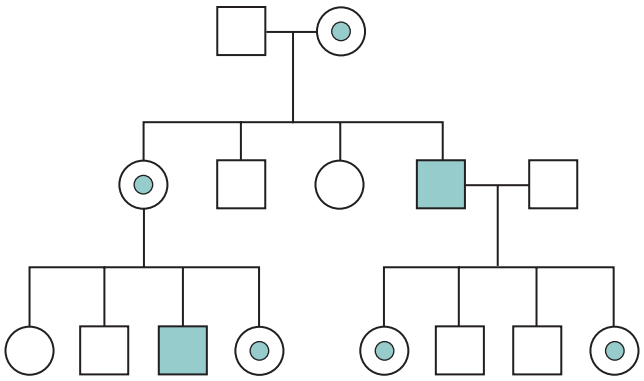

FIGURE 5-5. Sample pedigree for inheritance of an X-linked recessive trait. X-linked recessive traits are expressed phenotypically in the male offspring, whereas females are typically carriers for the trait. A *small shaded circle* represents a carrier female and the *larger shaded square*, the affected male. A carrier female will transmit her carrier status to 50% of her daughters and 50% of her sons will be affected. The affected male passes the mutant gene to all of his daughters, who become carriers of the trait. The affected male will have no affected sons.

For the females, the mutant X chromosome is dominant to the normal X chromosome. Although both sexes are affected, many times the mutation will be embryonic lethal for males (who only have the mutated X and a normal Y) or for homozygous mutant females. Affected females who are heterozygous with one mutant X chromosome and one normal X chromosome will transmit the disorder to 50% of their offspring regardless of sex. Affected males will have 100% affected daughters or 100% normal sons. This is explained because all sons inherited their father's Y chromosome, but the daughters inherited the mutated X chromosome from their father. Examples of X-linked dominant disorders include fragile X syndrome and Rett syndrome.

Fragile X Syndrome

Fragile X syndrome is a single-gene disorder that causes intellectual disability.[12] The mutation occurs at Xq27 on the fragile site and is characterized by amplification of a cytosine, guanine, guanine (CGG) repeat.[13] The disorder, which affects approximately 1 in 1250 males and 1 in 2500 females, is the most common form of inherited intellectual disability.[12]

Pathogenesis

The fragile X gene has been mapped to the long arm of the X chromosome, designated the *FMR1* (fragile X mental retardation 1) site.[13] The gene product, the fragile X mental retardation protein (FMRP), is a widely expressed cytoplasmic protein. It is most abundant in the brain and testis, the organs most affected by the disorder. Each gene contains a promoter region and an instruction region that carries the directions for protein synthesis. The promoter region of the *FMR1* gene contains repeats of a specific CGG triplet code that, when normal, controls gene activity. Once the repeat exceeds a threshold length for the disease, no FMRP is produced, resulting in the fragile X phenotype.[13]

Clinical Manifestations and Diagnosis

Affected boys are intellectually disabled and share a common physical phenotype that includes a long face with large mandible and large, everted ears. Hyperextensible joints, a high-arched palate, and mitral valve prolapse, which are observed in some cases, mimic a connective tissue disorder.[12] Some physical abnormalities may be subtle or absent. Because girls have two X chromosomes, they are more likely to have relatively normal cognitive development, or they may show a learning disability in a particular area.

Diagnosis of fragile X syndrome is based on mental and physical characteristics. DNA tests can be done to confirm the presence of an abnormal *FMR1* gene. Fragile X screening is now often offered along with routine prenatal screening to determine if the woman is a carrier.

KEY POINTS

Single-Gene Disorders

- Genetic disorders can be inherited as autosomal dominant disorders, in which the phenotype is seen in both the homozygous dominant or heterozygous genotype, or as autosomal recessive disorders, in which the phenotype is only seen in the homozygous recessive genotype.
- Sex-linked disorders almost always are associated with the X chromosome and are predominantly recessive.

Inherited Multifactorial Disorders

Multifactorial disorders are caused by the influence of multiple genes along with environmental factors. These traits do not follow the same clear-cut pattern of inheritance as do single-gene disorders because the appearance of the disorder phenotype will be dependent on environmental changes in addition to genetic mutations. Disorders of multifactorial inheritance can be present at birth, or they may be expressed later in life. Congenital disorders that are thought to arise through multifactorial inheritance include cleft lip or palate, clubfoot, congenital dislocation of the hip, congenital heart disease, pyloric **stenosis**, and urinary tract malformation. Environmental factors are thought to play an even greater role in disorders of multifactorial inheritance that develop in adult life, such as coronary artery disease, diabetes mellitus, hypertension, and cancer.

Although multifactorial traits cannot be predicted with the same degree of accuracy as mendelian single-gene mutations, characteristic patterns do exist for congenital disorders. First, multifactorial congenital malformations tend to involve a single organ or tissue derived from the same embryonic developmental field. Second, the risk of recurrence in future pregnancies is

high for the same or a similar defect. For instance, this means that parents of a child with a cleft palate defect have an increased risk of having another child with a cleft palate defect. Third, first-degree relatives of an affected person have an increased risk (as compared with the general population) of having a child with the disease. The risk increases with increasing numbers of the incidence of the defect among relatives.

Cleft Lip and Cleft Palate

Cleft lip with or without cleft palate is one of the most common birth defects, occurring in about 0.1% of all pregnancies.[14] It is also one of the more conspicuous birth defects, resulting in an abnormal facial appearance and defective speech.

Developmentally, the defect has its origin at about the 35th day of gestation when the frontal prominences of the craniofacial structures fuse with the **maxillary** process to form the upper lip.[14] This process is under the control of many genes, and disturbances in these (whether hereditary or environmental) at this time may result in cleft lip with or without cleft palate (Fig. 5-6). The defect may also be caused by **teratogens** (*e.g.*, rubella, anticonvulsant drugs) and is often encountered in children with chromosomal abnormalities.

Cleft lip and palate defects may vary from a small notch in the vermilion border of the upper lip to complete separation involving the palate and extending into the floor of the nose. The clefts may be unilateral or bilateral and may involve the alveolar ridge. The condition may be accompanied by deformed, supernumerary, or absent teeth. Isolated cleft palate occurs in the midline and may involve only the uvula or may extend into or through the soft and hard palates.

A child with cleft lip or palate may require years of special treatment by medical and dental specialists. The immediate problem in an infant with cleft palate is feeding. Nursing at the breast or nipple depends on suction developed by pressing the nipple against the hard palate with the tongue. Although infants with cleft lip usually have no problems with feeding, those with cleft palate usually require specially constructed, soft artificial nipples with large openings and a squeezable bottle. As the child ages, speech may be impaired because of these issues.

Major advances in the care of children born with cleft lip and palate have occurred within the last quarter of the 20th century.[15] Surgical closure of the lip is usually performed by 3 months of age, with closure of the palate usually done before 1 year of age. Depending on the extent of the defect, additional surgery may be required as the child grows.

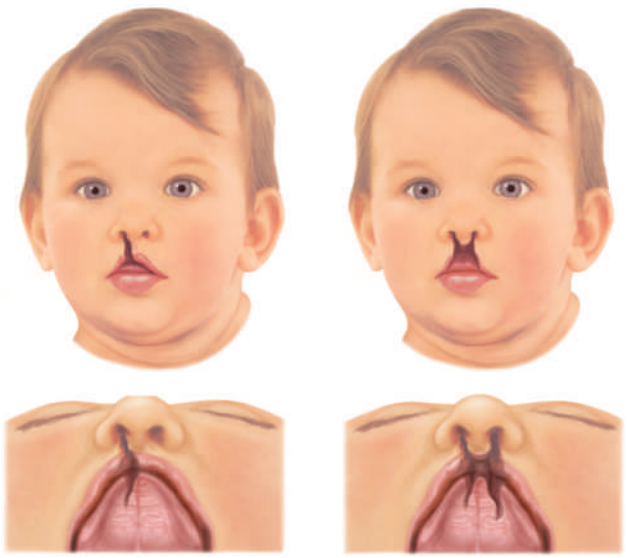

FIGURE 5-6. Cleft lip and cleft palate.

Chromosomal Disorders

Chromosomal disorders form a major category of genetic disease, accounting for a large proportion of early miscarriages, congenital malformations, and intellectual disability. The study of chromosomal disorders is called *cytogenetics*.

During mitosis in human somatic cells, the chromosomes replicate so that each cell receives a total of 23 pairs of chromosomes. But in germ cells undergoing meiosis, these pairs are reduced so that each daughter cell only receives 23 individual chromosomes. At the time of conception, the set of 23 individual chromosomes in the ovum and the set of 23 individual chromosomes in the sperm join to produce an offspring with 23 pairs, or 46 total chromosomes.

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

Structural Chromosomal Abnormalities

The aberrations underlying chromosomal disorders can be an abnormal number of chromosomes, but there can also be alterations to the structure of one or more chromosomes. Structural changes in chromosomes usually result from breakage in one or more of the chromosomes during meiosis followed by rearrangement or deletion of chromosome parts. Among the factors believed to cause chromosome breakage are exposure to radiation sources such as x-rays, influence of certain chemicals, extreme changes in the cellular environment, and viral infections.

Several patterns of chromosome breakage and rearrangement can occur (Fig. 5-7). There can be a *deletion* of the broken portion of the chromosome. When one chromosome is involved, the broken parts may be *inverted*. *Isochromosome formation* occurs when the centromere of the chromosome separates horizontally instead of vertically. *Ring formation* results when deletion is followed by uniting of the chromatids to form a ring. *Translocation* occurs when there are simultaneous breaks in two chromosomes from different pairs, with

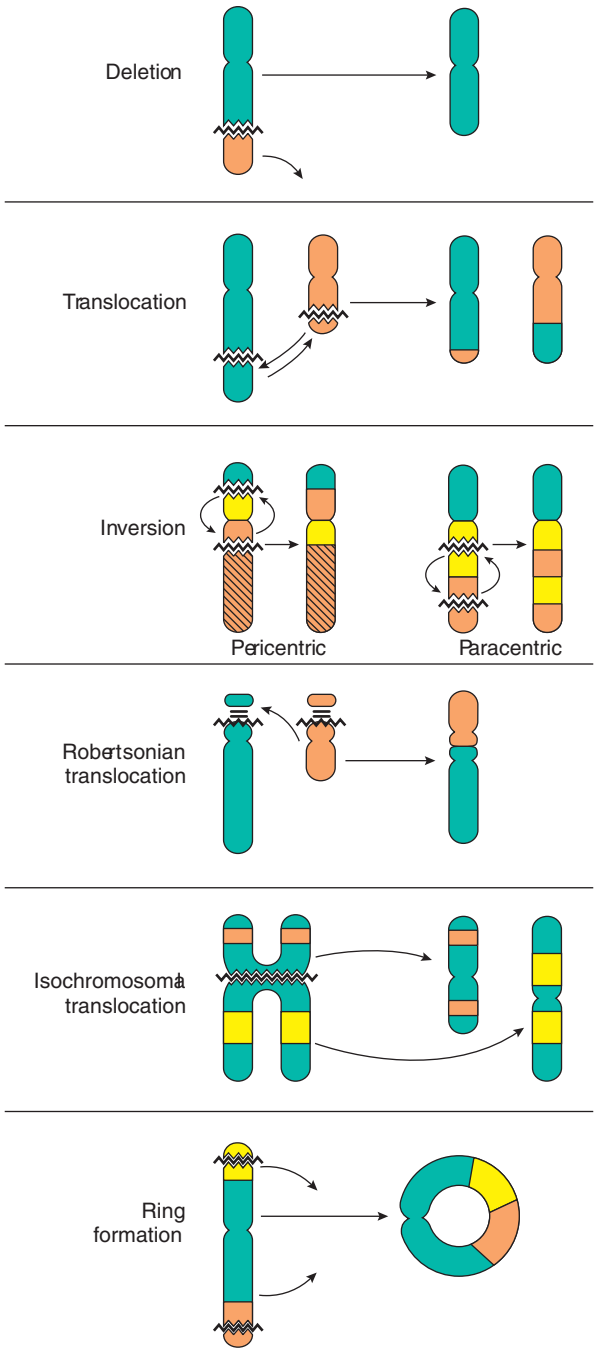

FIGURE 5-7. Structural abnormalities in the human chromosome. The deletion of a portion of a chromosome leads to loss of genetic material and shortened chromosome. A **reciprocal translocation** involves breaks on two nonhomologous chromosomes, with exchange of the acentric segment. An **inversion** requires two breaks in a single chromosome. If the breaks are on opposite sides of the centromere, the inversion is **pericentric**; it is **paracentric** if the breaks are on the same arm. A **robertsonian translocation** occurs when two nonhomologous acrocentric chromosomes break near their centromeres, after which the long arms fuse to form one large metacentric chromosome. **Isochromosomes** arise from faulty centromere division, which leads to duplication of the long arm (iso q) and deletion of the short arm, or the reverse (iso p). Ring chromosomes form involve breaks in both telomeric portions of a chromosome, deletion of the acentric fragments, and fusion of the remaining centric portion. (From Rubin R, Strayer D. S. (Eds.) (2015). *Rubin's pathology: Clinicopathologic foundations of medicine* (7th ed., Fig. 6-8, p. 253). Philadelphia, PA: Lippincott Williams & Wilkins.)

exchange of chromosome parts. With a balanced reciprocal translocation, no genetic information is lost; therefore, persons with translocations usually are normal.

Centric fusion or *robertsonian translocation* involves two acrocentric chromosomes in which the centromere is near the end, most commonly chromosomes 13 and 14, or 14 and 21. Typically, the break occurs near the centromere affecting the short arm in one chromosome and the long arm in the other. Transfer of the chromosome fragments leads to one long and one extremely short fragment. The short fragment is usually lost during subsequent divisions. In this case, the person has only 45 chromosomes, but the amount of genetic material that is lost is so small that it often goes unnoticed. Difficulty, however, arises during meiosis; the result is gametes with an unbalanced number of chromosomes. The chief clinical importance of this type of translocation is that carriers of a robertsonian translocation involving chromosome 21 are at high risk for producing a child with Down syndrome.

The manifestations of aberrations in chromosome structure depend to a great extent on the amount of genetic material that is lost or displaced. Many cells sustaining major unrestored breaks are eliminated within the next few replication cycles because of deficiencies that may in themselves be fatal. This is beneficial because it prevents the damaged cells from becoming a permanent part of the organism or, if it occurs in the gametes, from giving rise to grossly defective zygotes.

Numeric Disorders Involving Autosomes

Having an abnormal number of chromosomes is referred to as **aneuploidy**. Many times, this happens when there is a failure of the chromosomes to separate during oogenesis or spermatogenesis. This can occur in either the autosomes or the sex chromosomes and is called *nondisjunction* (Fig. 5-8). Nondisjunction gives rise to germ cells that have an even number of chromosomes.[16,17] The products of conception formed from this even number of chromosomes have an uneven number of chromosomes, 45 or 47. *Monosomy* refers to the presence of only one member of a chromosome pair. The defects associated with monosomy of the autosomes are severe and often cause miscarriage in utero.

Polysomy, or the presence of more than two chromosomes to a set, occurs when a germ cell (either egg or sperm) containing more than 23 chromosomes is involved in conception. In contrast to Down syndrome, most other trisomies are much more severe, and these infants rarely survive beyond the first years of life.[6]

Down Syndrome

First described in 1866 by John Langdon Down, trisomy 21, or Down syndrome, causes a combination of birth defects including some degree of intellectual disability, characteristic facial features, and other health problems. It is the most common chromosomal disorder.

Approximately 95% of cases of Down syndrome are caused by nondisjunction or an error in cell division during meiosis, resulting in a trisomy of chromosome 21. A rare form of Down syndrome can occur in the offspring of people in whom there has been a robertsonian

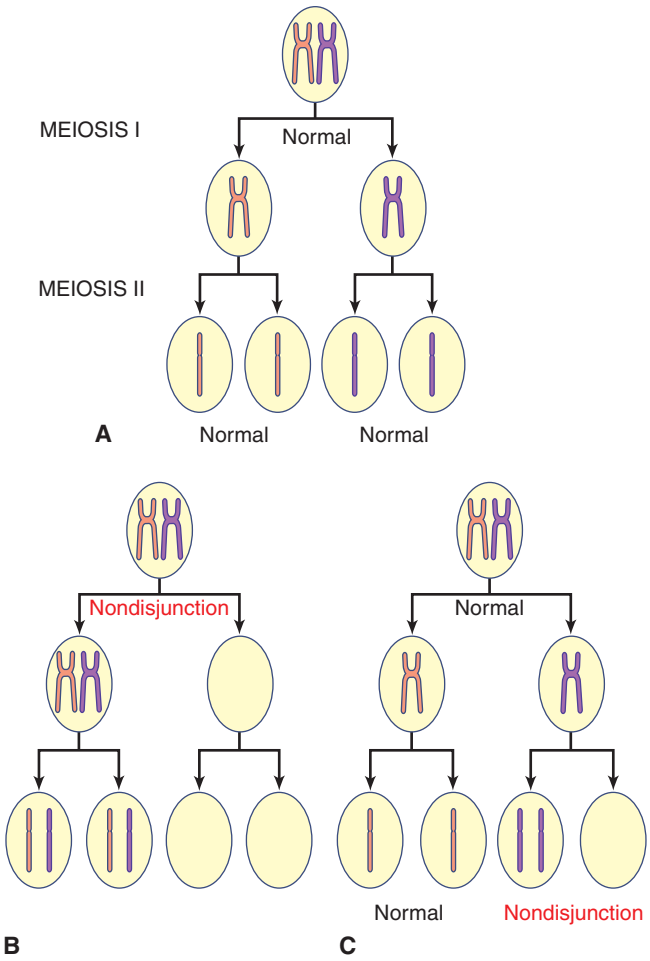

FIGURE 5-8. Nondisjunction as a cause of disorders of chromosomal numbers. (**A**) Normal distribution of chromosomes during meiosis I and II. (**B**) If nondisjunction occurs at meiosis I, the gametes contain either a pair of chromosomes or a lack of chromosomes. (**C**) If nondisjunction occurs at meiosis II, the affected gametes contain two of copies of one parenteral chromosome or a lack of chromosomes.

translocation (see Fig. 5-7) involving the long arm of chromosome 21q and the long arm of one of the acrocentric chromosomes (most often 14 or 22). The translocation adds to the normal long arm of chromosome 21. Therefore, the person with this type of Down syndrome has 46 chromosomes, but a trisomy of the long arm of chromosome 21 (21q).[18]

The risk of having a child with Down syndrome increases with maternal age. The reason for the correlation between maternal age and nondisjunction is unknown, but is thought to reflect some aspect of aging of the oocyte. Although men continue to produce sperm throughout their reproductive life, women are born with all the oocytes they ever will have. These oocytes may change as a result of the aging process and are likely to have chromosomal abnormalities.

A child with Down syndrome has specific physical characteristics that are evident at birth. These features include a small and rather square head. There is a flat facial profile, with a small nose and somewhat depressed nasal bridge; small folds on the inner corners of the eyes (epicanthal folds) and upward slanting of the eyes; small, low-set, and malformed ears; a fat pad at the back of the neck; an open mouth; and a large, protruding tongue (Fig. 5-9). The child's hands usually are short and stubby, with fingers that curl inward, and there usually is only a single palmar (*i.e.*, simian) crease. There is excessive space between the large and second toes. There often are accompanying congenital heart defects and an increased risk of gastrointestinal malformations. In addition, there is an increased risk of Alzheimer disease among older people with Down syndrome.

There are several prenatal screening tests that can be done to determine the risk of having a child with Down syndrome.[19] The most commonly used are blood tests that measure maternal serum levels of α-fetoprotein (AFP), human chorionic gonadotropin (hCG), **unconjugated** estriol, inhibin A, and pregnancy-associated plasma protein A (PAPP-A) (see section on Diagnosis and Counseling). The results of three or four of these tests, together with the woman's age, often are used to determine the probability of a pregnant woman having a child with Down syndrome. Between 10 and 13 weeks, women can have an ultrasound that assesses for nuchal translucency (sonolucent space on the back of the fetal

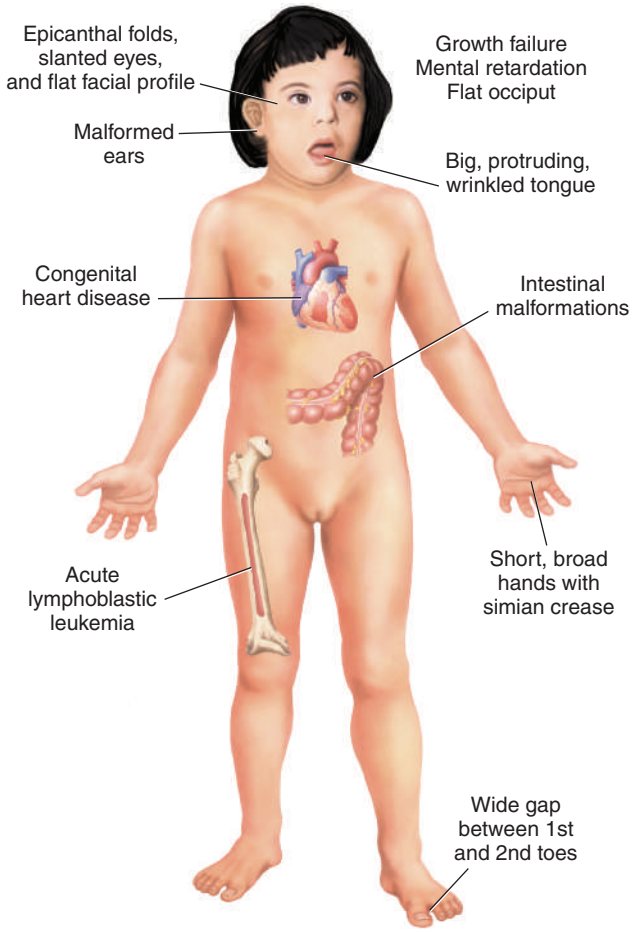

FIGURE 5-9. Clinical features of a child with Down syndrome.

neck). The fetus with Down syndrome tends to have a greater area of translucency as compared to a chromosomally normal infant. But the definitive diagnosis of Down syndrome in the fetus is through chromosome analysis using chorionic villus sampling, amniocentesis, or percutaneous umbilical blood sampling, which is discussed later in this chapter.

Numeric Disorders Involving Sex Chromosomes

Chromosomal disorders associated with the sex chromosomes are much more common than those related to the autosomes, except for trisomy 21. Furthermore, imbalances in the number (either excesses or deletions) are much better tolerated than those chromosomal abnormalities involving the autosomes. This is related in a large part to two factors that are peculiar to the sex chromosomes:

1. All but one X chromosome is inactivated.
2. There are very few genes that are carried on the Y chromosome.

Although females normally receive both a paternal and a maternal X chromosome, the clinical manifestations of X chromosome abnormalities can be quite variable because of the process of X inactivation. In somatic cells of females, only one X chromosome is transcriptionally active and creates protein from the DNA template. The other chromosome is inactive. The process of X inactivation, which is random, occurs early in embryonic life and is usually complete at about the end of the first week of development. After one X chromosome has become inactivated in a cell, all cells descended from that cell will have the same active and inactive X chromosome. Although much of one X chromosome is inactivated in females, several regions do contain genes that escape inactivation and can continue to be expressed by both X chromosomes. These genes may explain some of the variations in clinical symptoms seen in cases of numeric abnormalities of the X chromosome.

Turner Syndrome

Turner syndrome describes an absence of all (45,X/0) or part of the X chromosome. Some women with Turner syndrome may have part of the X chromosome, and some may display a **mosaicism** where one or more additional cell lines are active. This disorder affects approximately 1 of every 2500 live births and is the most frequently occurring genetic disorder in women.[20]

Characteristically, a female with Turner syndrome is short in stature, but her body proportions are normal (Fig. 5-10). Females with Tuner syndrome lose the majority of their oocytes by the age of 2 years. Therefore, they do not menstruate and show no signs of secondary sex characteristics. There are variations in the syndrome, with abnormalities ranging from essentially a normal phenotype to cardiac abnormalities such as bicuspid aortic valve and **coarctation** of the aorta, and a small webbed neck.[20]

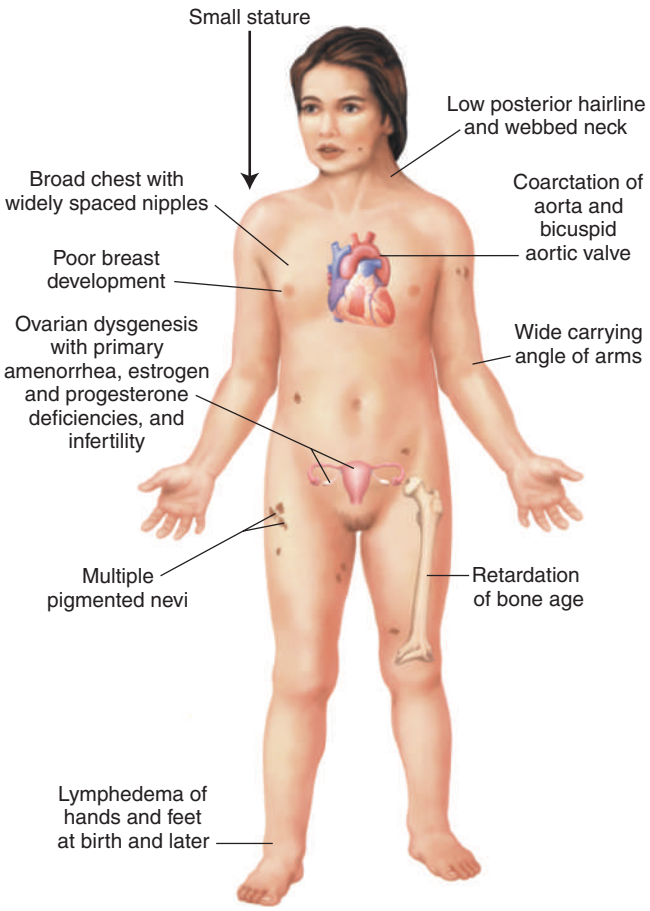

FIGURE 5-10. Clinical features of Turner syndrome.

Because the phenotype can be somewhat variable, the diagnosis of Turner syndrome often is delayed until late childhood or early adolescence in girls who do not present with all of the classic features of the syndrome. It is important to diagnose girls with Turner syndrome as early as possible, so treatment plans can be implemented and managed throughout their lives. Growth hormone therapy generally can result in a gain of 6 to 10 cm in final height. Estrogen therapy, which is instituted around the normal age of puberty, is used to promote development and maintenance of secondary sexual characteristics.[20]

Klinefelter Syndrome

Klinefelter syndrome is a condition of testicular **dysgenesis** accompanied by the presence of one or more extra X chromosomes in excess of the normal male XY complement.[19] Most males with Klinefelter syndrome have one extra X chromosome (47,XXY). In rare cases, there may be more than one extra X chromosome (48,XXXY). The presence of the extra X chromosome in the 47,XXY male results from nondisjunction during meiotic division in one of the parents, but the cause of the nondisjunction is unknown. Advanced maternal age increases the risk, but only slightly. Klinefelter syndrome occurs in approximately 1 per 700 newborn male infants.[19]

Although the presence of the extra chromosome is fairly common, it is still a rare diagnosis as the phenotype is again variable. Many men live their lives without being aware that they have an additional chromosome. For this reason, it has been suggested that the term *Klinefelter syndrome* be replaced with *47,XXY male*.[19]

Phenotypic changes common to Klinefelter syndrome include enlarged breasts, sparse facial and body hair, small testes, and the inability to produce sperm (Fig. 5-11). Regardless of the number of X chromosomes present, the male phenotype is retained. The condition often goes undetected at birth. The infant usually has normal male genitalia, but at puberty, the testes do not respond to stimulation from the gonadotropins and undergo degeneration. This leads to a tall stature with abnormal body proportions in which the lower part of the body is longer than the upper part. Later in life, the body build may become heavy, with a female distribution of subcutaneous fat and variable degrees of breast enlargement. There may be deficient secondary male sex characteristics, such as a voice that remains feminine in pitch and sparse beard and pubic hair. Although the intellect usually is normal, most 47,XXY males have some degree of language impairment.[19]

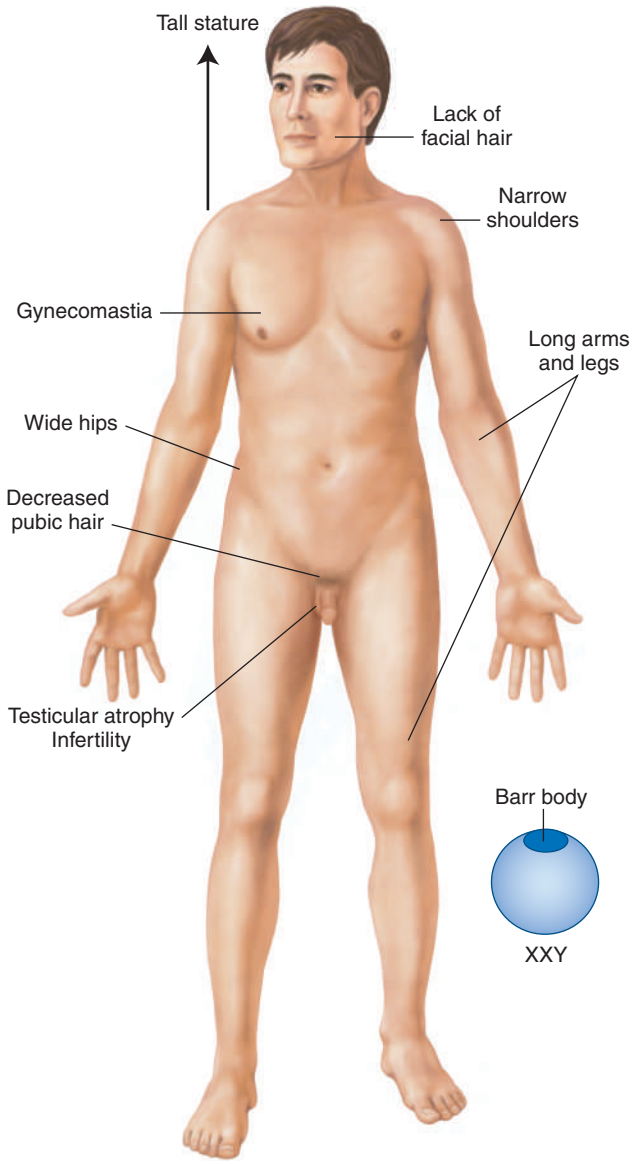

FIGURE 5-11. Clinical features of Klinefelter syndrome.

Adequate management of Klinefelter syndrome requires a comprehensive neurodevelopmental evaluation. Males with Klinefelter syndrome have congenital hypogonadism and decreased sperm count. **Androgen** therapy is usually initiated when there is evidence of a testosterone deficit. If sperm are present, cryopreservation may be useful for future family planning.[19] However, genetic counseling is advised because of the increased risk of autosomal and sex chromosomal abnormalities.

Mitochondrial Gene Disorders

The mitochondria contain their own DNA, which is distinct from the DNA contained in the cell nucleus. Although the majority of inherited disorders come from nuclear DNA abnormalities, there are multiple disease causing rearrangements and mutations that can occur in mitochondrial DNA (mtDNA). This DNA is packaged in a double-stranded circular chromosome and contains 37 genes: 2 ribosomal RNA genes, 22 transfer RNA genes, and 13 structural genes encoding subunits of the mitochondrial respiratory chain enzymes, which participate in oxidative phosphorylation and generation of adenosine triphosphate.

Because mtDNA is inherited only from the mother, all disorders of mtDNA are also inherited on the maternal line. Ova contain numerous mitochondria in their abundant cytoplasm, whereas spermatozoa contain few, if any, mitochondria. Thus, the mtDNA in the zygote is derived solely from the mother. The zygote and its daughter cells have many mitochondria, allowing for a mixture of normal and mutant DNA. The clinical expression of a disease produced by a given mutation of mtDNA depends on the total content of mitochondrial genes and the proportion that is mutant.

mtDNA mutations generally affect tissues that are dependent on oxidative phosphorylation to meet their high needs for metabolic energy. Thus, mtDNA mutations frequently affect the neuromuscular system and produce disorders such as encephalopathies, myopathies, retinal degeneration, loss of extraocular muscle function, and deafness. The range of mitochondrial diseases is broad, however, and may include liver dysfunction, bone marrow failure, and pancreatic islet cell dysfunction and diabetes, among other disorders. Table 5-2 describes representative examples of disorders due to mutations in mtDNA.

TABLE 5-2 Some Disorders of Organ Systems Associated with Mitochondrial DNA Mutations

Disorder	Manifestations
Chronic progressive external ophthalmoplegia	Progressive weakness of the extraocular muscles
Deafness	Progressive sensorineural deafness, often associated with aminoglycoside antibiotics
Kearns–Sayre syndrome	Progressive weakness of the extraocular muscles of early onset with heart block, retinal pigmentation
Leber hereditary optic neuropathy	Painless, subacute, bilateral visual loss, with central blind spots (scotomas) and abnormal color vision
Leigh disease	Proximal muscle weakness, sensory neuropathy, developmental delay, ataxia, seizures, dementia, and visual impairment due to retinal pigment degeneration
MELAS	*M*itochondrial *e*ncephalomyopathy (cerebral structural changes), *l*actic *a*cidosis, and *s*trokelike syndrome, seizures, and other clinical and laboratory abnormalities; may manifest only as diabetes mellitus
MERRF	*M*yoclonic *e*pilepsy, *r*agged *r*ed *f*ibers in muscle, ataxia, sensorineural deafness
Myoclonic epilepsy with ragged red fibers	Myoclonic seizures, cerebellar ataxia, mitochondrial myopathy (muscle weakness, fatigue)

SUMMARY CONCEPTS

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

Chromosomal disorders result from a change in chromosome number or structure. A change in chromosome number is called *aneuploidy. Monosomy* involves the presence of only one member of a chromosome pair. *Polysomy* refers to the presence of more than two chromosomes in a set. Alterations in chromosome structure involve deletion or addition of genetic material, or a translocation of genetic material from one chromosome pair to another.

The mitochondria contain their own DNA, which is distinct from nuclear DNA. This mtDNA is only inherited maternally. Disorders of mitochondrial genes interfere with oxidative phosphorylation and the production of cellular energy. The range of mitochondrial gene disorders is diverse, with neuromuscular disorders predominating.

Disorders due to Environmental Influences

The developing embryo is subject to many nongenetic influences. After conception, development is influenced by the environmental factors that the embryo shares with the mother. The physiologic status of the mother—her hormone balance, her general state of health, her nutritional status, and the drugs she takes undoubtedly influences the development of the unborn child. For example, maternal smoking is associated with lower than normal neonatal weight. Maternal use of alcohol is known to cause fetal abnormalities. Various drugs can cause early miscarriage. Measles and other infectious agents cause congenital malformations. Other agents, such as radiation, can cause chromosomal and genetic defects and produce developmental disorders.

Period of Vulnerability

The embryo's development is most easily disturbed during the period when differentiation and development of the organs are taking place. This time interval, which is

often referred to as the period of *organogenesis*, extends from day 15 to day 60 after conception. Environmental influences during the first 2 weeks after fertilization may interfere with implantation and result in abortion or early **resorption** of the products of conception. Each organ has a critical period during which it is highly susceptible to environmental derangements (Fig. 5-12).

Teratogenic Agents

A teratogenic agent is a chemical, physical, or biologic agent that produces abnormalities during embryonic or fetal development. Maternal disease or altered metabolic state also can affect the development of the embryo or fetus. Theoretically, teratogenic agents can cause birth defects in three ways:

1. By direct exposure of the pregnant female and the embryo or fetus to the agent.
2. Through exposure of the soon to be pregnant female to an agent that has a slow clearance rate, such that a teratogenic dose is retained during early pregnancy.
3. As a result of **mutagenic** effects of an environmental agent that occur before pregnancy, causing permanent damage to a female's or a male's reproductive cells.

For the purposes of discussion, teratogenic agents have been divided into three groups: radiation, drugs and chemical substances, and infectious agents. Chart 5-1 lists commonly identified agents in each of these groups.

Radiation

Heavy doses of ionizing radiation are teratogenic and mutagenic and have the capacity to effect inheritable changes in genetic materials. Specifically, excessive levels of radiation have been shown to cause microcephaly, skeletal malformations, and mental retardation. There is no evidence that *diagnostic* levels of radiation (*e.g.*, from a chest x-ray) cause congenital abnormalities, but all efforts to shield the fetus are taken when possible. In situations where a study is necessary for the woman's health, the benefits to her of having proper diagnostic imaging must outweigh potential theoretical risks to the fetus.

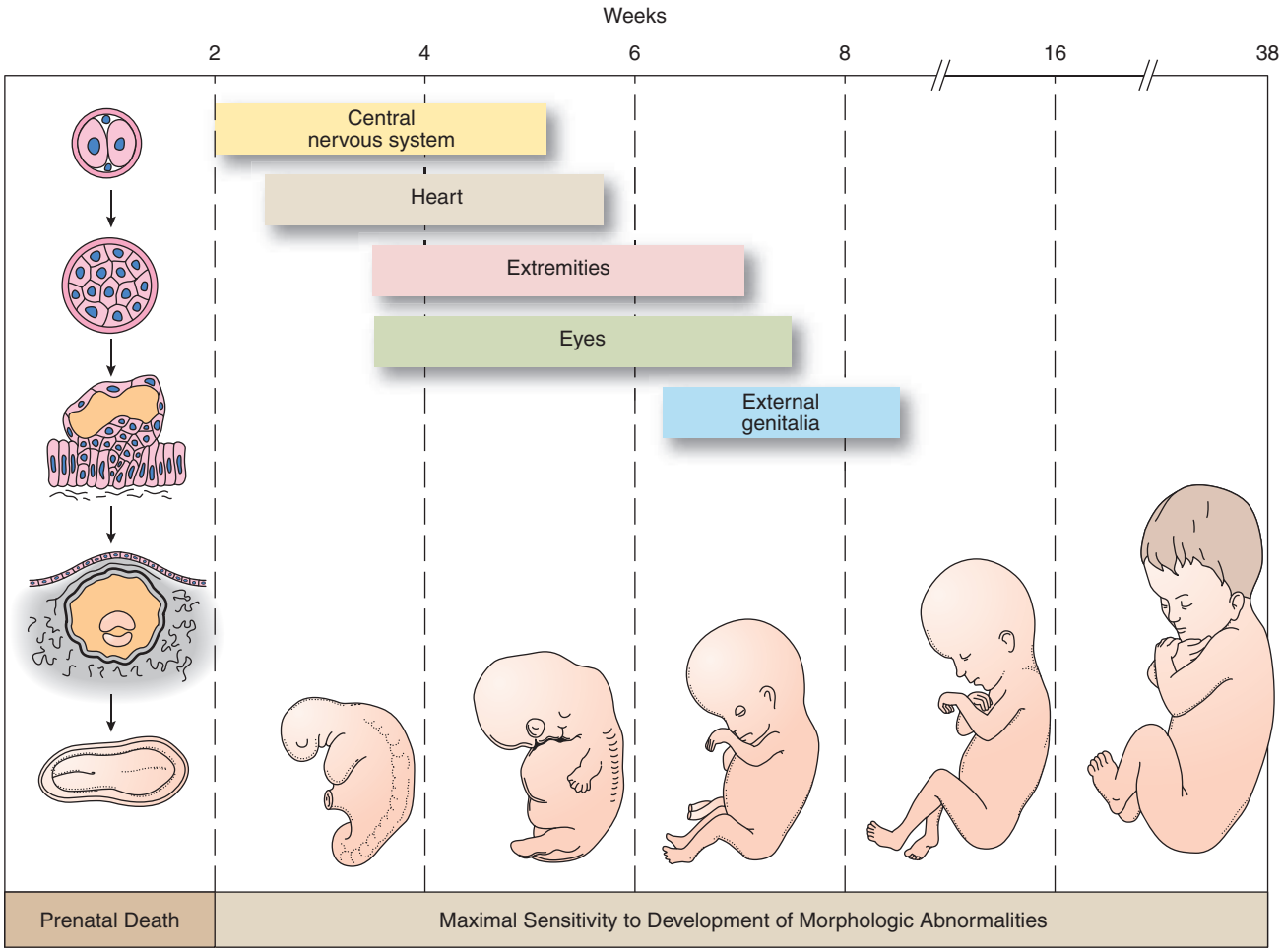

FIGURE 5-12. Sensitivity of specific organs to teratogenic agents at critical periods in embryogenesis. Exposure to adverse influences in the preimplantation and early postimplantation stages of development (*far left*) leads to prenatal death. Periods of maximal sensitivity to teratogens (*horizontal bars*) vary for different organ systems, but overall are limited to the first 8 weeks of pregnancy. (From Strayer D. S., Rubin E. (Eds.) (2015). *Rubin's pathology: Clinicopathologic foundations of medicine* (7th ed., Fig. 6-2, p. 246). Philadelphia, PA: Lippincott Williams & Wilkins.)

CHART 5-1

TERATOGENIC AGENTS*

Radiation

Drugs and Chemical Substances

Alcohol

Anticoagulants

- Warfarin

Antibiotics

- Quinolones
- Tetracycline

Antiepileptics

Anti-hypertension

- Angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers

Antipsychotics

- Lithium

Cancer drugs

- Aminopterin
- Methotrexate
- 6-Mercaptopurine

Isotretinoin (Accutane)

Thalidomide

Infectious Agents

Viruses

- Cytomegalovirus
- Herpes simplex virus
- Measles (rubella)
- Mumps
- Varicella-zoster virus (chickenpox)

Nonviral factors

- Syphilis
- Toxoplasmosis

*Not inclusive.

Chemicals and Drugs

Environmental chemicals and drugs can cross the placenta and cause damage to the developing embryo and fetus. Some of the best-documented environmental teratogens are the organic mercurials, which cause neurologic deficits and blindness. Certain fish and water sources may be contaminated by mercury. The precise mechanisms by which chemicals and drugs exert their teratogenic effects are largely unknown. They may produce cytotoxic (cell killing), antimetabolic, or growth-inhibiting effects to the embryonic and fetal development.

Drugs top the list of chemical teratogens. Many drugs can cross the placenta and expose the fetus to both the pharmacologic and teratogenic effects. Factors that affect placental drug transfer and drug effects on the fetus include the rate at which the drug crosses the placenta, the duration of exposure, and the stage of placental and fetal development at the time of exposure. Lipid-soluble drugs tend to cross the placenta more readily and enter the fetal circulation. The molecular weight of a drug also influences the rate and amount of drug transferred across the placenta.

Several medications have been considered teratogenic. However, perhaps the best known of these drugs is thalidomide, which has been shown to give rise to a full range of malformations, including phocomelia (*i.e.*, short, flipper-like appendages) of all four extremities. Other drugs known to cause fetal abnormalities are those used in the treatment of cancer, the anticoagulant drug warfarin, several of the anticonvulsant drugs, ethyl alcohol, and cocaine. More recently, vitamin A and its derivatives (the retinoids) have been targeted for concern because of their teratogenic potential. Concern over the teratogenic effects of vitamin A derivatives arose with the introduction of the acne drug isotretinoin (Accutane).

In 1983, the U.S. Food and Drug Administration (FDA) established a system for classifying drugs according to probable risks to the fetus. According to this system, drugs are put into five categories: A, B, C, D, and X. Drugs in category A are the least dangerous, and categories B, C, and D are increasingly more dangerous. Those in category X are contraindicated during pregnancy because of proven teratogenicity. Recently, the FDA added modifications to the categories with narrative descriptions and potential reproductive risks.[21]

Because many drugs are suspected of causing fetal abnormalities, and even those that were once thought to be safe are now being viewed critically, it is recommended that women in their childbearing years avoid unnecessary use of drugs. This pertains to nonpregnant women as well as pregnant women because many developmental defects occur early in pregnancy.

Fetal Alcohol Syndrome

A drug that is often abused and can have deleterious effects on the fetus is alcohol. The term *fetal alcohol syndrome* (FAS) refers to a group of physical, behavioral, and cognitive fetal abnormalities that occur secondary to drinking alcohol while pregnant.[21] Alcohol, which is lipid soluble and has a molecular weight between 600 and 1000, passes freely across the placental barrier. Concentrations of alcohol in the fetus are at least as high as in the mother. Unlike many other teratogens, the harmful effects of alcohol are not restricted to the sensitive period of early gestation but extend throughout pregnancy.

Alcohol has widely variable effects on fetal development. There may be prenatal or postnatal growth retardation; central nervous system (CNS) involvement, including neurologic abnormalities, developmental delays, behavioral dysfunction, intellectual impairment, and skull and brain malformation; and a characteristic set of facial features that include small palpebral **fissures** (*i.e.*, eye openings), a thin vermilion border (upper lip), and an elongated, flattened midface and

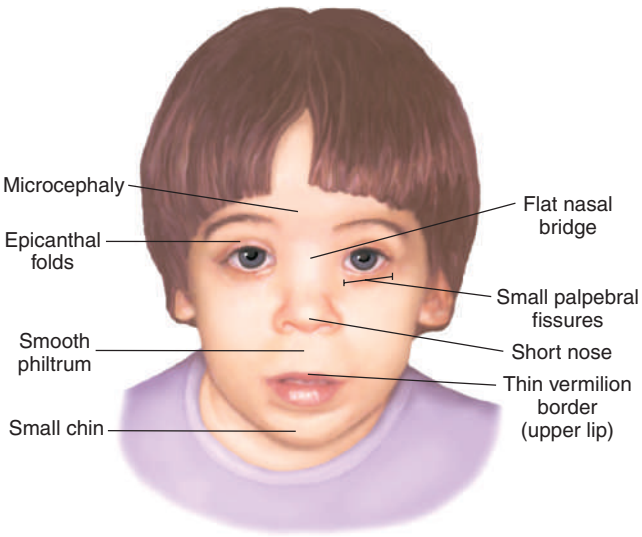

FIGURE 5-13. Clinical features of fetal alcohol syndrome.

philtrum (*i.e.*, the groove in the middle of the upper lip) (Fig. 5-13).[22] The facial features of FAS may not be as apparent in the newborn but become more prominent as the infant develops. As the children grow into adulthood, the facial features become more subtle, making diagnosis of FAS in older people more difficult. Each of these defects can vary in severity, probably reflecting the timing of alcohol consumption in terms of the period of fetal development, amount of alcohol consumed, and hereditary and other environmental influences.

The amount of alcohol that can be safely consumed during pregnancy is unknown. Even small amounts of alcohol consumed during critical periods of fetal development may be teratogenic. For example, if alcohol is consumed during the period of organogenesis, a variety of skeletal and organ defects may result. If alcohol is consumed later in gestation, when the brain is undergoing rapid development, there may be behavioral and cognitive disorders in the absence of physical abnormalities. Chronic alcohol consumption throughout pregnancy may result in a variety of effects, ranging from physical abnormalities to growth retardation and compromised CNS functioning. Evidence suggests that short-lived high concentrations of alcohol, such as those that occur with binge drinking, may be particularly significant, with abnormalities being unique to the period of exposure.[22] Because of the possible effect on the fetus, it is recommended that women abstain completely from alcohol during pregnancy.

Infectious Agents

Many microorganisms cross the placenta and enter the fetal circulation, often producing multiple malformations. The acronym TORCH stands for *t*oxoplasmosis, *o*ther, *r*ubella (*i.e.*, German measles), *c*ytomegalovirus, and *h*erpes, which are the agents most frequently implicated in fetal anomalies.[16] Other infections that can cause fetal anomalies include varicella-zoster virus infection, listeriosis, leptospirosis, Epstein–Barr virus infection, tuberculosis, and syphilis.[16] Human immunodeficiency virus and human parvovirus (B19) have been suggested as other potential additions to the list. Common clinical and pathologic manifestations include growth retardation and abnormalities of the brain (microcephaly, hydrocephalus), eye, ear, liver, hematopoietic system (anemia, thrombocytopenia), lungs (pneumonitis), and heart (myocarditis, congenital heart disorders).[16] These manifestations will vary among symptomatic newborns, however, and only a few present with multisystem abnormalities.

KEY POINTS

Teratogenic Agents

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

Folic Acid Deficiency

Although most birth defects are related to exposure to a teratogenic agent, deficiencies of nutrients and vitamins also may be a factor. Folic acid deficiency has been implicated in the development of neural tube defects (NTDs) (*e.g.*, anencephaly, spina bifida, encephalocele). Studies have shown a significant decrease in NTDs when folic acid was taken long term by women of reproductive age. Therefore, it is recommended that all women of childbearing age receive 400 μg (0.4 mg) of folic acid daily and then continue upon becoming pregnant.

SUMMARY CONCEPTS

A teratogenic agent is one that produces abnormalities during embryonic or fetal life. It is during the early part of pregnancy (15 to 60 days after conception) that environmental agents are most apt to produce their deleterious effects on the developing embryo. A number of environmental agents can be damaging to the unborn child, including radiation, drugs and chemicals, and infectious agents. Because many drugs have the potential for causing fetal abnormalities, often at an early stage of pregnancy, it is recommended that women of childbearing age avoid unnecessary use of drugs.

Diagnosis and Counseling

Genetic Assessment

Assessment of genetic risk and prognosis usually is directed by a clinical geneticist, often with the aid of laboratory and clinical specialists. A detailed family history (*i.e.*, pedigree), a pregnancy history, and detailed accounts of the birth process and postnatal health and development are included. A careful physical examination of the affected child and often of the parents and siblings usually is needed. Laboratory tests, including chromosomal analysis and biochemical studies, often precede a definitive diagnosis.

Prenatal Screening and Diagnosis

The purpose of prenatal screening and diagnosis is not only to detect fetal abnormalities but also to allay anxiety and provide assistance to prepare for a child with a specific disability. Prenatal screening cannot be used to rule out all possible fetal abnormalities. It is limited to determining whether the fetus has (or probably has) predesignated conditions as indicated by late maternal age, family history, or well-defined risk factors.

There are multiple methods that can assist in diagnosing a fetus regarding genetic disorders, including ultrasonography, maternal serum (blood) screening tests, amniocentesis, chorionic villus sampling, and percutaneous umbilical fetal blood sampling (Fig. 5-14). Prenatal diagnosis can also provide the information needed for prescribing prenatal treatment for the fetus or making appropriate plans for the birth of a child with a known disease.

Ultrasonography

Ultrasonography is a noninvasive diagnostic method that uses reflections of high-frequency sound waves to visualize soft tissue structures. Since its introduction in 1958, it has been used during pregnancy to determine the number of fetuses, fetal size and position, amount of amniotic fluid, and placental location. But improved resolution and real-time units have enhanced the ability of ultrasound scanners to detect congenital anomalies. Ultrasonography makes possible the in utero diagnosis of cardiac defects, hydrocephalus, spina bifida, facial

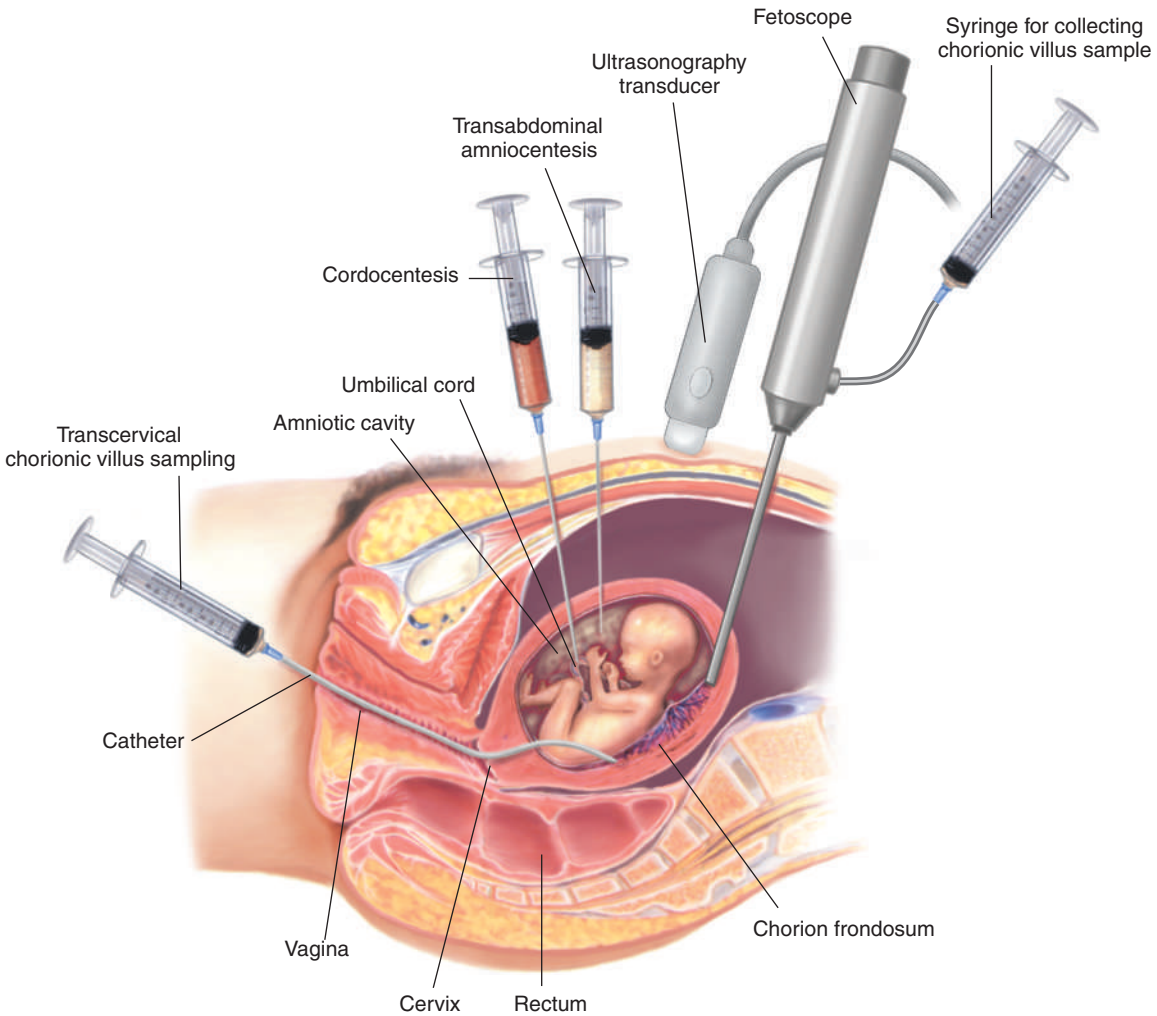

FIGURE 5-14. Methods of prenatal screening.

defects, congenital heart defects, congenital diaphragmatic hernias, disorders of the gastrointestinal tract, skeletal anomalies, and various other defects. Three-dimensional sonography has become useful in better assessing facial profiles and abdominal wall defects. A fetal echocardiogram can be done as follow-up for possible cardiac anomalies. Fetal magnetic resonance imaging can be done to better assess skeletal, neurologic, and other anomalies. Intrauterine diagnosis of congenital abnormalities permits better monitoring, further workup and planning with appropriate specialties, preterm delivery for early correction, selection of cesarean section to reduce fetal injury, and, in some cases, intrauterine therapy.

Maternal Serum Markers

Maternal blood testing began in the early 1980s. Current maternal testing favors first trimester screening for all women between 11 and 13 weeks combining nuchal translucency seen on sonogram with PAPP-A level, hCG level, and maternal age to determine a risk for trisomy 21, 13, and 18. PAPP-A, which is secreted by the placenta, has been shown to play an important role in promoting cell differentiation and proliferation in various body systems. When used along with maternal age, free β-hCG, and ultrasonographic measurement of nuchal translucency, serum PAPP-A levels can reportedly detect 85% to 95% of affected pregnancies with a false-positive rate of approximately 5%.

The quad screen checks for markers of four substances—AFP, hCG, estriol, and inhibin A—providing a formula for the probability of carrying a child with a chromosomal abnormality.

AFP is a major fetal plasma protein made initially by the yolk sac, gastrointestinal tract, and liver. Fetal plasma levels of AFP peak at approximately 10 to 13 weeks' gestation and decrease until the third trimester when the level peaks again. Maternal and amniotic fluid levels of AFP are elevated in pregnancies where the fetus has an NTD or certain other malformations such as an **anterior** abdominal wall defect. Although NTDs have been associated with elevated levels of AFP, decreased levels have been associated with Down syndrome.

A complex glycoprotein, hCG, is produced exclusively by the outer layer of the trophoblast shortly after implantation in the uterine wall. It increases rapidly in the first 8 weeks of gestation, declines steadily until 20 weeks, and then plateaus. The single maternal serum marker that yields the highest detection rate for Down syndrome is an elevated level of hCG. Inhibin A, which is secreted by the corpus luteum and fetoplacental unit, is also a maternal serum marker for fetal Down syndrome.

Unconjugated estriol is produced by the placenta from precursors provided by the fetal adrenal glands and liver. It increases steadily throughout pregnancy to a higher level than that normally produced by the liver. Unconjugated estriol levels are decreased in Down syndrome and trisomy 18.

KEY POINTS

Diagnosis and Counseling

- Sonography, first trimester screening, quad screening, amniocentesis, chorionic villi sampling, and percutaneous umbilical cord blood sampling are important procedures that allow prenatal diagnosis and management.

Amniocentesis

Amniocentesis is an invasive diagnostic procedure that involves the withdrawal of a sample of amniotic fluid from the pregnant uterus usually using a transabdominal approach (see Fig. 5-14). The procedure is useful in women with elevated risk on first trimester screen or quad screen, abnormal fetal findings on sonogram, or in parents who are carriers or with a strong family history of an inherited disease. Ultrasonography is used to gain additional information and to guide the placement of the amniocentesis needle. The amniotic fluid and cells that have been shed by the fetus are studied. Amniocentesis can be performed on an outpatient basis starting at 15 weeks. For chromosomal analysis, the fetal cells are grown in culture and the result is available in 10 to 14 days.

Chorionic Villus Sampling

Chorionic villus sampling is an invasive diagnostic procedure that obtains tissue that can be used for fetal chromosome studies, DNA analysis, and biochemical studies. Sampling of the chorionic villi usually is done after 10 weeks' gestation. Performing the test before 10 weeks is not recommended because of the danger of limb reduction defects in the fetus. The chorionic villi are the site of exchange of nutrients between the maternal blood and the embryo—the chorionic sac encloses the early amniotic sac and fetus, and the villi are the primitive blood vessels that develop into the placenta. The sampling procedure can be performed using either a transabdominal or transcervical approach (see Fig. 5-14).

Percutaneous Umbilical Cord Blood Sampling

Percutaneous umbilical cord blood sampling is an invasive diagnostic procedure that involves the transcutaneous insertion of a needle through the uterine wall and into the umbilical artery. It is performed under ultrasonographic guidance and can be done any time after 16 weeks' gestation. It is used for prenatal diagnosis of hemoglobinopathies, coagulation disorders, metabolic and cytogenetic disorders, and immunodeficiencies. Fetal infections such as rubella and toxoplasmosis can be detected through measurement of immunoglobulin M antibodies or direct blood cultures. Because the procedure carries a greater risk of pregnancy loss compared to amniocentesis, it is usually reserved for situations in which rapid cytogenetic analysis is needed

or in which diagnostic information cannot be obtained by other methods.

Cytogenetic and DNA Analyses

Amniocentesis and chorionic villus sampling yield cells that can be used for cytogenetic and DNA analyses. Cytogenetic studies are used for fetal karyotyping to detect abnormalities of chromosome number and structure in the fetus. Karyotyping also reveals the sex of the fetus. This may be useful when an inherited defect is known to affect only one sex.

Analysis of DNA can be done on cells extracted from the amniotic fluid, chorionic villi, or fetal blood from percutaneous umbilical sampling. These analyses are used to detect genetic defects that cause inborn errors of metabolism, such as Tay–Sachs disease, glycogen storage diseases, and familial hypercholesterolemia. Prenatal diagnoses are possible for more than 70 inborn errors of metabolism.

The newest realm of fetal diagnosis involves looking at fetal DNA in the maternal blood. Some private companies and many research institutions are exploring the efficacy of looking at fetal DNA for sex determination and other genetic testing. More research is needed before this will be offered to all women.

SUMMARY CONCEPTS

Genetic and prenatal diagnosis and counseling are done in an effort to determine the risk of having a child with a genetic or chromosomal disorder. They often involve a detailed family history (*i.e.*, pedigree), examination of any affected and other family members, and laboratory studies including chromosomal analysis and biochemical studies. These examinations are usually done by a genetic counselor and a specially prepared team of health care professionals. Prenatal screening and diagnosis are used to detect fetal abnormalities. Ultrasonography is used for fetal anatomic imaging. It is used for determination of fetal size and position and for the presence of structural anomalies. Maternal serum screening is used to identify pregnancies that are at increased risk for some disorders. Amniocentesis and chorionic villus sampling may be used to obtain specimens for cytogenetic and biochemical studies.

Review Exercises

1. A 23-year-old woman with sickle cell disease and her husband want to have a child but worry that the child will be born with the disease.
   - **A.** What is the mother's genotype in terms of the sickle cell gene? Is she heterozygous or homozygous?
   - **B.** If the husband is found not to have the sickle cell gene, what is the probability of their child having the disease or being a carrier of the sickle cell trait?
2. A couple has a child who was born with a congenital heart disease.
   - **A.** Would you consider the defect to be the result of a single gene or a polygenic trait?
   - **B.** Would these parents be at greater risk of having another child with a heart defect or would they be at equal risk of having a child with a defect in another organ system, such as cleft palate?
3. A couple has been informed that their newborn child has the features of Down syndrome, and it is suggested that genetic studies be performed.
   - **A.** The child is found to have trisomy 21. Use Figure 5-8, which describes the events that occur during meiosis, to explain the origin of the third chromosome 21.
   - **B.** If the child had been found to have the robertsonian chromosome, how would you explain the origin of the abnormal chromosome?
4. An 8-year-old boy has been diagnosed with mitochondrial myopathy. His major complaints are those of muscle weakness and exercise intolerance. His mother gives a report of similar symptoms, but to a much lesser degree.
   - **A.** Explain the cause of this boy's symptoms.
   - **B.** Mitochondrial disorders follow a non-mendelian pattern of inheritance. Explain.
5. A 26-year-old woman is planning to become pregnant.
   - **A.** What information would you give her regarding the effects of medications and drugs on the fetus? What stage of fetal development is associated with the greatest risk?
   - **B.** What is the rationale for ensuring that she has an adequate intake of folic acid before conception?

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