:
Title: *Professional Guide to Diseases, 9th Edition*

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Genetic disorders

Introduction

Genetic diseases result from single-gene (Mendelian) alterations, chromosomal abnormalities, or multifactorial errors. Over 6,000 such abnormalities have been identified in humans, ranging from mild differences (as in certain hemoglobin abnormalities) to fatal or overwhelmingly disabling conditions, such as trisomy 18 (Edwards') syndrome and trisomy 13 (Patau's) syndrome. The risk of single gene disorders is estimated at 1 in 200 births.

Although genetic disorders are determined mainly by genetic makeup, they can also interact with environmental factors. For example, albinism (an inherited inability to generate the protective pigment melanin) greatly increases susceptibility to skin cancer with excessive exposure to sunlight.

Genetic analysis

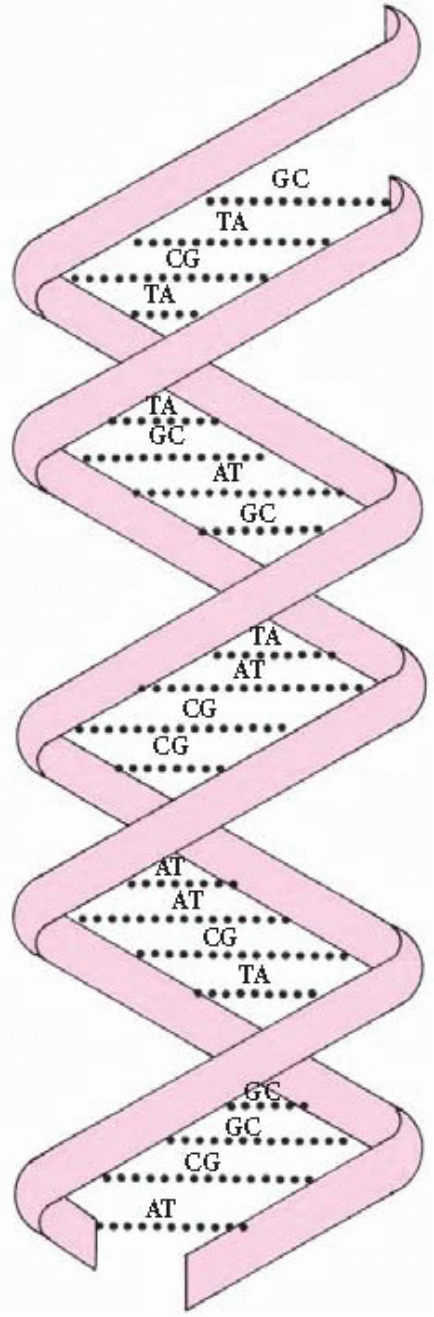
Genetics, the study of heredity, involves analysis of defects in chromosomal reproduction or disease processes that can be passed from one generation to the next. Various tests are used to unravel the effects of altered genes and the patterns of inheritance. As heredity becomes better understood, genetic influences are likely to assume greater importance in health care delivery.

DNA AND HOW IT WORKS

Deoxyribonucleic acid (DNA) is a doublehelix polymer (macromolecule) made up of individual units called

nucleotides. Each nucleotide is composed of one sugar (deoxyribose), one phosphate, and one nitrogencontaining base — either a purine or a pyrimidine. The purine bases are adenine (A) and guanine (G). The pyrimidine bases are thymine (T) and cytosine (Q). The two polynucleotide chains of each DNA macromolecule are attached by hydrogen bonds between the bases (see illustration). The base pairing is very specific: adenine pairs only with thymine and cytosine pairs only with guanine. The DNA within the human genome (22 different autosomes and two different sex chromosomes) is made up of about 3 billion base pairs.

Genes make up approximately 10% of the human genome. A gene is a segment of DNA that ultimately determines the linear sequence of an amino acid chain. Through a complex process, a gene is transcribed into messenger ribonucleic acid (mRNA), which eventually is translated into an amino acid chain. A sequence of three mRNA nucleotides is called a codon. An mRNA codon can mark the beginning of translation, the end of translation, or a specific amino acid. Our genetic code is made up of 64 different codons, 61 of which actually code for amino acids. The eventual translated strand of amino acids must undergo further modification within the cell before it becomes a functional protein. The Human Genome Project is an international effort that officially began in 1990 and was completed in 2003 with the sequencing of the entire human genome. Emphasis is now on determining gene and protein function and how the environment influences these. With this information, treatment of genetic-based conditions is occurring at the molecular and cellular levels.



The essential ingredient of heredity is *deoxyribonucleic acid* (DNA), which makes up *genes,* basic units of hereditary material that are arranged into threadlike organelles called *chromosomes* in the cell nucleus. (See *DNA and how it works*, and *DNA replication*.) Together, these elements contribute to a person's genotype (gene composition) and phenotype (outward appearance). In humans, each body cell (except ova and sperm) has 46 chromosomes consisting of 22 pairs of

autosomes and 1 pair of sex chromosomes. Females have a matched (homologous) pair of X sex chromosomes; males have an unmatched (heterologous) pair of sex chromosomes — an X and a Y.

Thus, the normal human chromosome complement is 46,XX in females and 46,XY in males. The 22 autosomes are all homologous. Each chromosome has a short arm (p) and a long arm (q) joined at the centromere.

The position that the gene for a given trait occupies on a chromosome is called a *locus*. Different loci exist for hair color, blood group, and so on. The number and arrangement of the loci on homologous chromosomes are the same. When the two genes are identical, the individual is homozygous at that locus. When the genes aren't identical, the individual is heterozygous at that locus. A different form of the same gene that occupies a corresponding locus on a homologous chromosome is called an *allele;* it determines alternative (and inheritable) forms of the same characteristic. Some alleles control normal trait variation such as hair color; other defective alleles may cause a congenital defect or even induce a spontaneous abortion. Both heterologous (codominant) alleles may express their own effects, or one (the dominant allele) may be expressed and the other (the recessive) suppressed.

A mutation is a permanent, inheritable change in a DNA sequence. When a mutation occurs in a gene's DNA sequence it may cause serious, even lethal defects, or it may be relatively benign. Mutations can occur spontaneously or can be caused by exposure to teratogenic agents, such as radiation, drugs, viruses, and synthetic chemicals. Paternal and maternal age also have effects on genetics.

Types of genetic disorders

Genetic disorders occur in several different forms. (See *Patterns of transmission in genetic disorders,* page 1108.)

- *Mendelian* or *single-gene disorders* are inherited in clearly identifiable patterns.
- *Chromosomal aberrations or abnormalities* include structural defects within a chromosome, such as deletion and translocation, plus

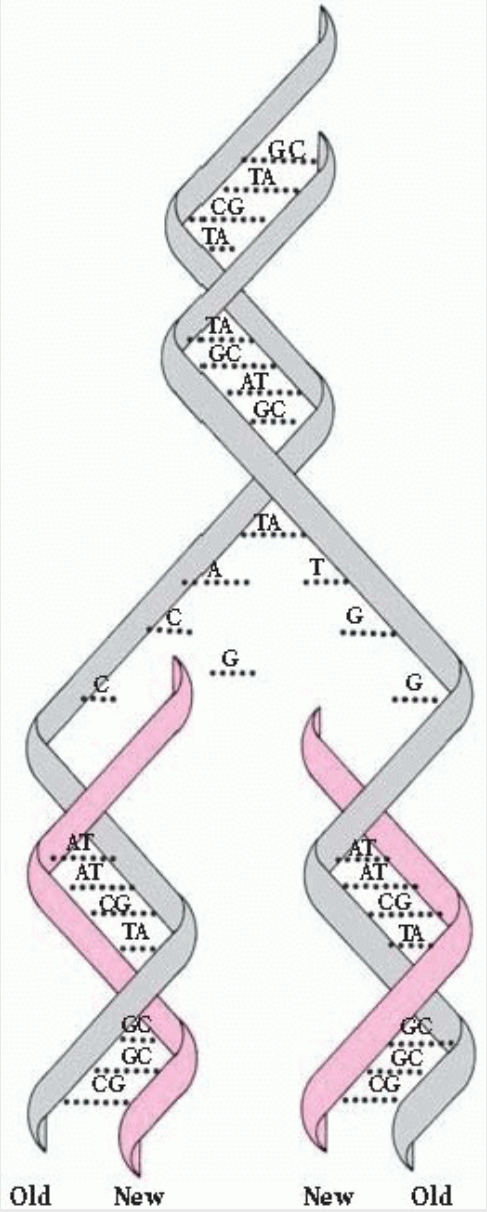
absence or addition of complete chromosomes.

- *Multifactorial disorders* reflect the interaction of at least two abnormal genes and environmental factors to produce a defect.

DNA REPLICATION

The body grows and replaces all dividing cells other than germ cells (sperm and ova) by *mitosis*. In mitosis, the cell's deoxyribonucleic acid (DNA) replicates itself exactly and leads to the creation of a new daughter cell with the identical genetic makeup as the parent cell. Each new cell has a diploid number of chromosomes (in humans, 46).

Germ cells, however, form by *meiosis*. In meiosis, DNA first replicates. Then, through a complicated process, two cell divisions create four daughter cells (a sperm or ovum) from each parent cell, each of which has a haploid number of chromosomes (in humans, 23).



PATTERNS OF TRANSMISSION IN GENETIC DISORDERS

Autosomal dominant

Achondroplasia (dwarfism)

Colorectal polyposis

Hereditary hemorrhagic telangiectasia

Huntington's disease
Hyperlipidemias (some types)
Hypoparathyroidism
Marfan syndrome
Neurofibromatosis (most cases)
Osteogenesis imperfecta (most cases)
Pituitary diabetes insipidus
Polycystic kidney disease
Retinoblastoma
Spherocytosis
Von Willebrand's disease

Autosomal recessive

Albinism (some cases)
Congenital adrenal hyperplasia
Cretinism
Cystic fibrosis
Cystinuria
Fabry's disease
Fanconi's anemia
Galactosemia
Niemann-Pick disease
Osteogenesis imperfecta (some cases)
Phenylketonuria
Retinitis pigmentosa (some cases)
Sickle cell anemia
Tay-Sachs disease
Thalassemia (alpha and beta)
Xeroderma pigmentosum (most cases)

X-linked

Duchenne type muscular dystrophy
Fragile X mental retardation
Glucose-6-phosphate dehydrogenase deficiency
Hemophilia (most types)
Pseudohypoparathyroidism
Some immunodeficiencies

Chromosomal

Cri du chat syndrome
Down syndrome (trisomy 21)
Edwards' syndrome (trisomy 18)
Klinefelter's syndrome (XXY)
Patau's syndrome (trisomy 13)
Turner's syndrome (XO)

Multifactorial

Cleft lip or palate (some cases)
Congenital heart defects (some cases)
Diabetes mellitus (some cases)
Mental retardation (some cases)
Neural tube defects

Single-gene disorders

Single-gene disorders may be autosomal (resulting from a single altered gene or a pair of altered genes on one of the 22 pairs of autosomes) or X-linked (resulting from an altered gene on the X chromosome). Single-gene disorders may be further classified as dominant or recessive, depending on whether the altered gene is a dominant or a recessive allele.

Single-gene inheritance patterns

A dominant allele produces its effect in heterozygotes (people who also carry a normal gene for the same trait) because the dominant allele

masks the effects of the normal paired gene *(autosomal dominant inheritance)*. Because a person with an autosomal dominant disease is usually a heterozygote and carries one dominant gene as well as one normal gene, his children have a 50% chance of inheriting the dominant gene and the disease. This probability remains the same for each pregnancy. Unaffected people (homozygote for the normal gene) don't carry the altered gene and therefore can't transmit it, except as a new mutation. (See *Inheritance patterns*.)

Sex doesn't influence transmission of an autosomal dominant allele. However, in some autosomal dominant diseases (such as Huntington's disease) the severity of symptoms can vary in offspring, depending on which parent transmits the dominant allele. Unless the dominant allele has arisen as a new mutation or is nonpenetrant

in an individual, every affected person has an affected parent. Thus, autosomal dominant traits don't skip generations. However, the severity of symptoms can range from very mild to severe among persons who inherit the allele. This variation of severity is known as *expressivity*.

Because a recessive allele can produce a disorder only when paired with another disease-causing allele *(autosomal recessive inheritance)*, offspring must receive one copy of the disease causing allele from each parent to inherit the recessive trait. A carrier has a diseased gene, but is phenotypically normal. Autosomal recessive disorders affect males and females equally. Because both parents must be heterozygous carriers, autosomal recessive disorders are more common in children of consanguineous parents (blood relatives).

In *X-linked recessive inheritance*, nearly all affected persons are males because females have two X chromosomes and males have an X and a Y chromosome. There's very little DNA sequence in common between the X and the Y chromosomes. Therefore, recessive alleles on a male's X chromosome are expressed. Females who carry a disease-causing recessive allele on only one X chromosome are usually unaffected because they have two X chromosomes —one with the disease-causing allele and one with the normal dominant allele. However, every cell in the female, except the oocytes, undergoes a normal process called X inactivation where one X chromosome is turned off. This process is

random. Therefore, females who carry only one copy of a disease-causing allele may have mild symptoms if a disproportionate number of cells have the X chromosome with the disease-causing allele turned on and the X chromosome with the normal allele turned off.

In *X-linked dominant inheritance,* which is rare, females are affected to varying degrees. These disorders tend to be lethal in males. A family history of multiple male miscarriages or stillbirths is usually a clue to an X-linked dominant disorder.

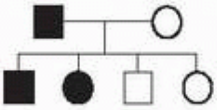
Sex does influence transmission of X-linked alleles. An affected male transmit's the disease-causing allele to all of his female offspring, but to none of his male offspring. This is because males have only one X chromosome. When a sperm containing an X chromosome joins an ovum (which can only have an X chromosome), a female offspring results. When the X chromosome

contains a disease-causing recessive allele, female offspring are typically unaffected carriers. When the X chromosome contains a disease-causing dominant allele, all female offspring are affected. Male offspring receive a Y chromosome from their father, therefore not receiving the disease-causing allele.

INHERITANCE PATTERNS

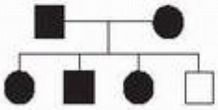
AUTOSOMAL DOMINANT DISORDERS

One heterozygous affected parent



50% recurrence risk, regardless of sex

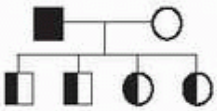
Both heterozygous affected parents



75% recurrence risk, regardless of sex

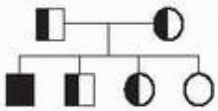
AUTOSOMAL RECESSIVE DISORDERS

One parent affected



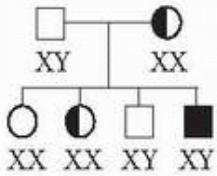
0% offspring affected, 100% carriers

Both parents carriers

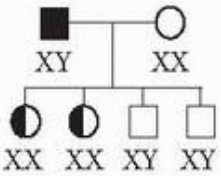


25% risk for being affected; 50% risk for being a carrier, regardless of sex

SEX-LINKED RECESSIVE DISORDERS



50% risk with every pregnancy with a male fetus; 50% carrier risk with every pregnancy with a female fetus



100% sons normal; 100% daughters carriers

KEY

Male

Female

Carrier

Persons affected by disease

Chromosomal abnormalities

During germ cell formation by meiosis, failure of chromosomes to divide *(nondisjunction)* results in a germ cell that contains fewer or more than the normal 23 pairs of chromosomes. Usually, such abnormal germ cells fail to unite at conception; if fertilization does take place, the embryo is usually miscarried early in the pregnancy. Experts believe that up to 60% of spontaneous abortions at less than 90 days' gestation result from an abnormal number of fetal chromosomes; offspring with some chromosomal abnormalities are probably never even implanted. Absence of an autosomal chromosome is incompatible with life, but absence of a sex chromosome, as in Turner's syndrome, is better tolerated. The presence of an extra chromosome (*trisomy*), as in Down syndrome, commonly produces physical malformation, mental retardation, or both.

Chromosomal disorders may also result from structural changes within chromosomes. For instance, in *deletion,* loss of part of a chromosome during cell division produces varying effects in the offspring, depending on the type and amount of genetic material lost. An example is velocardiofacial syndrome, in which part of the long arm of chromosome 22 is missing.

In *translocation,* part of a chromosome attaches itself to another chromosome. If little or no genetic material is lost, the translocation is balanced (symmetrical) and the person displays no effects but may have reproductive problems, such as miscarriage, infertility, or children with malformations, cognitive effects, or both. The person may produce unaffected children, each of whom has a 50% chance of being a balanced translocation carrier, like the parent.

Another abnormality, *ring chromosomes,* results when a chromosome loses a section of genetic material from each end and the remaining stumps join together to form a ring. The effect varies, depending on the type of genetic material lost and on the specific chromosome that's involved.

In *mosaicism,* abnormal chromosomal division in the zygote results in two or more cell lines with different chromosomes. (One cell line may be normal and the other abnormal.) The patient's phenotype depends on the percentage of normal cells and on the varying effects of the abnormal cell line, which depend on the percentage of abnormal cells in each type of tissue.

Originally, Gregory Mendel's theories of heredity pointed to the understanding that an individual's phenotype is the same no matter which parent donates the allele. Now, it's known that this isn't always true. When a deletion on 15q11-13 is inherited from the father, the child will have Prader-Willi syndrome (obesity, short structure, hypogonadism). If the deletion is inherited from the mother, the child will have Angelman's syndrome (mental retardation, no verbal language, seizures). This indicates that different genes are active on chromosome 15 depending on which parent provided the chromosome.

Multifactorial disorders

Multifactorial disorders are abnormalities that result from the interaction of at least two inherited abnormal genes and environmental factors. They include common malformations, such as neural tube defects, cleft lip, and cleft palate, as well as disorders that may not appear until later in life such as diabetes mellitus. Such disorders don't follow the Mendelian patterns of inheritance, but the increased incidence of specific birth defects within families suggests familial transmission.

Detecting genetic disorders

Genetic testing and counseling can help prevent genetic disorders and help patients and their families deal with them when they do develop. Genetic diagnosis relies primarily on pedigree (family tree) analysis, karyotype (chromosomal) analysis, and biochemical analysis of blood, urine, or body tissues (including tissues obtained by

amniocentesis or chorionic villus sampling [CVS]) to detect abnormal gene products. Neonatal screening for inherited metabolic disorders such as phenylketon uria has become standard, and prompt treatment of such disorders can prevent or minimize their effects.

Simple blood tests can detect carriers of recessive-gene disorders, such as Tay-Sachs disease and sickle cell anemia. DNA testing can detect some autosomal recessive, autosomal dominant, and X-linked recessive disorders. This gives a couple at risk the option of prenatal diagnosis (by

amniocentesis or possibly CVS) for some disorders, to detect affected offspring.

A *pedigree,* a diagram of family relationships and diseases and cause of death of individual family members, helps determine a disorder's inheritance pattern, including the probability of occurrence. The pedigree chart begins with the patient (proband, or index case) and traces all living and deceased blood relatives in order of their birth, listing:

- current age or age at death
- health status of all relatives, including miscarriages and stillbirths (and the reasons for them), the site and nature of congenital anomalies, and the presence of mental and growth retardation
- relationships (if the patient is a twin, involved in a consanguineous marriage, or divorced).

This information can be obtained from the patient's memory, autopsy and pathology reports, photographs, and medical records. The pedigree chart is analyzed in relation to the clinical features of the suspected genetic disorder and appropriate laboratory tests or medical records. In one such test, the *karyotype,* white blood cells obtained from a venous blood sample are grown in a special culture until a specific stage of mitosis, when chromosomes are most easily seen with a microscope. Then the cells are broken open and stained to show specific bands on the chromosomes. Staining techniques can be varied to help identify each chromosome and the bands it contains.

Amniocentesis, needle aspiration of amniotic fluid after transabdominal puncture of the uterus under ultrasound guidance, can now detect over 600 genetic disorders before birth by:

- karyotyping cultured amniocytes
- using fluorescent in situ hybridization on cultured amniocytes to detect submicroscopic chromosome deletions, duplications, or translocations
- measuring enzyme levels or activity on cultured amniocytes
- performing DNA mutation or linkage analysis on cultured amniocytes

- measuring proteins (for example, alphafetoprotein) or biochemical substrates in amniotic fluid.

Amniocentesis allows parents to make informed decisions for a pregnancy before the birth of a child with a genetic disorder. It's recommended to patients with:

- maternal age over 34 at delivery
- family history of chromosomal abnormalities
- history of previous children or a firstor second-degree relative with an open or closed neural tube defect or scoliosis with spinal dysraphism
- history of multiple reproductive losses
- parents who are known carriers of a genetic disorder that's detectable by biochemical or DNA testing.

The benefits of amniocentesis must be carefully weighed against the potential complications, which may include amniotic fluid leakage, miscarriage, and (rarely) infection. The risk of complications is estimated to be 0.5% (1 in 200) or less. Genetic counseling is done to help the patient and family weigh the risks against the benefits so they can make an informed decision about testing. For some patients, CVS, another method of collecting genetic information from the fetus, may be an alternative. Using a vaginal or abdominal approach, with ultrasound as a guide, the physician collects a small amount of chorionic tissue, which is then analyzed in much the same way as the amniocentesis. Biochemical tests that are typically done on amniotic fluid can't be done on CVS tissue.

Researchers are currently studying new methods of earlier prenatal diagnosis, such as amniocyte filtration and karyotyping of fetal cells in maternal blood.

Prenatal diagnosis may be considered even when a couple would continue an affected

pregnancy because knowing the diagnosis ahead of time can help the health care team provide the optimal timing and method of delivery, thus improving the neonate's outcome. It also gives the couple more

time to look into financial, educational, and psychological support services to prepare for the birth of a child with special needs.

Health care providers may recommend genetic testing for selected children and adolescents; it's indicated for prevention, decreasing the need for surveillance, and examining treatment availability.

Helping the family cope

Genetic counseling helps a family to understand its risk for a particular genetic disorder and to cope with the disorder if that risk becomes reality. Counseling sessions make it easier for the family to comprehend:

- medical facts (diagnosis, prognosis, treatment)
- how heredity works (risks to other relatives)
- options for dealing with the problem
- consequences of their decision.

Psychological support to relieve stress and improve the child's or parents' self-concept is as important as obtaining the correct information. The birth of a child with a genetic defect may provoke parental feelings of guilt, anxiety, isolation, insecurity, and helplessness and may place undue stress on all members of the family. Family members may experience a period of shock and denial, followed by grief and mourning. Following acceptance of the diagnosis, parents may continue to experience periods of denial; guilt; and chronic sorrow, a phenomenon that manifests as episodes of sadness, particularly around developmental milestones. These feelings are a normal response to having a child with a disability.

When testing confirms a genetic disorder, here's how you can provide psychological support:

- Refer the family for genetic counseling. The following organizations can be contacted to obtain a list of qualified health professionals throughout the United States who can provide genetic evaluation, diagnosis, counseling, and management services:
    - American College of Medical Genetics
    - International Society of Nurses in Genetics

- March of Dimes Birth Defects Foundation
- National Society of Genetic Counselors.

- Find out the services that are offered by the counseling center so you can tell the family what to expect.
- Provide the genetic professional with pertinent medical records and information about the family's special concerns, such as religious beliefs and social preferences.
- After counseling sessions, make sure family members understand the new information presented to them, and reinforce the information provided. Communicate with them in an unhurried and nontechnical manner, and make sure your facts are accurate.
- Inform the family about community resources, agencies, and available support groups to help them deal with genetic disorders. If they're interested, help them get in touch with the families of other patients with the same disorder. The Alliance of Genetic Support Groups or the National Organization for Rare Disorders are valuable resources for locating support groups and parent networking opportunities.
- Coordinate the assistance needed from other members of the health care team, such as physicians, psychologists, and social workers.
- Recognize the parents' stresses in caring for their child, and allow them to express their feelings.

AUTOSOMAL DOMINANT INHERITANCE

Neurofibromatosis

Neurofibromatosis is a group of inherited developmental disorders of the nervous system, muscles, bones, and skin that causes

formation of multiple, pedunculated, soft tumors (neurofibromas), and café-au-lait spots. The most common types are NF-1 (von Recklinghausen disease) and NF-2 (bilateral acoustic neurofibromatosis). About 80,000 Americans are known to have neurofibromatosis; in many others, the disorder is overlooked because symptoms are mild. The prognosis varies;

however, spinal or intracranial tumors can shorten the patient's life span.

Causes and incidence

NF-1 is an autosomal dominant disorder of chromosome 17 that occurs in about 1 in 3,000 births. About 50% of affected families have a negative family history; in many of these families, the father is older, suggesting that advanced paternal age may influence the NF-1 mutation. NF-2 is an autosomal dominant disorder of chromosome 22; however, many patients have a negative family history.

Signs and symptoms

Signs and symptoms of NF-1 vary greatly from one family to another and within members of the same family. A patient who initially seems to have mild symptoms may develop more severe problems later.

An infant with this form may present with only café-au-lait spots or may also have congenital glaucoma, plexiform neurofibromas, or pseudoarthrosis. About 90% of patients have Lisch nodules on the iris; as many as 15% develop optic pathway gliomas, which may cause a significant loss of vision.

Cutaneous and other neurofibromas may begin to develop or become more prominent at puberty; pregnancy may exacerbate tumor growth. Some tumors become malignant; about 8% of patients develop neurofibrosarcoma (cancer of the nerve sheath). Other less-specific features may include other types of tumors (such as meningiomas), short stature, seizures, speech and learning disabilities, mental retardation (occasionally), and abnormalities of the cerebral, GI, and renal arteries.

The first sign of NF-2 is usually a central nervous system tumor, such as a spinal or intracranial meningioma, an acoustic neuroma, and occasionally a schwannoma or spinal astrocytoma. Cutaneous neurofibromas may be less conspicuous in this form, and café-au-lait spots may be minimal or even absent. Learning disabilities and other less-specific features characteristic of NF-1 aren't typically seen in NF-2.

Diagnosis

Diagnosis rests on typical clinical findings, especially neurofibromas and café-au-lait spots. Diagnostic criteria for NF-1 include two or more of the following:

- first-degree relative (parent, sibling, child) with known NF-1
- six or more café-au-lait spots over 5 mm in diameter in a prepubertal patient and 15 mm or more in a postpubertal patient
- freckling in the axillary or inguinal region
- optic pathway glioma
- two or more Lisch nodules on the iris
- osseous lesion, such as sphenoid dysplasia or thinning long-bone cortex.

Diagnostic criteria for NF-2 include a first-degree relative with NF-2 and two of the following:

- neurofibroma, meningioma, schwannoma, glioma, juvenile posterior subcapsular lenticular opacity
- unilateral eighth nerve mass
- bilateral eighth nerve masses seen on magnetic resonance imaging (MRI) or computed tomography (CT) scan.

X-rays, MRI, and CT scan may be indicated to determine the presence of widening internal auditory meatus and intervertebral foramen. An eye examination to look for Lisch nodules should be done on patients suspected of having NF-1. Myelography may be used to identify spinal cord tumors, and lumbar puncture with cerebrospinal fluid analysis will reveal elevated protein concentration in the presence of spinal neurofibromas and acoustic tumors. Deoxyribonucleic acid analysis and prenatal diagnosis may also be done in some families.

Treatment

Neurofibromatosis has no specific treatment. Management consists of surgical removal of intracerebral or intraspinal tumors (when possible) and correction of kyphoscoliosis. Tumors that cause pain and

loss of function are removed on an individual basis. If the entire tumor can't be removed during surgery, radiation may also be used to help relieve symptoms.

ALERT

Tumors that grow rapidly should be removed promptly because they may become malignant.

Cosmetic surgery for disfiguring or disabling growths may be done; however, regrowth is likely. Special schooling for individuals with learning disorders or attention deficit hyperactivity disorder may be required. Annual eye exams should be performed.

Researchers are currently investigating experimental treatments for severe tumors.

Special considerations

- Disfigurement may cause overwhelming embarrassment and social regression. By showing acceptance, you can help the patient adjust to his condition.
- Advise the patient to choose attractive clothing that covers unsightly nodules; suggest special cosmetics to cover skin lesions.
- Refer the patient for genetic counseling to discuss the 50% risk of transmitting this disorder to offspring. Recommend contacting the National Neurofibromatosis Foundation.

Osteogenesis imperfecta

Osteogenesis imperfecta (brittle bones) is a hereditary disease of bones and connective tissue that may cause varying degrees of skeletal fragility, thin skin, blue sclerae, poor teeth, hypermobility of joints, and progressive deafness. This disease occurs in many forms. In the rare congenital form, fractures are present at birth. This form is usually fatal within the first few days or weeks of life. In the late-appearing form, the child appears normal at birth but develops recurring fractures (mostly of the extremities) after the first year of life.

Causes and incidence

Osteogenesis imperfecta can result from autosomal dominant inheritance of a defect in the amount of Type I collagen, an important part of the bone matrix. Clinical signs may result from defective osteoblastic activity and a defect of mesenchymal collagen (embryonic connective tissue) and its derivatives (sclerae, bones, and ligaments). The reticulum fails to differentiate into mature collagen or causes abnormal collagen development, leading to immature and coarse bone formation. Cortical bone thinning also occurs.

Type I, the most common form of osteogenesis imperfecta, occurs in about 1 in 30,000 live births. Both types I and IV are thought to be inherited as an autosomal dominant trait. Types II and III are believed to be inherited as an autosomal recessive trait.

Complications

- Deafness (caused by otosclerosis)
- Scoliosis
- Multiple deformities
- Short stature

Signs and symptoms

Clinical severity varies, depending on the type. In type I, fractures characteristically occur from minimal trauma. The sclerae are a deep blue-black color, and the teeth may be yellow or even grayish blue from opalescent dentin. Patients with dental abnormalities are shorter and have more fractures at birth, more frequent fractures, and more severe skeletal deformities than type I patients with normal teeth.

Bowing of the lower limbs is common in this type, as is kyphosis in adults. About 40% of all adults with type I have severely impaired hearing, and virtually all adults have some degree of hearing impairment by age 50. The number of fractures may spontaneously decrease in adolescence.

Type II is characterized by intrauterine fractures due to extreme bone fragility, leading to intrauterine or early infant death. Death usually results from complications of bone fragility, heart failure, pulmonary hypertension, or respiratory failure. Therapeutic intervention doesn't usually increase survival.

Type III is generally nonlethal. Fractures are usually present at birth and occur frequently in childhood; they typically lead to progressive skeletal deformity and, eventually, impaired mobility. Patients have a poor growth rate; most fall below the third

percentile in height for their age. Their sclerae are usually normal or light blue, and their teeth aren't usually opalescent.

Type IV is characterized by osteoporosis, which leads to increased bone fragility. The sclerae may be light blue at birth but appear normal in adolescents and adults. Bowed limbs may be present at birth, but only 25% of patients have fractures at birth. The number of fractures may decrease spontaneously at puberty, but the majority of patients are short. A few have a skull deformity.

Diagnosis

Family history and characteristic features, such as blue sclerae or deafness, establish the diagnosis. Whenever possible, collagen biochemical studies of cultured skin fibroblasts should be performed. Prenatal diagnosis may be available for certain families with an identified mutation. Prenatal ultrasound performed as early as 16 weeks may show evidence of severe osteogenesis imperfecta. X-rays showing evidence of multiple old fractures and skeletal deformities and a skull X-ray showing wide sutures with small, irregularly shaped islands of bone (wormian bones) between them support the diagnosis. These findings can help differentiate osteogenesis imperfecta from child abuse or from other disorders such as juvenile idiopathic osteoporosis.

In a family with a history of type II osteogenesis imperfecta, diagnostic serial ultrasound should be considered for future pregnancies to detect limb shortening, in utero fractures, and polyhydramnios.

Treatment

Treatment aims to prevent deformities by traction, immobilization, or both and to aid normal development and rehabilitation. Fractures must be repaired quickly to avoid deformities. Surgical procedures such as inserting metal rods through bones can help strengthen bones and prevent deformity. The use of bisphosphonates in children with osteogenesis imperfecta is being researched, as are growth hormone and gene therapies. Starting bisphosphonates after diagnosis at birth decreases fracture rates and helps spur growth. Research is also being done on the benefits of bone marrow transplantation and increasing density in trabecular bone formation. Supportive measures include:

- checking the patient's circulatory, motor, and sensory abilities
- encouraging the patient to walk when possible (Children with osteogenesis imperfecta develop a fear of walking.)
- teaching preventive measures, such as avoiding contact sports or strenuous activities or wearing knee pads, helmets, or other protective devices when engaging in sports
- assessing for and treating scoliosis, a common complication
- promoting preventive dental care and repair of dental caries.

Special considerations

- Educate the family about the disorder. Teach the parents and child how to recognize fractures and how to correctly splint them. Also teach the parents how to protect the child during diapering, dressing, and other activities of daily living.
- Advise the parents to encourage their child to develop interests that don't require strenuous physical activity and to develop his fine motor skills. These actions will promote the child's self-esteem.
- Advise the parents that physical and rehabilitation therapy is beneficial. Swimming is an excellent conditioning exercise.
- Teach the child to assume some responsibility for precautions during physical activity to help foster his independence.

- Stress the importance of good nutrition to heal bones and optimize muscle strength.
- Refer the parents and child for genetic counseling to assess the recurrence risk.
- Administer analgesics, as ordered, to relieve pain from frequent fractures, a hallmark of this disease.
- Monitor dental and hearing needs. Stress the need for regular dental care and immunizations.
- Instruct the parents to provide a medical identification bracelet for the child.

Marfan syndrome

Marfan syndrome is a rare, inherited, degenerative, generalized disease of the connective

tissue that causes ocular, skeletal, and cardiovascular anomalies. It probably results from elastin and collagen abnormalities. Death is usually attributed to cardiovascular complications and may occur any time from early infancy to adulthood, depending on the severity of the symptoms. Marfan syndrome affects males and females equally.

Causes and incidence

Marfan syndrome is inherited as an autosomal dominant trait of chromosome 15. It's caused by mutations in gene fibrillin-1, producing changes in elastic tissues, especially of the aorta, eye, and skin. Mutations of fibrillin-1 also cause overgrowth of long bones. In 85% of patients with this disease, the family history confirms Marfan syndrome in one parent as well. In the remaining 15%, a negative family history suggests a fresh mutation, possibly from advanced paternal age.

Complications

- Mitral valve insufficiency
- Endocarditis

- Dislocated lens

Signs and symptoms

The most common signs and symptoms of this disorder are skeletal abnormalities, particularly excessively long tubular bones and an arm span that exceeds the patient's height. The patient is usually taller than average for his family (in the 95th percentile for his age), with the upper half of his body shorter than average and the lower half, longer. His fingers are long and slender (arachnodactyly). Weakness of ligaments, tendons, and joint capsules results in joints that are loose, hyperextensible, and habitually dislocated. Excessive growth of the rib bones gives rise to chest deformities such as pectus excavatum (funnel chest).

Eye problems are also common; 75% of patients have crystalline lens displacement (ectopia lentis), the ocular hallmark of Marfan syndrome. Quivering of the iris with eye movement (iridodonesis) typically suggests this disorder. Most patients are severely myopic, many have retinal detachment, and some have glaucoma.

The most serious complications occur in the cardiovascular system and include weakness of the aortic media, which leads to progressive dilation or dissecting aneurysm of the ascending aorta. Such dilation appears first in the coronary sinuses and is commonly preceded by aortic insufficiency. Less-common cardiovascular complications include mitral valve prolapse and endocarditis.

Other associated problems include sparsity of subcutaneous fat, frequent hernias, cystic lung disease, recurrent spontaneous pneumothorax, and scoliosis or kyphosis.

Diagnosis

Because no specific test confirms Marfan syndrome, diagnosis is based on typical clinical features (particularly skeletal deformities and ectopia lentis) and a history of the disease in close relatives. Useful supplementary procedures, though not definitive for diagnosis, include X-rays for skeletal abnormalities and an echocardiogram to detect aortic

root dilation. Eye examination with slit-lamp may be used to diagnose a dislocated lens.

Treatment

Attempts to stop the degenerative process have met with little success. Therefore, treatment of Marfan syndrome is basically aimed at relieving symptoms—for example, surgical repair of aneurysms and ocular deformities. In young patients with early dilation of the aorta, prompt treatment with beta-adrenergic blockers may decrease ventricular ejection and protect the aorta; extreme dilation requires surgical replacement of the aorta and the aortic valve. Steroids and sex hormones have been successful (especially in girls) in inducing precocious puberty and early epiphyseal closure to prevent abnormal adult height. Genetic counseling is important, particularly because pregnancy and resultant increased cardiovascular workload can produce aortic rupture.

Special considerations

- High school and college athletes (particularly basketball players) who fit the criteria for Marfan syndrome should undergo a careful clinical and cardiac examination

  before being allowed to play, to avoid sudden death due to dissecting aortic aneurysm or other cardiac complications.
- Provide the patient with supportive care, as appropriate for his clinical status.
- Educate the patient and his family about the course of the disease and its potential complications.
- Stress the need for frequent checkups to detect and treat degenerative changes early.
- Emphasize the importance of taking prescribed medications and of avoiding contact sports and isometric exercise.

PEDIATRIC TIP

To encourage normal adolescent development, advise the parents to avoid unrealistic expectations for their child simply because he's tall and looks older than his years.

- Refer the patient and family to the National Marfan Foundation for additional information.

Stickler's syndrome

Stickler's syndrome also called (*arthroophthalmopathy*) is an autosomal dominant chondrodysplasia caused by structural defects in collagen. It's characterized by ocular, skeletal, auditory, and craniofacial abnormalities. Expression of clinical features is highly variable from one individual to another.

Causes and incidence

At least 19 different types of collagen have been identified. Collagen is an essential component of connective tissues. The collagen defect in most families with Stickler's syndrome is caused by a mutation in the type II collagen gene (COL2AI) located on chromosome l2q13. Other families demonstrate linkage to the COLIIA2 gene located on chromosome 6p2l.3 and others to the COLIJAI gene located on chromosome lp2l. COL2AI and COLIJA I are expressed in the hyaline cartilage, vitreous, intervertebral disc, and inner ear. COLIIA2 isn't expressed in the vitreous. Genetic studies have identified a few families who carry the clinical diagnosis of Stickler's syndrome yet don't demonstrate linkage to any of the three aforementioned collagen genes, suggesting further genetic heterogeneity (a pattern of traits caused by genetic factors in some cases and nongenetic factors in others).

About 1 in 10,000 people is affected with Stickler's syndrome. However, this incidence rate is considered conservative because persons with very mild symptoms may never be diagnosed with the syndrome.

Complications

- Glaucoma
- Retinal detachment

- Deafness
- Osteoarthritis
- Ear infections
- Difficulty breathing or feeding

Signs and symptoms

The clinical phenotype can consist of ocular, auditory, craniofacial, and skeletal abnormalities. The number of organ systems involved and the specific phenotypic features expressed can vary significantly between affected family members and, in particular, between unrelated affected persons.

Ocular symptoms, particularly high myopia, are common in persons with Stickler's syndrome, with the exception of those who have COLIJA2 mutations. Vitreal abnormalities are considered a hallmark of Stickler's syndrome, although the abnormalities in the vitreous differ in persons with a COL2AI mutation from those with a COLIIAI mutation. Retinal detachment resulting in blindness is the most serious ocular complication.

The vitreoretinal degeneration that leads to retinal detachment is much more common in persons with a COL2AI mutation. Persons with Stickler's syndrome can also have congenital cataracts and develop glaucoma. Ocular symptoms are typically absent in persons with linkage to COLIJA2.

Auditory symptoms include conductive hearing loss secondary to Eustachian tube dysfunction in children with cleft palate or collagen defects in the inner ear apparatus. Sensorineural hearing loss has an earlier onset and tends to be more progressive in persons with a COLIJAI mutation.

Craniofacial features may include micrognathia (small lower jaw) and a flattened midface and nasal bridge. Micrognathia

may be associated with some degree of cleft palate (bifid uvula to complete cleft of the palate). Micrognathia associated with glossoptosis

places neonates and infants with Stickler's syndrome at significant risk for episodic obstructive apnea during feeding and when lying flat.

Skeletal symptoms can include joint hypermobility in young children, spondyloepiphyseal dysplasia, and, later, degenerative arthropathy during early adult years. Also related to the collagen defect, scoliosis and mitral valve prolapse can develop in some persons with Stickler's syndrome.

Diagnosis

Diagnosis is based on the recognition of clinical features consistent with Stickler's syndrome. The number of genes involved in Stickler's syndrome and the complexity of sequencing large genes currently preclude the clinical utility of routine genetic testing for diagnostic purposes. Therefore, diagnosis must rely on the dysmorphology skills of the practitioner performing the physical examination.

Stickler's syndrome should be considered in neonates with the triad of micrognathia, cleft of the soft palate, and glossoptosis. This triad of features is known as *Pierre Robin syndrome*.

Severe myopia in infants and young children should be considered a possible symptom of Stickler's syndrome. The diagnosis should also be considered in persons with a family history of cleft palate and significant myopia, deafness, or spondyloepiphyseal dysplasia. A slit-lamp examination of the vitreous is necessary to determine the presence of vitreal abnormalities that are considered pathognomonic of Stickler's syndrome.

Treatment

Beginning with the first 6 months after birth, annual ophthalmology evaluation must be obtained to assess for myopia, vitreal abnormalities, and retinal degeneration and detachment. Persons who experience floaters or shadows in their vision require immediate assessment.

Persons with vitreoretinal degeneration need to avoid contact sports and other physical activity that can jar and detach the retina.

An auditory brain stem-evoked response evaluation should be done during the first month after birth. The schedule for regular follow-up

needs to be determined based on the results of the initial evaluation, frequency of otitis media episodes, and progress in language development.

Early use of corrective lenses and hearing aids is recommended to enable developmental progression at the infant or young child's full potential.

Depending on the infant's weight and health, surgical correction of the cleft palate can occur around age 9 months. With few exceptions, surgical closure of the palate should occur before age 2 to maximize speech and language development.

Special considerations

- To assess for obstructive apnea, neonates with the Pierre Robin syndrome triad need oxygen and carbon dioxide measurements while lying in different positions and while feeding.
- Neonates and infants with cleft palate may need a specialized cleft palate nurser to obtain adequate caloric intake.
- Screening for cardiac valvular disease should be considered in the older child and adult with Stickler's syndrome.
- Genetic counseling by a person trained in genetics should be offered to adults with Stickler's syndrome.
- Referral to appropriate support groups or networking groups should be offered to help with coping skills and to provide anticipatory guidance related to day-to-day needs of a person with Stickler's syndrome.

AUTOSOMAL RECESSIVE INHERITANCE

Cystic fibrosis

Cystic fibrosis is a generalized dysfunction of the exocrine glands that affects multiple

organ systems. Transmitted as an autosomal recessive trait, it's the most common fatal genetic disease in white children.

CYSTIC FIBROSIS TRANSMISSION RISK

The chance that a relative of a person with cystic fibrosis or a person with no family history will carry the cystic fibrosis gene appears in the chart below.

Relative of affected person	Carrier chance
Brother or sister	2 in 3 (67%)
Niece or nephew	1 in 2 (50%)
Aunt or uncle	1 in 3 (33%)
First cousin	1 in 4 (25%)
No known family history	**Carrier chance**
Whites	1 in 25 (4%)
Blacks	1 in 65 (1.5%)
Asians	1 in 150 (0.67%)

Cystic fibrosis is a chronic disease. With improvements in treatment over the past decade, the average life expectancy has risen from age 16 to age 40 and older.

Causes and incidence

The gene responsible for cystic fibrosis (located on chromosome 7) encodes a protein that involves chloride transport across epithelial membranes; over 100 specific mutations of the gene are known. (See *Cystic fibrosis transmission risk*.) The immediate causes of symptoms in cystic fibrosis are increased viscosity of bronchial, pancreatic, and other mucous gland secretions and consequent obstruction of glandular ducts. Cystic fibrosis accounts for almost all cases of pancreatic enzyme deficiency in children.

In the United States, the incidence of cystic fibrosis is highest in Whites of northern European ancestry (1 in 2,000 live births) and lowest in

Blacks (1 in 17,000 live births), Native Americans, and people of Asian ancestry. The disease occurs equally in both sexes.

Complications

- Bronchiectasis
- Pneumonia
- Atelectasis
- Hemoptysis
- Dehydration
- Distal intestinal obstruction syndrome
- Malnutrition
- Nasal polyps
- Gastroesophageal reflux
- Rectal prolapse
- Cor pulmonale
- Diabetes
- Pancreatitis
- Cholecystitis

Signs and symptoms

The clinical effects of cystic fibrosis may become apparent soon after birth or may take years to develop. They include major aberrations in sweat gland, respiratory, and GI function. Sweat gland dysfunction is the most consistent abnormality. Increased concentrations of sodium and chloride in the sweat lead to hyponatremia and hypochloremia and can eventually induce fatal shock and arrhythmias, especially in hot weather.

Respiratory symptoms reflect obstructive changes in the lungs: wheezy respirations; a dry, nonproductive paroxysmal cough; dyspnea; and tachypnea. These changes stem from thick, tenacious secretions in the

bronchioles and alveoli and eventually lead to severe atelectasis and emphysema. Children with cystic fibrosis

display a barrel chest, cyanosis, and clubbing of the fingers and toes. They suffer recurring bronchitis and pneumonia as well as associated nasal polyps and sinusitis. Death typically results from pneumonia, emphysema, or atelectasis.

The GI effects of cystic fibrosis occur mainly in the intestines, pancreas, and liver. One early symptom is meconium ileus; the neonate with cystic fibrosis doesn't excrete meconium, a dark green mucilaginous material found in the intestine at birth. He develops symptoms of intestinal obstruction, such as abdominal distention, vomiting, constipation, dehydration, and electrolyte imbalance. As the child gets older, obstruction of the pancreatic ducts and resulting deficiency of trypsin, amylase, and lipase prevent the conversion and absorption of fat and protein in the GI tract. The undigested food is then excreted in frequent, bulky, foul-smelling, pale stools with a high fat content. This malabsorption induces poor weight gain, poor growth, ravenous appetite, distended abdomen, thin extremities, and sallow skin with poor turgor. The inability to absorb fats results in a deficiency of fat-soluble vitamins (A, D, E, and K), leading to clotting problems, retarded bone growth, and delayed sexual development. Males may experience azoospermia and sterility; females may experience secondary amenorrhea but can reproduce. A common complication in infants and children is rectal prolapse secondary to malnutrition and wasting of perirectal supporting tissues.

In the pancreas, fibrotic tissue, multiple cysts, thick mucus, and eventually fat replace the acini (small, saclike swellings normally found in this gland), producing symptoms of pancreatic insufficiency: insufficient insulin production, abnormal glucose tolerance, and glycosuria. About 15% of patients have adequate pancreatic exocrine function for normal digestion and, therefore, have a better prognosis. Biliary obstruction and fibrosis may prolong neonatal jaundice. In some patients, cirrhosis and portal hypertension may lead to esophageal varices, episodes of hematemesis and, occasionally, hepatomegaly.

Diagnosis

CONFIRMING DIAGNOSIS

The Cystic Fibrosis Foundation has developed certain criteria for a definitive diagnosis: Two sweat tests using a pilocarpine solution (a sweat inducer) and either obstructive pulmonary disease, confirmed pancreatic insufficiency or failure to thrive, and a family history of cystic fibrosis.

The following test results may support the diagnosis:

- Chest X-rays indicate early signs of obstructive lung disease.
- Stool specimen analysis indicates the absence of trypsin, suggesting pancreatic insufficiency.
- Deoxyribonucleic acid testing can now locate the presence of the Delta F 508 deletion (found in about 70% of cystic fibrosis patients, although the disease can cause more than 100 other mutations). It allows prenatal diagnosis in families with a previously affected child.
- Pulmonary function tests reveal decreased vital capacity, elevated residual volume due to air entrapments, and decreased forced expiratory volume in 1 second. This test is used if pulmonary exacerbation already exists.
- Liver enzyme tests may reveal hepatic insufficiency.
- Sputum culture reveals organisms that cystic fibrosis patients typically and chronically colonize, such as *Staphylococcus* and *Pseudomonas*.
- Serum albumin measurement helps assess nutritional status.
- Electrolyte analysis assesses hydration status.

Treatment

The aim of treatment is to help the child lead as normal a life as possible. The type of treatment depends on the organ systems involved.

To combat electrolyte losses in sweat, salt foods generously and, in hot weather, administer sodium supplements.

To offset pancreatic enzyme deficiencies, give oral pancreatic enzymes with meals and snacks, as ordered. Maintain a diet that's low in fat, but high in protein and calories, and provide supplements of

water-miscible, fat-soluble vitamins (A, D, E, and K).

Management of pulmonary dysfunction includes chest physiotherapy, postural drainage, and breathing exercises several times daily to aid removal of secretions from lungs. Antihistamines are contraindicated because they have a drying effect on mucous membranes, making expectoration of mucus difficult or impossible. Aerosol therapy includes intermittent nebulizer treatments before postural drainage to loosen secretions.

Dornase alfa or DNase (recombinant human deoxyribonuclease), genetically engineered pulmonary enzymes given by aerosol nebulizer, helps thin airway mucus, improving lung function and reducing the risk of pulmonary infection.

Treatment of pulmonary infection requires:

- broad-spectrum antimicrobials
- oxygen therapy as needed
- loosening and removal of mucopurulent secretions, using an intermittent nebulizer and postural drainage to relieve obstruction. Use of a mist tent is controversial because mist particles may become trapped in the esophagus and stomach and never even reach the lungs.

Lung transplantation may be considered in some cases. Genetic research on curing cystic fibrosis by artificially inserting a “healthy” gene into a person through gene therapy is ongoing. The gene would be inserted by using an intranasal form. Research on correcting the disorder before birth is promising. Other areas of research include restoring salt transport in the cells, and use of mucus-thinning drugs and nutritional supplementation.

Special considerations

- Throughout this illness, teach the patient and his family about the disease and its treatment. The Cystic Fibrosis Foundation can provide educational and support services.
- Although many males with cystic fibrosis are infertile, females may become pregnant (due to increased life expectancies). As a result, more cystic fibrosis patients are now facing difficult reproductive decisions. Refer such patients (or the parents of an affected child) for genetic counseling so they can discuss family planning issues or prenatal diagnosis options if they're considering having more children.
- Be aware that some patients have recently undergone lung transplants to reduce the effects of the disease. Also, aerosol gene therapy shows promise in reducing pulmonary symptoms.

Research indicates that the genetic defect responsible for cystic fibrosis has also been identified in individuals experiencing some forms of unexplained pancreatitis.

Tay-Sachs disease

The most common of the lipid storage diseases, Tay-Sachs disease results from a congenital deficiency of the enzyme hexosaminidase A. It's characterized by progressive mental and motor deterioration and is usually fatal before age 5, although some adolescents and adults with variations of hexosaminidase A deficiency have been noted. These individuals have significantly reduced levels of Hex-A, rather than a complete absence of the enzyme.

Causes and incidence

Tay-Sachs disease (also known as *GM_2 gangliosidosis*) is an autosomal recessive disorder of chromosome 15 in which the enzyme hexosaminidase A is virtually absent or deficient. This enzyme is necessary for metabolism of gangliosides, water-soluble glycolipids found primarily in central nervous system (CNS) tissues. Without hexosaminidase A, accumulating lipid pigments distend and progressively destroy and demyelinate CNS cells.

Tay-Sachs disease appears in fewer than 100 neonates born each year in the United States. However, about it's 100 times more common in

persons of Eastern European Jewish (Ashkenazi) ancestry than in the general population, occurring in about l in 3,600 live births in this ethnic group. About 1 in 30 Ashkenazi Jews, French Canadians, and American Cajuns are heterozygous carriers. If two such carriers have children, each of their offspring has a 25% chance of having Tay-Sachs disease.

Complications

- Bronchopneumonia
- Death

Signs and symptoms

A neonate with classic Tay-Sachs disease appears normal at birth, although he may have an exaggerated Moro reflex. By age 3 to 6 months, he becomes apathetic and responds only to loud sounds. His neck, trunk, arm, and leg muscles grow weaker, and soon he can't sit up or lift his head. He has difficulty turning over, can't grasp objects, and has progressive vision loss.

By age 18 months, the infant is usually deaf and blind and has seizures, generalized paralysis, and spasticity. His pupils are dilated and don't react to light. Decerebrate rigidity and a vegetative state follow. The child suffers recurrent bronchopneumonia after age 2 and usually dies before age 5. A child who survives may develop ataxia and progressive motor retardation between ages 2 and 8.

The “ juvenile” form of Tay-Sachs disease generally appears between ages 2 and 5 as a progressive deterioration of psychomotor skills and gait. Patients with this type can survive to adulthood.

Diagnosis

CONFIRMING DIAGNOSIS

Typical clinical features point to Tay-Sachs disease, but serum analysis showing deficient hexosaminidase A is the key to diagnosis. An ophthalmologic examination showing

optic nerve atrophy and a distinctive cherry-red spot on the retina supports the diagnosis. (The cherry-red spot may be absent in the juvenile form.)

Diagnostic screening is essential for all couples when at least one partner is of Ashkenazi Jewish, French Canadian, or Cajun ancestry and for others with a family history of the disease. A blood test evaluating hexosaminidase A levels can identify carriers. Amniocentesis or chorionic villus sampling can detect hexosaminidase A deficiency in the fetus.

Treatment

Tay-Sachs disease has no known cure. Supportive treatment includes tube feedings of nutritional supplements, suctioning and postural drainage to remove pharyngeal secretions, skin care to prevent pressure ulcers in bedridden children, and mild laxatives to relieve neurogenic constipation. Anticonvulsants usually fail to prevent seizures. Because these children need constant physical care, many parents have full-time skilled home nursing care or place them in long-term special care facilities.

Special considerations

Your most important job is to help the family deal with inevitably progressive illness and death.

- Offer carrier testing to all couples from high-risk ethnic groups.
- Refer the parents for genetic counseling, and stress the importance of considering an amniocentesis in future pregnancies. Refer siblings for screening to determine if they're carriers. If they're carriers and are adults, refer them for genetic counseling, but stress that there's no danger of transmitting the disease to offspring if they don't marry another carrier.
- Some in-vitro fertilization centers have recently started offering preimplantation genetics. Refer the couple to an appropriate center if they express interest in assisted reproductive technology.
- Because the parents of an affected child may feel excessive stress or guilt because of the child's illness and the emotional and financial

burden it places on them, refer them for counseling if indicated.

- If the parents care for their child at home, teach them how to do suctioning, postural drainage, and tube feeding. Also teach them how to provide good skin care to prevent pressure ulcers.

For more information on this disease, refer parents to the National Tay-Sachs and Allied Diseases Association.

Phenylketonuria

Phenylketonuria (PKU) is an inborn error in phenylalanine metabolism that results in the accumulation of high serum levels of the enzyme phenylalanine in the blood. When left untreated, it results in cerebral damage and mental retardation.

Causes and incidence

PKU is transmitted by an autosomal recessive gene on chromosome 12. Patients with this disorder have insufficient hepatic phenylalanine hydroxylase, an enzyme that acts as a catalyst in the conversion of phenylalanine to tyrosine. As a result, phenylalanine and its metabolites accumulate in the blood, eventually causing mental retardation if left untreated. The exact biochemical mechanism that causes this retardation is unclear.

In the United States, this disorder occurs in 1 in about 14,000 births. (About 1 person in 60 is an asymptomatic carrier.) The gene is most common in Ireland, Scotland, Belgium, and West Germany and rare in Blacks, Asians, Native Americans, Finns, and Ashkenazi Jews.

Signs and symptoms

An infant with undiagnosed and untreated PKU appears normal at birth but by 4 months begins to show signs of arrested brain development, including mental retardation and, later, personality disturbances (schizoid and antisocial personality patterns and uncontrollable temper). Such a child may have a lighter complexion than unaffected siblings and typically has blue eyes. He may also have microcephaly; eczematous

skin lesions or dry, rough skin; and a musty (mousy) odor due to skin and urinary excretion of phenylacetic acid. About 80% of these children have abnormal EEG patterns, and about one-third have seizures, usually beginning between ages 6 and 12 months.

Children with PKU show a precipitous decrease in IQ in their first year, are usually hyperactive and irritable, and exhibit purposeless, repetitive motions. They have increased muscle tone and an awkward gait.

Although blood phenylalanine levels are near normal at birth, they begin to rise within a few days. By the time they reach significant levels (about 30 mg/dl), cerebral damage has begun. Such irreversible damage probably is complete by age 2 or 3. However, early detection and treatment can minimize cerebral damage, and children under strict dietary control can lead normal lives.

Diagnosis

All states require screening for PKU at birth; the Guthrie screening test on a capillary blood sample (bacterial inhibition assay) reliably detects PKU. However, because phenylalanine levels may be normal at birth, the neonate should be reevaluated after he has received dietary protein for 24 to 48 hours. The common practice of discharging new mothers from the hospital within 24 hours of delivery has resulted in failure to detect some neonates with PKU. For this reason, some states now require a minimum hospital stay of 48 hours after a vaginal delivery.

Adding a few drops of 10% ferric chloride solution to a wet diaper is another method of detecting PKU. If the area turns a deep, bluish green, phenylpyruvic acid is present in the urine.

CONFIRMING DIAGNOSIS

Detection of elevated blood levels of phenylalanine and the presence of phenylpyruvic acid in the infant's urine confirm the diagnosis. (Urine should also be tested 4 to 6 weeks after birth because urinary levels of phenylpyruvic acid vary with the amount of protein ingested.)

Chorionic villi sampling can be used to detect fetal PKU as a prenatal diagnosis. Enzyme assay can be used to detect the carrier state in

parents.

Treatment

Treatment consists of restricting dietary intake of the amino acid phenylalanine to keep phenylalanine blood levels between 3 and 9 mg/dl. Because most natural proteins contain 5% phenylalanine, they must be limited in the child's diet. An enzymatic hydrolysate of casein, such as Lofenalac powder or Pregestimil powder, is substituted for milk in the diets of affected infants. This milk substitute contains a minimal amount of phenylalanine, normal amounts of other amino acids, and added amounts of carbohydrate and fat. Dietary restrictions usually continue throughout life.

The special diet for PKU calls for careful monitoring. Because the body doesn't make phenylalanine, overzealous dietary restriction can induce phenylalanine deficiency, producing lethargy, anorexia, anemia, rashes, and diarrhea.

Special considerations

In caring for a child with PKU, it's especially important to teach both the parents and child about this disease and to provide emotional support and counseling. (Psychological and emotional problems may result from the difficult dietary restrictions.)

- Emphasize to the child and his parents the critical importance of adhering to the special diet. The child must avoid breads, cheese, eggs, flour, meat, poultry, fish, nuts, milk, legumes, and phenylalanine sugar substitutes.
- Inform the parents that the child will need frequent tests for urine phenylpyruvic acid and blood phenylalanine levels to evaluate the diet's effectiveness.
- As the child grows older and is supervised less closely, his parents will have less control over what he eats. As a result, deviation from the restricted diet becomes more likely, as does the risk of brain damage. Encourage the parents to allow the child some choices in the kinds of

low-protein foods he wants to eat; this will help make him feel trusted and more responsible.

- Teach the parents about normal physical and mental growth and development so that they can recognize any developmental delay that may point to excessive phenylalanine intake.

PEDIATRIC TIP

Infants should be routinely screened for PKU because detection of the disorder and control of phenylalanine intake soon after birth can prevent severe mental retardation.

- Refer females with PKU who reach reproductive age for genetic counseling because recent research indicates that their offspring may have a higher-than-normal incidence of brain damage, mental retardation, microcephaly, and major congenital malformations, especially of the heart and central nervous system. Such damage may be minimized with a low-phenylalanine diet before conception and during pregnancy. Even patients under good control remain at increased risk for offspring with this defect. During pregnancy, weekly blood tests should be done to make sure phenylalanine levels don't get too high.

Albinism

Albinism is a rare inherited defect in melanin metabolism of the skin and eyes (oculocutaneous albinism) or just the eyes (ocular albinism). Ocular albinism impairs visual acuity. Oculocutaneous albinism also causes severe intolerance to sunlight and increases susceptibility to skin cancer. Other forms are associated with deafness. About 1 in 17,000 people have one of the types of albinism.

Causes and incidence

Oculocutaneous albinism results from autosomal recessive inheritance; ocular albinism, from an X-linked recessive trait that causes hypopigmentation only in the iris and the ocular fundus.

Normally, melanocytes synthesize melanin. Melanosomes, melanin-containing granules within melanocytes, diffuse and absorb the sun's ultraviolet light, thus protecting the skin and eyes from its dangerous effects. In *tyrosinase-negative albinism* (the most common type), melanosomes don't contain melanin because they lack tyrosinase, the enzyme that stimulates melanin production. In *tyrosinase-positive albinism*, melanosomes contain tyrosine, a tyrosinase substrate, but a defect in the tyrosine transport system impairs melanin production.

In *tyrosinase-variable albinism* (rare), an unidentified enzyme defect probably impairs synthesis of a melanin precursor. Other rare forms of albinism are *Chédiak-Higashi syndrome* (tyrosine-negative albinism with hematologic and neurologic manifestations); *Hermansky-Pudlak syndrome* (tyrosinase-positive albinism with platelet dysfunction, bleeding abnormalities, and ceroidlike inclusions in many organs); and *Cross-McKusick-Breen syndrome* (tyrosinase-positive albinism with neurologic involvement).

In the United States, both types of albinism are more common in Blacks than in Whites. Native Americans have a high incidence of the tyrosine-positive form.

Complications

- Nystagmus
- Photosensitivity

- Errors of refraction
- Pigmented nevi
- Actinic keratoses
- Increased skin cancer risk

Signs and symptoms

Light-skinned Whites with tyrosinase-negative albinism have pale skin and hair color ranging from white to yellow; their pupils appear red because of translucent irides. Blacks with the same disorder have hair

that may be white, faintly tinged with yellow, or yellow-brown. Both Whites and Blacks with tyrosinase-positive albinism grow darker as they age. For instance, their hair may become straw-colored or light brown and their skin cream-colored or pink. People with tyrosinase-positive albinism may also have freckles and pigmented nevi that may require excision.

In tyrosinase-variable albinism, at birth the child's hair is white, his skin is pink, and his eyes are gray. As he grows older, though, his hair becomes yellow, his irides may become darker, and his skin may even tan slightly.

The skin of a person with albinism is easily damaged by the sun. It may look weather-beaten and is highly susceptible to precancerous and cancerous growths. The patient may also have photophobia, myopia, strabismus, and congenital horizontal nystagmus.

Diagnosis

Diagnosis is based on clinical observation and the patient's family history. Microscopic examination of the skin and of hair follicles determines the amount of pigment present. Testing plucked hair roots for pigmentation when incubated in tyrosine distinguishes tyrosinase-negative albinism from tyrosinase-positive albinism. Tyrosinase-positive hair bulbs will develop color.

Treatment

No specific treatment for albinism exists.

Special considerations

- To help the parents work through any feelings of guilt or depression, encourage early infant-parent bonding. Also inform the parents about cosmetic measures (glasses with tinted lenses, makeup) that can lessen the child's disfigurement when he's older.
- Teach the child and his parents what measures best protect him from solar radiation, and inform them of its danger signals (excessive drying of skin, crusty lesions on exposed skin, changes in skin color).

- Advise the patient to wear full-spectrum sunblocks, dark glasses, and appropriate protective clothing.
- If the patient's appearance causes him social and emotional problems, he may need psychological counseling. Such counseling may also be in order for his family, if they too find it difficult to accept his disorder.
- Stress the need for frequent refractions and eye examinations to correct visual defects.
- Refer the adult patient or the parents of an affected child for genetic counseling to learn about the probability of recurrence in future offspring.

Sickle cell anemia

A congenital hemolytic anemia that occurs primarily but not exclusively in Blacks, sickle cell anemia results from a defective hemoglobin (Hb) molecule (HbS) that causes red blood cells (RBCs) to roughen and become sickle-shaped. Such cells impair circulation, resulting in chronic ill health (fatigue, dyspnea on exertion, swollen joints), periodic crises, long-term complications, and premature death.

Penicillin prophylaxis can decrease morbidity and mortality from bacterial infections. Half of patients with sickle cell anemia die by their early twenties; few live to middle age.

Causes and incidence

Sickle cell anemia results from homozygous inheritance of the gene that produces HbS (chromosome 11). It's inherited as an autosomal recessive trait. Heterozygous inheritance of this gene results in sickle cell trait, a condition that usually produces no symptoms. (See *Sickle cell trait*, page 1126.) Sickle cell anemia is most common in tropical Africans and in people of African descent;

about 1 in 10 American Blacks carries the abnormal gene. However, sickle cell anemia also appears in other ethnic populations, including people of Mediterranean or East Indian ancestry.

SICKLE CELL TRAIT

Sickle cell trait is a relatively benign condition that results from heterozygous inheritance of the abnormal hemoglobin (Hb) S-producing gene. Like sickle cell anemia, this condition is most common in blacks. Sickle cell trait never progresses to sickle cell anemia.

In persons with sickle cell trait (known as *carriers*), 20% to 40% of their total Hb is HbS; the rest is normal.

Such persons usually have no symptoms. They have normal Hb and hematocrit values and can expect a normal life span. Nevertheless, they must avoid situations that provoke hypoxia, which can occasionally cause a sickling crisis similar to that in sickle cell anemia.

Genetic counseling is essential for sickle cell carriers. If two sickle cell carriers produce offspring, each of their children has a 25% chance of inheriting sickle cell anemia.

If two parents who are both carriers of sickle cell trait (or another hemoglobinopathy) have offspring, each child has a 25% chance of developing sickle cell anemia. (See *Inheritance patterns in sickle cell anemia*.) Overall, 1 in every 400 to 600 black children has sickle cell anemia. The defective HbS-producing gene may have persisted because, in areas where malaria is endemic, the heterozygous sickle cell trait provides resistance to malaria and is actually beneficial.

The abnormal HbS found in such patients' RBCs become insoluble whenever hypoxia occurs. As a result, these RBCs become rigid, rough, and elongated, forming a crescent or sickle shape. (See *Comparing normal and sickled red blood cells*, page 1128.) Such sickling can produce hemolysis (cell destruction). In addition, these altered cells tend to pile up in capillaries and smaller blood vessels, making blood more viscous. Normal circulation is impaired, causing pain, tissue infarctions, and swelling. Such blockage causes anoxic changes that lead to further sickling and obstruction.

Complications

- Chronic obstructive pulmonary disease
- Heart failure
- Organ infarction
- Splenomegaly
- Stroke
- Death

Signs and symptoms

Characteristically, sickle cell anemia produces tachycardia, cardiomegaly, systolic and diastolic murmurs, pulmonary infarctions (which may result in cor pulmonale), chronic fatigue, unexplained dyspnea or dyspnea on exertion, hepatomegaly, jaundice, pallor, joint swelling, aching bones, chest pains, ischemic leg ulcers (especially around the ankles), and increased susceptibility to infection. Such symptoms usually don't develop until after age 6 months because large amounts of fetal Hb protect infants for the first few months after birth. Low socioeconomic status and related problems, such as poor nutrition and education, may delay diagnosis and supportive treatment.

Infection, stress, dehydration, and conditions that provoke hypoxia—strenuous exercise, high altitude, unpressurized aircraft, cold, and vasoconstrictive drugs—may all provoke periodic crises. A painful crisis (vasoocclusive crisis, infarctive crisis), the most common crisis and the hallmark of the disease, usually appears periodically after age 5. It results from blood vessel obstruction by rigid, tangled sickle cells, which causes tissue anoxia and possible necrosis. This type of crisis is characterized by severe abdominal, thoracic, muscular, or bone pain and possibly worsening jaundice, dark urine, and a low-grade fever.

Autosplenectomy, in which splenic damage and scarring is so extensive that the

spleen shrinks and becomes impalpable, occurs in patients with long-term disease. This can lead to increased susceptibility to Streptococcus pneumoniae sepsis, which can be fatal without prompt treatment.

Infection may develop after the crisis subsides (in 4 days to several weeks), so watch for lethargy, sleepiness, fever, or apathy.

An aplastic crisis (megaloblastic crisis) results from bone marrow depression and is associated with infection, usually viral. It's characterized by pallor, lethargy, sleepiness, dyspnea, possible coma, markedly decreased bone marrow activity, and RBC hemolysis.

In infants between ages 8 months and 2 years, an acute sequestration crisis may cause sudden massive entrapment of RBCs in the spleen and liver. This rare crisis causes lethargy and pallor and, if untreated, commonly progresses to hypovolemic shock and death.

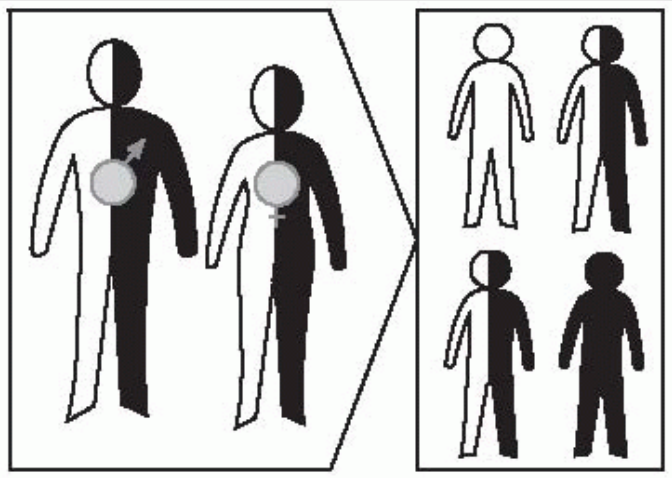
A hemolytic crisis is quite rare and usually occurs in patients who also have glucose-6-phosphate dehydrogenase deficiency. It probably results from complications of sickle cell anemia, such as infection, rather than from the disorder itself. Hemolytic crisis causes liver congestion and hepatomegaly as a result of degenerative changes. It worsens chronic jaundice, although increased jaundice doesn't always point to a hemolytic crisis.

Suspect any of these crises in a sickle cell anemia patient with pale lips, tongue, palms, or nail beds; lethargy; listlessness; sleepiness with difficulty awakening; irritability; severe pain; a fever over 104° F (40° C); or a fever of 100° F (37.8° C) that persists for 2 days.

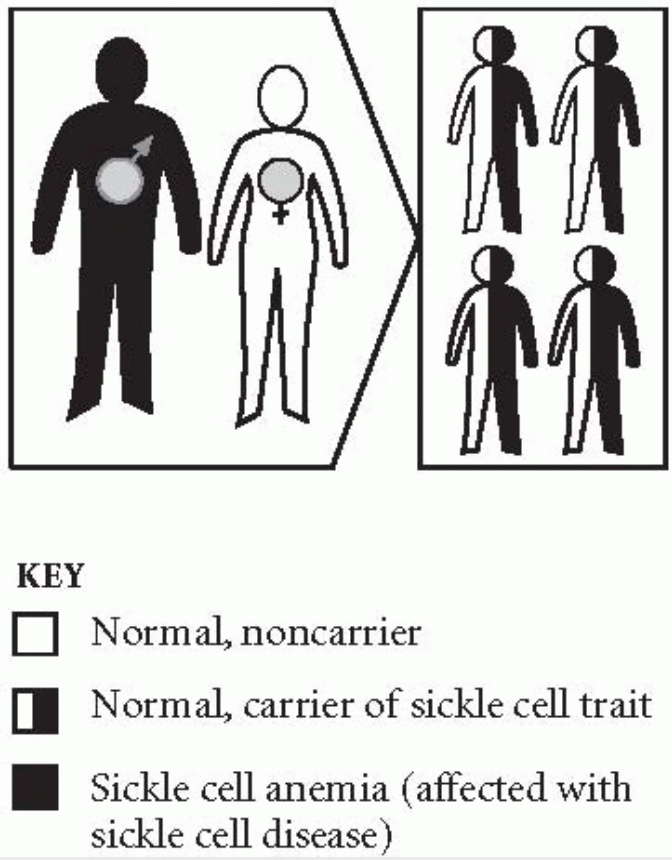
Sickle cell anemia also causes long-term complications. Typically, the child is small for his age and has delayed puberty. (However, fertility isn't impaired.) If he reaches adulthood, his body build tends to be spiderlike — narrow shoulders and hips, long extremities, curved spine, barrel chest, and elongated skull. An adult usually has complications from organ infarction, such as retinopathy and nephropathy. Premature death commonly results from infection or from repeated occlusion of small blood vessels and consequent infarction or necrosis of major organs (such as cerebral blood vessel occlusion causing stroke).

INHERITANCE PATTERNS IN SICKLE CELL ANEMIA

When both parents are carriers of sickle cell trait, each child has a 25% chance of developing sickle cell anemia, a 25% chance of being a normal (unaffected) noncarrier, and a 50% chance of being a carrier of sickle cell trait.



When one parent has sickle cell anemia and one is normal, all offspring will be carriers of sickle cell trait.



Diagnosis

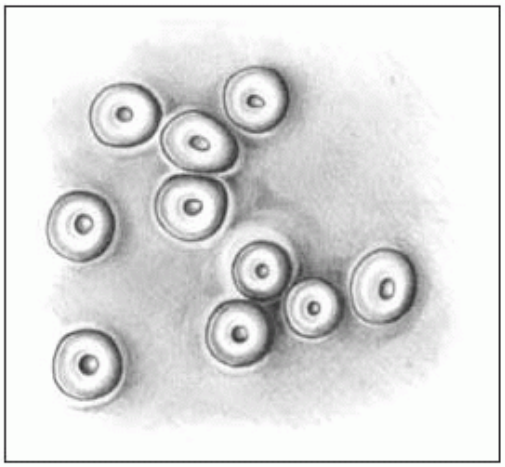
A positive family history and typical clinical features suggest sickle cell anemia. Hb electrophoresis showing HbS or other hemoglobinopathies can also confirm it.

Electrophoresis should be done on umbilical cord blood samples at birth to provide sickle cell disease screening for all neonates at risk.

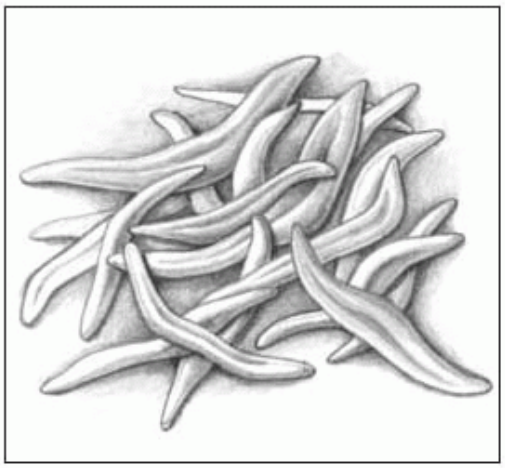
COMPARING NORMAL AND SICKLED RED BLOOD CELLS

When a person with sickle cell anemia develops hypoxia, the abnormal hemoglobin S found in his red blood cells (RBCs) becomes insoluble. This causes the RBCs to become rigid, rough, and elongated, forming the characteristic sickle shape.

NORMAL RBCS



SICKLE CELLS



Additional laboratory studies may show a low RBC count, elevated white blood cell and platelet counts, decreased erythrocyte sedimentation rate, increased serum iron, decreased RBC survival, and reticulocytosis. Hb levels may be low or normal. During early childhood, palpation may reveal splenomegaly, but, as the child grows older, the spleen shrinks.

Treatment

Treatment begins before age 4 months with prophylactic penicillin. If the patient's Hb drops suddenly or if his condition deteriorates rapidly, he'll need to be hospitalized for a transfusion of packed RBCs. In a sequestration crisis, treatment may include sedation, administration of

analgesics, a blood transfusion, oxygen administration, and large amounts of oral or I.V. fluids.

Daily folic acid supplementation is recommended to prevent megaloblastic crisis. Hydroxyurea, which causes an increase in the synthesis of fetal Hb and a significant reduction in crises, is being used for some patients with sickle cell anemia. Researchers have found it helpful for some patients because it reduces the frequency of painful crises and episodes of acute chest syndrome and decreases the need for blood transfusions.

Newer drugs are being developed to manage sickle cell anemia. Some of these agents try to induce the body to produce more fetal Hb, which helps decrease the amount of sickling. Others work by increasing the binding of oxygen to sickle cells. Currently, bone marrow transplantation offers the only cure for sickle cell anemia. Gene therapy (replacing HbS with normal HbA) may be the ideal treatment, but it's difficult to perform.

Special considerations

Supportive measures during crises and precautions to avoid them are important. Here are some actions you can take during a painful crisis:

- Apply warm compresses to painful areas, and cover the child with a blanket. (Never use cold compresses because they aggravate the condition.)
- Administer an analgesic-antipyretic, such as aspirin or acetaminophen. (Additional pain relief may be required during an acute crisis.)
- Encourage fluids and bed rest, and place the patient in a sitting position. If dehydration or severe pain occurs, hospitalization may be necessary.

- When cultures indicate, give antibiotics as appropriate.

During remissions:

- Advise the patient to avoid tight clothing that restricts circulation.

- Warn against strenuous exercise, vasoconstricting medications, cold temperatures (including drinking large amounts of ice water and swimming), unpressurized aircraft, high altitude, and other conditions that provoke hypoxia.

PEDIATRIC TIP

Stress the importance of normal childhood immunizations, meticulous wound care, good oral hygiene, regular dental checkups, and a balanced diet as safeguards against infection.

- Emphasize the need for prompt treatment of infection.
- Inform the patient of the need to increase fluid intake to prevent dehydration due to impaired ability to concentrate urine properly. Tell parents to encourage the child to drink more fluids, especially in the summer, by offering fluids such as milkshakes and ice pops.

During pregnancy or surgery:

- Warn women with sickle cell anemia that they may have increased obstetrical risks. However, use of hormonal contraceptives may also be risky; refer them for birth control counseling to a qualified obstetric or gynecologic health care provider.
- If such women *do* become pregnant, they should maintain a balanced diet and may benefit from a folic acid supplement.
- During general anesthesia, a patient who has sickle cell anemia requires optimal ventilation to prevent hypoxic crisis. Make sure the surgeon and the anesthesiologist know that the patient has sickle cell anemia. Provide a preoperative transfusion of packed RBCs, as needed.

General tips:

- To encourage normal mental and social development, warn parents against being overprotective. Although the child must avoid strenuous exercise, he can enjoy most everyday activities.
- Refer parents of children with sickle cell anemia for genetic counseling to answer their questions about the risk to future offspring.

Recommend screening of other family members to determine if they're heterozygote carriers. These parents may also need psychological counseling to cope with guilt feelings. In addition, suggest they join an appropriate community support group.

- Adolescents or adult males with sickle cell anemia may develop sudden, painful episodes of priapism. Such episodes are common and, if prolonged, can have serious reproductive consequences. Advise the patient to contact the physician when these episodes occur.

X-LINKED INHERITANCE

Hemophilia

Hemophilia is a hereditary bleeding disorder resulting from a deficiency of specific clotting factors. After a person with hemophilia forms a platelet plug at a bleeding site, the clotting factor deficiency impairs the blood's capacity to form a stable fibrin clot. Bleeding occurs primarily into large joints, especially after trauma or surgery. Spontaneous intracranial bleeding can occur and may be fatal.

Advances in treatment have greatly improved the prognosis for patients with hemophilia, many of whom live normal life spans. Surgical procedures can be done safely at special treatment centers under the guidance of a hematologist.

Causes and incidence

Both hemophilia A and B are inherited as X-linked recessive traits. This means that female carriers have a 50% chance of transmitting the gene to each daughter, who would then be a carrier, and a 50% chance of transmitting the gene to each son, who would be born with hemophilia. Hemophilia A (classic hemophilia), which affects more than 80% of patients with hemophilia, results from a deficiency of factor VIII-C; hemophilia B (Christmas disease), which affects about 15% of patients with hemophilia, results from a deficiency of factor IX-C.

The factor VIII gene is located within the Xq28 region, and the factor IX gene is located within Xq27. Females with one defective factor VIII gene are carriers of hemophilia. A large number of disease-causing mutations have been identified in both genes. A specific inversion mutation in the noncoding region of the factor VIII gene is present in about 45% of families with severe hemophilia A. Hemophilia A is the most common X-linked genetic disease, occurring in about 1 in 10,000 live male births. It is five times more common than hemophilia B.

Signs and symptoms

Hemophilia produces abnormal bleeding, which may be mild, moderate, or severe, depending on the degree of factor deficiency.

Mild hemophilia commonly goes undiagnosed until adulthood because the patient doesn't bleed spontaneously or after minor trauma but has prolonged bleeding if challenged by major trauma or surgery. Postoperative bleeding continues as a slow ooze or ceases and starts again, up to 8 days after surgery.

Severe hemophilia causes spontaneous bleeding. In many cases, the first sign of severe hemophilia is excessive bleeding after circumcision. Later, spontaneous bleeding or severe bleeding after minor trauma may produce large subcutaneous and deep intramuscular hematomas. Bleeding into joints (hemarthrosis) and muscles causes pain, swelling, extreme tenderness and, possibly, permanent deformity.

Moderate hemophilia causes symptoms similar to severe hemophilia but produces only occasional spontaneous bleeding episodes.

Bleeding near peripheral nerves may cause peripheral neuropathy, pain, paresthesia, and muscle atrophy. If bleeding impairs blood flow through a major vessel, it can cause ischemia and gangrene. Pharyngeal, lingual, intracardial, intracerebral, and intracranial bleeding may all lead to shock and death.

Diagnosis

Development of a large cephalohematoma or intracranial hemorrhage after prolonged labor or delivery by forceps or vacuum extraction may be the first indication of a bleeding problem. After the neonatal period,

a history of prolonged bleeding after surgery (including dental extractions) or trauma or of episodes of spontaneous bleeding into muscles or joints usually indicates some defect in the hemostatic mechanism. Hemophilia A and B may be clinically indistinguishable, but specific coagulation factor assays can diagnose the type and severity of the disease. A positive family history, prenatal diagnosis, and carrier testing can also help diagnose hemophilia, but nearly one-third of all patients have no family history.

Characteristic findings in hemophilia A include:

- factor VIII-C assay, 0% to 30% of normal
- prolonged partial thromboplastin time (PTT)
- normal platelet count and function, bleeding time, and prothrombin time.

Characteristics of hemophilia B include:

- deficient factor IX-C
- baseline coagulation results similar to hemophilia A, with normal factor VIII.

In both types of hemophilia, the degree of factor deficiency determines severity:

- mild hemophilia—factor levels 5% to 40% of normal
- moderate hemophilia—factor levels 1% to 5% of normal
- severe hemophilia—factor levels less than 1% of normal.

Treatment

Hemophilia isn't curable, but treatment can prevent crippling deformities and prolong life expectancy. Correct treatment quickly stops bleeding by increasing plasma levels of deficient clotting factors to help prevent disabling deformities that result from repeated bleeding into muscles and joints. (See *Factor replacement products*.)

Desmopressin (DDAVP—1-deamino-8-D-arginine vasopressin) administered I.V. or intranasally is usually sufficient to manage bleeding episodes of

children and adolescents with mild hemophilia A. Persons with moderate to severe hemophilia A require commercially prepared factor VIII concentrates to treat bleeding episodes. Concentrates derived from human plasma are virally attenuated by one or more available methods significantly minimizing the risk for human immunodeficiency virus (HIV)-1, HIV-2, hepatitis B, and hepatitis C contamination. However, no currently available method has been successful in eradicating parvovirus B 19 from blood products. Factor VIII concentrate derived from recombinant technology (rFVIII) has been shown in multiple clinical trials to be as effective as virally attenuated plasmaderived concentrate. Risk for viral contamination is essentially nonexistent in preparations of rFVIII that avoid human serum albumin as a stabilizer.

In hemophilia B, administration of factor IX concentrate during bleeding episodes increases factor IX levels.

The U.S. National Hemophilia Foundation first recommended prophylaxis with factor concentrates in 1994 after investigators in Sweden demonstrated repeated success with this approach. The ultimate goal is to prevent irreversible destructive arthritis that results from repeated hemarthrosis and synovial hypertrophy. Prophylaxis of persons with hemophilia A or B may begin as early as age 1 or 2.

A person with hemophilia who undergoes surgery needs careful management by a hematologist with expertise in hemophilia care. The patient will require replacement of the deficient factor before and after surgery, possibly even for minor surgery such as a dental extraction. (DDAVP may be given before dental extractions and surgery to prevent bleeding.) In addition, epsilon-aminocaproic acid is commonly used for oral bleeding to inhibit the active fibrinolytic system present in the oral mucosa.

Development of factor VIH or factor XI inhibitors occurs in up to 3.5% of children with severe hemophilia A and up to 3% of those with hemophilia B. Studies indicate that certain gene mutations predispose to an increased risk for inhibitor development. Patients with hemophilia who can't achieve hemostasis after use of previously effective factor concentrate doses should be evaluated for factor inhibitors.

FACTOR REPLACEMENT PRODUCTS

Cryoprecipitate

- Contains factor VIII (70 to 100 units/bag); doesn't contain factor IX
- Can be stored frozen up to 12 months but must be used within 6 hours after it thaws
- Given through a blood filter; compatible with normal saline solution only
- No longer treatment of choice because of the risk of human immunodeficiency virus and hepatitis infection; can still contain viruses despite greatly improved screening and purification procedures for viral inactivation in blood products

Lyophilized factor VIII or IX

- Freeze-dried
- Can be stored up to 2 years at about 36° to 46° F (2° to 8° C), up to 6 months at room temperature not exceeding 88° F (31.1° C)
- Labeled with exact units of factor VIII or IX contained in vial
- 200 to 1,500 units of factor VIII or IX per vial; 20 to 40 ml after reconstitution with diluent
- No blood filter needed; usually given by slow I.V. push through a butterfly infusion set

Fresh frozen plasma

- Contains approximately 0.75 unit/ml of factor VII and approximately 1 unit/ml of factor IX; not practical for most people with hemophilia because a large volume is needed to raise factors to hemostatic levels
- Can be stored frozen up to 12 months but must be used within 2 hours after it thaws

- Given through a blood filter; compatible with normal saline solution only

MANAGING HEMOPHILIA

The following guidelines can help parents care for their child with hemophilia.

- Instruct parents to notify the physician immediately after even a minor injury, but especially after an injury to the head, neck, or abdomen. Such injuries may require special blood factor replacement. Also, tell them to check with the physician before allowing dental extractions or any other surgery.
- Educate the patient and his parents on the early signs and symptoms of hemarthrosis: stiffness, tingling, or ache in joint, followed by decreased range of motion. If signs and symptoms are recognized early, treatment can begin earlier, potentially decreasing the possibility of long-term disability.
- Stress the importance of regular, careful toothbrushing with a soft-bristled toothbrush to prevent the need for dental surgery.
- Teach parents to be alert for signs of severe internal bleeding, such as severe pain or swelling in a joint or muscle, stiffness, decreased joint movement, severe abdominal pain, blood in urine, black tarry stools, and severe headache.
- Advise parents that the child is at risk for hepatitis from blood components. Early signs—headache, fever, decreased appetite, nausea, vomiting, abdominal tenderness, and pain over the liver—may appear 3 weeks to 6 months after treatment with blood

components. Tell them to discuss with their physician the possibility of hepatitis vaccination.

- Discuss the increased risk of human immunodeficiency virus (HIV) infection if the child received a blood product before routine screening of blood products for HIV began. Tell parents to ask the physician about periodic testing for HIV.
- Urge parents to make sure their child wears a medical identification bracelet at all times.
- Teach parents never to give their child aspirin, which can aggravate the tendency to bleed. Advise them to give acetaminophen instead.
- Instruct parents to protect their child from injury, but to avoid unnecessary restrictions that impair his normal development. For example, they can sew padded patches into the knees and elbows of a toddler's clothing to protect these joints during falls. They shouldn't allow an older child to participate in contact sports such as football but can encourage him to swim or to play golf.
- Teach parents to elevate and apply cold compresses or ice bags to an injured area and to apply light pressure to a bleeding site. To prevent recurrence of bleeding, advise parents to restrict the child's activity for 48 hours after bleeding is under control.
- If parents have been trained to administer blood factor components at home to avoid frequent hospitalization, make sure they know proper venipuncture and infusion techniques and don't delay treatment during bleeding episodes.
- Instruct parents to keep blood factor concentrate and infusion equipment on hand at all times, even on vacation.

- Emphasize the importance of having the child keep routine medical appointments at the local hemophilia center.
- Daughters of individuals with hemophilia should undergo genetic screening to determine if they're hemophilia carriers. Affected males should undergo counseling as well. If they produce offspring with a noncarrier, all of their daughters will be carriers; if they produce offspring with a carrier, each child has a 25% chance of being affected.
- For more information, refer parents to the National Hemophilia Foundation.

Preventive measures include teaching the patient how to avoid trauma, manage minor bleeding, and recognize bleeding that requires immediate medical intervention. Genetic counseling helps carriers understand how this disease is transmitted. (See *Managing hemophilia*.)

Antifibrinolytic drugs such as aminocaproic acid (Amican) are used in addition to factor VIII replacement to treat oral mucosal hemorrhage, and for prophylaxis before dental procedures.

Special considerations

During bleeding episodes:

- Give clotting agents as ordered. The body uses up factor VIII in 48 to 72 hours, so repeat infusions, as indicated, until bleeding stops.
- Apply cold compresses or ice bags and raise the injured part.
- To prevent recurrence of bleeding, restrict activity for 48 hours after bleeding is under control.
- Control pain with an analgesic, such as acetaminophen, propoxyphene, codeine, or meperidine, as appropriate. Avoid I.M. injections because of possible hematoma formation at the injection site. Aspirin and aspirin-containing medications are contraindicated

because they decrease platelet adherence and may increase the bleeding. Caution should be used when trying other nonsteroidal anti-inflammatory drugs, for example, ibuprofen or ketoprofen.

If the patient has bled into a joint:

- Immediately elevate the joint.
- To restore joint mobility, begin range-of-motion exercises, if ordered, at least 48 hours after the bleeding is controlled. Tell the patient to avoid weight bearing until bleeding stops and swelling subsides.

After bleeding episodes and surgery:

- Watch closely for signs of further bleeding, such as increased pain and swelling, fever, or symptoms of shock.
- Closely monitor PTT.
- Teach parents special precautions to prevent bleeding episodes.
- Refer new patients to a hemophilia treatment center for evaluation. The center will devise a treatment plan for such patients' primary physicians and is a resource for other medical and school personnel, dentists, and others involved in their care.
- Persons who have been exposed to HIV through contaminated blood products need special support.
- Refer patients and carriers for genetic counseling.

Fragile X syndrome

Fragile X syndrome is the most common inherited cause of mental retardation. The condition is typically caused by a well-defined mutation at a specific locus of the fragile X mental retardation 1 (FMR1) gene on the X chromosome. About 85% of males and 50% of females who inherit the FMR1 mutation will demonstrate clinical features of the syndrome. Post-pubescent males with fragile X syndrome usually have distinct physical features, behavioral difficulties, and cognitive impairment. Females with fragile X syndrome tend to have more subtle symptoms.

Causes and incidence

Fragile X syndrome is an X-linked condition that doesn't follow a simple X-linked inheritance pattern. The normal sequence of the FMR1 gene was identified at Xq27.3 in 1991. The unique mutation that results in fragile X syndrome consists of an expanding region of a specific triplet of nitrogenous bases: cytosine, guanine, guanine (CGG) within the gene's deoxyribonucleic acid (DNA) sequence. Normally, FMR1 contains 6 to 50 sequential copies of the CGG triplet. When the number of CGG triplets expands to the range of 50 to 200 repeats, the region of DNA becomes unstable and is referred to as a premutation. A full mutation consists of over 200 CGG triplet repeats.

The full mutation typically causes abnormal methylation (methyl groups attach to components of the gene) of FMR1. Methylation inhibits gene transcription and thus protein production. The reduced or absent protein product (FNIRP) is responsible for the clinical features of fragile X syndrome. About 15% to 20% of males with a full mutation don't have fragile X.

This may be explained by either the ability of unmethylated portions (of their mutated FMR1) to be transcribed for eventual protein production, or that these males are mosaic for the FMR1 premutation. In asymptomatic mosaic males it's believed that the cells with a premutation can produce enough protein to compensate for the cells that contain a full mutation and consequently produce no protein.

About 50% of females who inherit a full mutation from their mother have clinical features of fragile X syndrome. This is primarily due to the normal process of random X inactivation. At the time of meiosis, both X chromosomes must be activated. However, shortly after the zygote stage, an X chromosome is inactivated in every cell. Clinically measurable effects of the full FMR1 mutation will be more likely in relevant tissues or organs that have a disproportionate number of cells in which the normal X chromosome has been inactivated.

Males with a premutation don't have fragile X. They're considered unaffected or normal-transmitting males. Because males have only one X chromosome, all daughters of a transmitting male will inherit their father's X chromosome with the premutation. None of the male's sons

will inherit the premutation because they inherit their father's Y chromosome rather than the X chromosome.

Females with the premutation don't have fragile X syndrome. However, the premutation can expand into the full mutation range (more than 200 CGG triplets) when it's transmitted from a premutation carrier mother to her offspring. This expansion can occur during or after maternal meiosis. Therefore, the following possibilities exist for every pregnancy of a mother with a premutation.

- A female conceptus receives the mother's X chromosome with the nonmutated FMR1 gene. She won't be affected with fragile X. None of her future offspring will be at risk for inheriting the syndrome from her.
- A male conceptus receives the mother's X with the nonmutated FMR1 gene. He won't be affected with fragile X. None of his future offspring will be at risk for inheriting the syndrome from him.
- A female conceptus receives the mother's X chromosome with the FMR1 premutation. She'll be a carrier like her mother but won't have fragile X syndrome. Her future offspring will be at risk for inheriting a full mutation from her.
- A male conceptus receives the mother's X with the FMR1 premutation. He won't be affected with fragile X. All of his future daughters but none of his future sons will inherit the premutation from him.
- A female conceptus receives the mother's X chromosome with the FMR1 gene whose premutation expanded into a full mutation during or after maternal meiosis. Depending on the outcome of random X inactivation, the daughter may have clinically definable fragile X syndrome. Her future offspring will be at risk for inheriting the full mutation and, thus, the syndrome from her.
- A male conceptus receives the mother's X chromosome with the FMR1 gene whose premutation has expanded into a full mutation during or after maternal meiosis. In 85% of cases, the son in this situation will have fragile X syndrome. Evidence indicates, however, that the FMR1 gene in the son's gametes will have the CGG triplet repeat within the premutation range, not the full mutation range like his somatic cells.

Therefore, his future daughters wouldn't be expected to have fragile X syndrome.

It should be noted that most commonly the FMR1 status of a mother is subsequently determined after her son is clinically and later molecularly diagnosed with fragile X syndrome. Health care professionals need to be sensitive to the fact that the mother could either find out she's a carrier of a premutation or she has a full mutation. Consequently, not only will she learn her son's diagnosis but she, herself, could be diagnosed with fragile X if she has a full mutation and clinical symptoms.

Fragile X syndrome is estimated to occur in about 1 in 1,500 males and 1 in 2,500 females. It has been reported in almost all races and ethnic populations.

Signs and symptoms

Small children may have relatively few identifiable physical characteristics; behavioral or learning difficulties may be the initial presenting features.

Many adult male patients display a prominent jaw and forehead and a head circumference exceeding the 90th percentile. A long, narrow face with long or large ears that may be posteriorly rotated can be a helpful finding at all ages. Connective tissue abnormalities—including hyperextension of the fingers, a floppy mitral valve (in 80% of adults), and mild to severe pectus excavatum—have also been reported. Unusually large testes, found in most affected males after puberty, are an important identifying factor of the disorder.

The average IQ of a person with fragile X syndrome is comparable to that of a person with Down syndrome; however, the behavioral characteristics are quite different. Hyperactivity, speech difficulties, language delay, and autistic-like behaviors may be attributed to other disorders, such as attention deficit hyperactivity disorder, and thus delay the diagnosis.

About 50% of females with the FMR1 full mutation will have clinical symptoms, although the degree of severity and number of symptoms

vary widely among females with fragile X syndrome. Those who are symptomatic typically have a much milder clinical presentation than males due to having an unaffected X chromosome in addition to the one with an FMR1 full mutation. Some degree of cognitive impairment is usually present in symptomatic females. Learning disabilities—math difficulties, language deficits, and attentional problems—are most common. Some females can have IQ scores in the mental retardation range. Although affected females can have autistic-like features, excessive shyness or social anxiety are the more common behavioral symptoms. Prominent ears and the connective tissue manifestations may be as significant as in males. Although males with the FMR1 permutation are asymptomatic, some female carriers of an FMR1 premutation can have associated symptoms. These symptoms include significantly earlier menopause and a low normal performance IQ.

Diagnosis

CONFIRMING DIAGNOSIS

Diagnosis of fragile X syndrome requires identification of clinical symptoms and a positive genetic test. DNA analysis of blood or buccal samples is used to detect the size of the CGG repeat and the methylation status of FMR1.

A specific genetic test (polymerase chain reaction) can also be performed to diagnose this disease. This test looks for an expanded mutation (called a triplet repeat*) in the FRAXA gene.*

Before identification of the FMR1 mutation, a special cytogenetic (chromosome) blood test was used to microscopically detect the fragile site on the long arm of the affected X chromosome. It's now common knowledge that a full FMR1 mutation doesn't always result in a cytogenetically detectable fragile site. Therefore, chromosome analysis alone can provide falsenegative results. Chromosome analysis still has utility together with FMR1 mutation analysis when performing a genetic evaluation on a male with mental retardation of unknown etiology.

In addition to diagnosing fragile X syndrome, genetic testing can determine whether the mother of a diagnosed individual is a carrier of the FMR1 premutation or has a full mutation. This information can be used for preconceptional genetic counseling by a trained professional and prenatal testing if the woman so chooses. FMR1 mutation analysis can also be subsequently performed on at-risk family members. It should be noted, however, that communication of genetic test results to at-risk family members constitutes a breech of patient confidentiality and privacy unless prior written permission to communicate results has been obtained from the previously tested patients.

Treatment

Fragile X syndrome has no known cure. Treatment is aimed at controlling individual symptoms. Surgery may be needed to repair a defective mitral valve.

Special considerations

- Individuals who have been identified as carriers may experience guilt and grief; provide support to help the carrier and family members accept the diagnosis.
- Parents of an affected child may need help to deal with their grief over unmet expectations for the child; refer them for appropriate counseling if necessary.
- Refer the family (and possibly the extended family) to a professional trained in genetics to discuss the diagnosis, testing, and the risk of recurrence in future offspring.
- Recurrent otitis media is common. To maximize the affected child's potential for language development, early diagnosis and aggressive treatment of otitis media are essential.
- Throughout childhood, assess and refer the patient and his family for history of seizure activity.

PEDIATRIC TIP

Encourage parents to enroll infants and toddlers in early intervention programs. Advocate for special education services and individualized speech, language, and occupational therapy services for this child during school years.

- Assess and refer for hyperactivity, attention deficit, or both.
- The patient and his family can contact the National Fragile X Foundation for additional information and support.

CHROMOSOMAL ABNORMALITIES

Down syndrome

The first disorder attributed to a chromosome aberration, Down syndrome (trisomy 21) characteristically produces mental retardation, dysmorphic facial features, and other distinctive physical abnormalities. It's commonly associated with congenital heart defects (in about 60% of patients) and other abnormalities.

Life expectancy for patients with Down syndrome has increased significantly because of improved treatment for related complications (heart defects, respiratory and other infections, acute leukemia). Nevertheless, up to 44% of such patients who have congenital heart defects die before age 1 year.

Causes and incidence

Down syndrome usually results from trisomy 21, a spontaneous chromosomal abnormality in which chromosome 21 has three copies instead of the normal two because of faulty meiosis (nondisjunction) of the ovum or, sometimes, the sperm. This results in a karyotype of 47 chromosomes instead of the normal 46. In about 4% of patients, Down syndrome results from an unbalanced translocation in which the long arm of chromosome 21 breaks and attaches to another chromosome. Most commonly, this is a robertsonian translocation and results in an increased risk of having multiple children with Down syndrome. The disorder may also be due to chromosomal mosaicism with two cell lines—

one with a normal number of chromosomes (46) and one with 47 (an extra chromosome 21).

Down syndrome occurs in 1 in 660 live births, but the incidence increases with advanced parental age, especially when the mother is age 34 or older at delivery or the father is older than age 42. At age 20, a woman has about one chance in 2,000 of having a child with Down syndrome; by age 49, she has one chance in 12. However, if a woman has had one child with Down syndrome, the risk of recurrence is 1% to 2% unless the trisomy results from translocation.

Complications

- Congenital heart defects
- Premature dementia
- Increased incidence of leukemia, acute and chronic infections, diabetes mellitus, and thyroid disorders

Signs and symptoms

The physical signs of Down syndrome (especially hypotonia) as well as some dysmorphic facial features and heart defects may be apparent at birth. The degree of mental retardation may not become apparent until the infant grows older. People

with Down syndrome typically have craniofacial anomalies, such as slanting, almond-shaped eyes with epicanthic folds; a flat face; a protruding tongue; a small mouth and chin; a single transverse palmar crease (simian crease); small white spots (Brushfield's spots) on the iris; strabismus; a small skull; a flat bridge across the nose; slow dental development, with abnormal or absent teeth; small ears; a short neck; and cataracts.

Other physical effects may include dry, sensitive skin with decreased elasticity; umbilical hernia; short stature; short extremities, with broad, flat, and squarish hands and feet; clinodactyly (small little finger that curves inward); a wide space between the first and second toe; and

abnormal fingerprints and footprints. Hypotonic limb muscles impair reflex development, posture, coordination, and balance.

Congenital heart disease (septal defects or pulmonary or aortic stenosis), duodenal atresia, megacolon, and pelvic bone abnormalities are common. The incidence of leukemia and thyroid disorders (particularly hypothyroidism) may be increased. Frequent upper respiratory infections can be a serious problem. Genitalia may be poorly developed and puberty delayed. Females may menstruate and be fertile. Males are infertile with low serum testosterone levels; many have undescended testicles.

Patients with Down syndrome may have an IQ between 30 and 70; however, social performance is usually beyond that expected for mental age and fewer than 10% will have severe mental retardation. The level of intellectual function depends greatly on the environment and the amount of early stimulation received in addition to the IQ.

Diagnosis

Physical findings at birth, especially hypotonia, may suggest this diagnosis, but no physical feature is diagnostic in itself.

CONFIRMING DIAGNOSIS

A karyotype showing the specific chromosomal abnormality provides a definitive diagnosis. Amniocentesis allows prenatal diagnosis and is recommended for pregnant women older than age 34 even if the family history is negative. Amniocentesis is also recommended for a pregnant woman of any age when either she or the father carries a translocated chromosome.

Treatment

Down syndrome has no known cure. Surgery to correct heart defects and other related congenital abnormalities and antibiotic therapy for recurrent infections have improved life expectancy considerably. Plastic surgery is occasionally done to correct the characteristic facial traits,

especially the protruding tongue. Benefits beyond improved appearance may include improved speech, reduced susceptibility to dental caries, and fewer orthodontic problems later. Most patients with Down syndrome are now cared for at home and attend special education classes. As adults, some may work in a sheltered workshop or live in a group home facility.

Special considerations

Support for the parents of a child with Down syndrome is vital. By following the guidelines listed below, you can help them meet their child's physical and emotional needs.

- Establish a trusting relationship with the parents, and encourage communication during the difficult period soon after diagnosis. Recognize signs of grieving.
- Teach parents the importance of a balanced diet for the child. Stress the need for patience while feeding the child, who may have difficulty sucking and may be less demanding and seem less eager to eat than normal babies.
- Encourage the parents to hold and nurture their child.
- Emphasize the importance of adequate exercise and maximum environmental stimulation; refer the parents for early intervention as soon as the diagnosis of Down syndrome is made.

PEDIATRIC TIP

Balanced nutrition and exercise gain increased importance as the child ages. Obesity commonly becomes problematic.

PEDIATRIC TIP

All children with Down syndrome need to be checked for atlantoaxial instability before they engage in exercise or sports.

- Refer the parents and older siblings for genetic and psychological counseling, as

appropriate, to help them evaluate future reproductive risks. Discuss options for prenatal testing.

- Encourage the parents to remember the emotional needs of other children in the family.
- Refer the parents to national or local Down syndrome organizations and support groups such as the National Down Syndrome Congress.

Trisomy 18 syndrome

Trisomy 18 syndrome (also known as *Edwards' syndrome*) is the second most common multiple malformation syndrome. Most affected infants have *full trisomy 18*, involving an extra (third) copy of chromosome 18 in each cell, but *partial trisomy 18* (with varying phenotypes) and *translocation types* have also been reported. Most infants with this disorder present with intrauterine growth retardation, congenital heart defects, microcephaly, and other malformations.

Full trisomy 18 syndrome is generally fatal or has an extremely poor prognosis; 30% to 50% of infants with full trisomy 18 syndrome die within the first 2 months after birth; 90% die within the first year. Most patients who survive exhibit profound mental retardation.

Causes and incidence

Most cases of trisomy 18 syndrome are caused by spontaneous meiotic nondisjunction. The risk of chromosomal abnormalities typically increases with maternal age; however, the mean maternal age for this disorder is 32½. Incidence is 1 in 3,000 neonates, with females three times more likely to be affected than males.

Signs and symptoms

Growth retardation begins in utero and remains significant after birth. Initial hypotonia may soon give way to hypertonia. Common findings include microcephaly and dolichocephaly, micrognathia, genital and perineal abnormalities (including imperforate anus), diaphragmatic hernia, and various renal defects. Congenital heart defects, such as

ventricular septal defect, tetralogy of Fallot, transposition of the great vessels, and coarctation of the aorta, occur in 80% to 90% of patients and may be the cause of death in many infants.

Other findings may include a short and narrow nose with upturned nares; unilateral or bilateral cleft lip and palate; low-set, slightly pointed ears; a short neck; a conspicuous clenched hand with overlapping fingers (usually seen on ultrasound as well); neural tube defects; omphalocele; cystic hygroma; choroid plexus cysts (also seen in some healthy infants); and oligohydramnios.

Diagnosis

Multiple marker maternal serum screening tests involving different combinations of alpha-fetoprotein, human chorionic gonadotropin, and unconjugated estriol may be abnormal in many pregnant women with an affected fetus; however; these tests aren't diagnostic. Fetal ultrasound may reveal varying degrees of abnormalities, but many fetuses have few detectable defects. Diagnosis should be based on karyotype, done either prenatally or using peripheral blood of skin fibroblasts after birth.

Treatment

Treatment is aimed at providing comfort for the infant and emotional support for the parents. Because the infant's sucking reflex is poor, nutrition is maintained using gavage feedings. Teach parents about home care and feeding techniques.

Special considerations

- Allow adequate time for the parents to bond with and hold their child.
- Refer the parents to early intervention if the infant is medically stable.
- Refer the parents of an affected child for genetic counseling to explore the cause of the disorder and discuss the risk of recurrence in a future pregnancy.
- Refer the parents to a social worker or grief counselor for additional support if needed.

- Refer the parents to the Support Organization for Trisomy 18, 13 and Related Disorders (S.O.F.T.) national support group to allow them interaction with other

  parents of infants with trisomy 18 and trisomy 13.

Trisomy 13 syndrome

Trisomy 13 syndrome (also known as *Patau's syndrome*) is the third most common multiple malformation syndrome. Most affected infants have *full trisomy 13* at birth; a few have the rare *mosaic partial trisomy 13* syndrome (with varying phenotypes) or *translocation types*. Infants with this disorder typically have brain and facial abnormalities as well as major cardiac, GI, and limb malformations. Full trisomy 13 syndrome is fatal. Many trisomic zygotes are spontaneously aborted; 50% to 70% of infants with full trisomy 13 syndrome die within 1 month after birth and 75% by the first year. Only isolated cases of survival beyond 5 years have been reported in full trisomy 13 patients. All survivors have profound mental retardation.

Causes and incidence

About 75% of all cases of trisomy 13 syndrome are caused by chromosomal nondisjunction. About 20% of cases are due to chromosomal translocation involving a rearrangement of chromosomes 13 and 14. About 5% of cases are estimated to be mosaics; the clinical effects in these cases may be less severe.

Incidence is estimated to be 1 in every 5,000 neonates. The risk of chromosomal abnormalities typically increases with advanced maternal age; however, the mean maternal age for this abnormality is about 31 years.

Signs and symptoms

Infants with trisomy 13 syndrome may present with microcephaly, varying degrees of holoprosencephaly, sloping forehead with wide sutures and fontanel, and a scalp defect at the vertex. Micro-ophthalmia, cataracts, and other eye abnormalities are seen in most

patients with full trisomy 13. Bilateral cleft lip with associated cleft palate is seen in at least 45% of patients. Most are born with a congenital heart defect, especially hypoplastic left heart, ventricular septal defect, patent ductus arteriosus, or dextroposition, which may significantly contribute significantly to the cause of death.

Other possible findings include a flat and broad nose, low-set ears and inner ear abnormalities, polydactyly of the hands and feet, club feet, omphaloceles, neural tube defects, cystic hygroma, genital abnormalities, cystic kidneys, hydronephrosis, and musculoskeletal abnormalities. Affected infants may also experience failure to thrive, seizures, apnea, and feeding difficulties.

Diagnosis

Multiple marker maternal serum screening tests, involving different combinations of alpha-fetoprotein, human chorionic gonadotropin (HCG) or free beta-HCG in some labs, and unconjugated estriol, may be abnormal in some pregnant women with an affected fetus; however, these tests aren't diagnostic.

Ultrasound commonly reveals multiple abnormalities in the fetus; however, because many multiple malformation syndromes have similar features, the diagnosis should be based on karyotype, done either prenatally or on peripheral blood lymphocytes or skin fibroblasts in a neonate or an aborted fetus. The neonate may have a single umbilical artery at birth. Magnetic resonance imaging or a computed tomography scan of the head may reveal a structural abnormality of the brain (holoprosencephaly) where the two cerebral hemispheres are fused.

Treatment

Supportive care is the only treatment for the infant with trisomy 13 syndrome.

Special considerations

- Maintain the infant's fluid balance, and position him for comfort.
- Refer the parents to early intervention if the infant is medically stable.

- Provide the family with emotional support.
- Allow adequate time for the parents to bond with and hold their child.
- Refer the parents of an affected infant for genetic counseling to explore the cause

  of the disorder and to discuss the risk of recurrence in future pregnancies.
- Refer the parents to a social worker or grief counselor for additional support if needed.
- Refer the parents to the Support Organization for Trisomy 18, 13, and Related Disorders (S.O.F.T.) national support group to allow them interaction with other parents of infants with trisomy 18 and trisomy 13.

Turner's syndrome

In Turner's syndrome, one of the X chromosomes (or part of the second X chromosome) may be lost from the ovum or sperm through nondisjunction or chromosome lag. Mixed aneuploidy may result from miotic nondisjunction.

It's the most common disorder of gonadal dysgenesis in females. It occurs in about 1 per 3,000 births; 95% of fetuses with this syndrome are spontaneously aborted. The syndrome produces characteristic signs, which are irreversible.

Causes and incidence

Turner's syndrome occurs when an X chromosome (or part of the second X chromosome) is missing from either the ovum or sperm through nondisjunction or chromosome lag. Mixed aneuploidy may result from mitotic nondisjunction.

Complications

- Diabetes mellitus

- Thyroid disease
- Osteoarthritis
- Osteoporosis
- Cardiomyopathy
- Renal dysfunction
- Precocious aging
- Sterility

Signs and symptoms

Turner's syndrome produces obvious characteristic signs. At birth, 50% of infants with this syndrome measure below the third percentile in length. Commonly, they have swollen hands and feet, a wide chest, and a low hairline that becomes more obvious as they grow. They may have severe webbing of the neck, and some have coarse, enlarged, prominent ears. Gonadal dysgenesis is seen at birth. Other signs and symptoms include pigmented nevi, lymphedema, hypoplasia, or malformed nails.

As the child grows, short stature is common. The patient may exhibit average to slightly below-average intelligence. Developmental problems include right-left disorientation for extrapersonal space and defective figure drawing. The patient is typically immature and socially naive.

Auscultation of the infant's chest indicates cardiovascular malformations, such as coarctation of the aorta and ventricular septal defects.

Diagnosis

Turner's syndrome can be diagnosed by chromosome analysis. Differential diagnosis should rule out mixed gonadal dysgenesis, Noonan's syndrome, and other similar disorders.

Treatment

Cardiovascular malformations must be corrected surgically. Hormonal replacement should begin in childhood and include androgen, human

growth hormone and, possibly, small doses of estrogen. Later, progesterone and estrogen can induce sexual maturation.

Special considerations

- Encourage the patient and his family to verbalize feelings about the patient's condition and to discuss fear of rejection by others. Offer emotional support and a realistic assessment of the patient's condition.
- Help the patient and his family to develop coping strategies. Refer them for sexual or genetic counseling as necessary.
- Provide appropriate preoperative and postoperative care for the infant with cardiovascular malformations.
- Explain the surgical procedure and its expected outcomes to the parents of the infant with cardiovascular malformations. Help them participate in the child's care and make informed decisions about treatment options. Explain all procedures and provide ongoing information about the infant's condition.

- Teach the parents about normal growth and development and how their child may differ. Clarify any misconceptions and explain the treatment. Suggest strategies to help the child achieve agerelated skills.
- Teach family members and, if appropriate, the patient about long-term hormone replacement therapy. Stress the importance of strictly complying with therapy.

Klinefelter's syndrome

Klinefelter's syndrome is a relatively common genetic abnormality that results from an extra X chromosome. It affects only males and usually becomes apparent at puberty, when the secondary sex characteristics develop; the testicles fail to mature, and degenerative testicular changes begin that eventually result in irreversible infertility. It commonly causes gynecomastia and is also associated with a tendency toward learning disabilities.

Klinefelter's syndrome is unlike Turner's syndrome, which results from the loss of an X chromosome.

Causes and incidence

Klinefelter's syndrome, probably the most common cause of hypogonadism, appears in about 1 in every 500 males. This disorder usually results from one extra X chromosome, giving such patients a 47,XXY complement instead of the normal 46,XY. (See *Fertilization in Klinefelter's syndrome*.) In the rare mosaic form of this syndrome, some cells contain the extra X chromosomes, whereas others contain the normal XY complement.

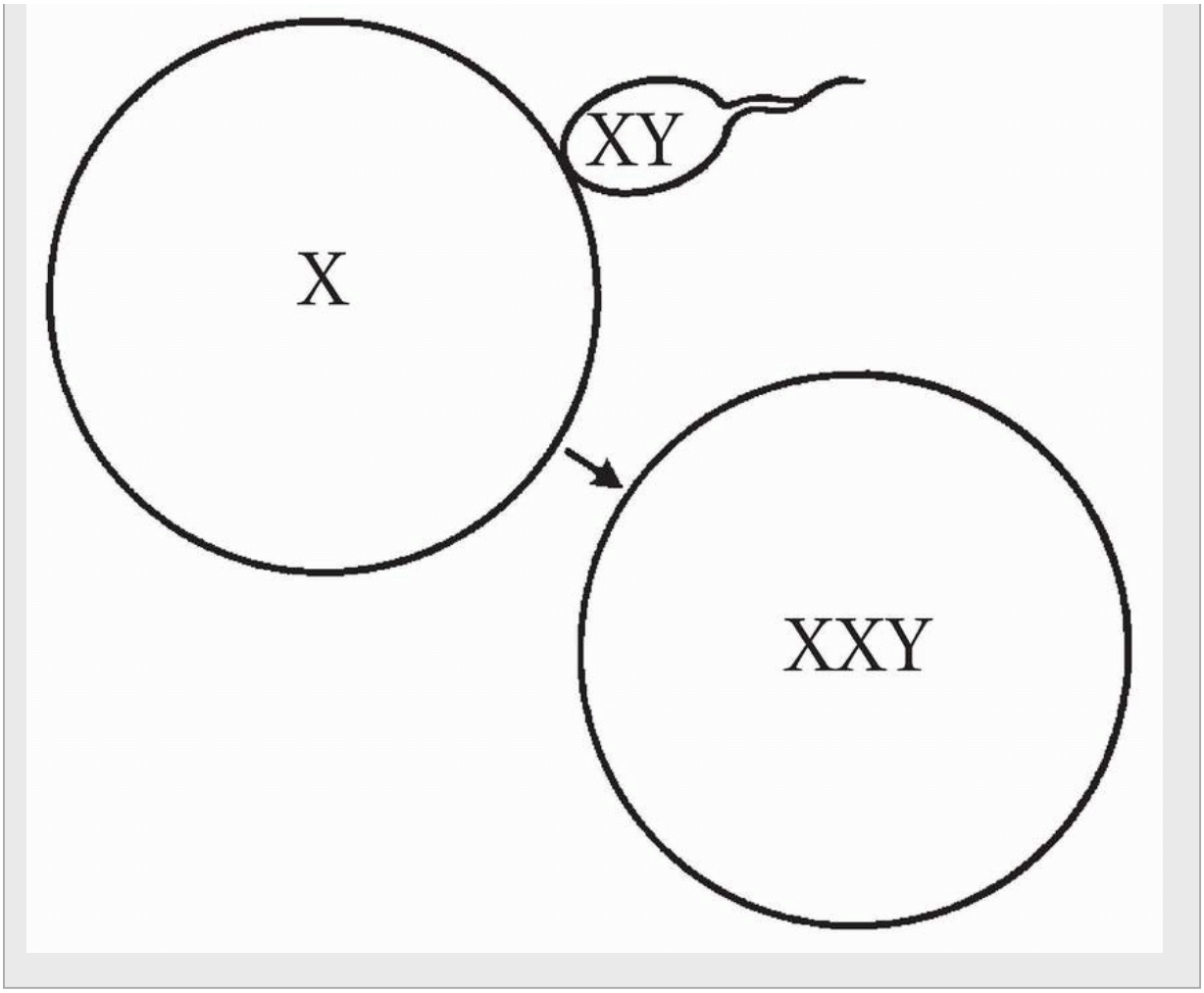
The extra chromosome responsible for Klinefelter's syndrome probably results from either meiotic nondisjunction during parental gametogenesis or from meiotic nondisjunction in the zygote. The incidence of meiotic nondisjunction increases with maternal age.

Signs and symptoms

Klinefelter's syndrome may not be apparent until puberty or later in mild cases. Because many of these patients aren't mentally retarded, behavioral problems in adolescence or infertility may be the only presenting features initially.

FERTILIZATION IN KLINEFELTER'S SYNDROME

Fertilization by a sperm with X and Y chromosomes produces an XXY zygote.



The syndrome's characteristic features include a small penis and prostate gland, small testicles, sparse facial and abdominal hair, feminine distribution of pubic hair (triangular shape), sexual dysfunction (impotence, lack of libido) and, in fewer than 50% of patients, gynecomastia. Aspermatogenesis and infertility result from progressive sclerosis and hyalinization of the seminiferous tubules in the testicles and from testicular fibrosis during and after puberty. In the mosaic form of Klinefelter's syndrome, such pathologic changes and resulting infertility may be delayed.

Klinefelter's syndrome may also be associated with osteoporosis, abnormal body build (long legs with short, obese trunk), tall stature, learning disabilities characterized by poor verbal skills and, in some individuals, behavioral problems beginning in adolescence. It's also associated with an increased incidence of pulmonary disease and

varicose veins and a significantly increased rate of breast cancer because of the extra X chromosome.

Diagnosis

CONFIRMING DIAGNOSIS

Typical clinical features suggest Klinefelter's syndrome, but only a karyotype (chromosome analysis) determined by culturing

lymphocytes from the patient's peripheral blood can unequivocally confirm the disorder.

Characteristically, Klinefelter's syndrome decreases urinary 17-ketosteroid levels, increases the excretion of follicle-stimulating hormone, and decreases the levels of plasma testosterone after puberty.

Treatment

Depending on the severity of symptoms, treatment may include mastectomy in patients with persistent gynecomastia and supplemental testosterone to induce secondary sexual characteristics of puberty.

Special considerations

- Psychological counseling may be indicated for body image problems or emotional maladjustment due to sexual dysfunction.
- Genetic counseling is essential for patients with the mosaic form of the syndrome who are fertile; they may transmit this chromosomal abnormality as well as others.
- Encourage patients to discuss feelings of confusion and rejection that may arise, and try to reinforce their male identity.
- Improve compliance with hormone replacement therapy by making sure patients understand the potential benefits and adverse effects of testosterone administration.

Velocardiofacial syndrome

Velocardiofacial syndrome (VCFS) is considered a chromosomal microdeletion syndrome. Most persons with VCFS have a de novo submicroscopic deletion. However, the deletion is dominantly inherited from an affected parent in up to one-third of reported cases. The phenotype demonstrates interfamilial variability consisting of over 150 possible clinical features.

Causes and incidence

VCFS occurs in at least 1 in 5,000 live births. The syndrome is caused by a submicroscopic deletion of chromosome 22ql 1.2. In most persons with VCFS, the chromosome deletion is too small to be detected by routine chromosome analysis. Although small, the deleted region, containing 1.5 to 3 megabases, is thought to contain several genes. Neonates or infants clinically diagnosed with DiGeorge syndrome (a similar disorder) commonly test positive for a 22ql 1.2 deletion. Therefore, in most cases, persons with DiGeorge syndrome represent the severe end of the VCFS clinical spectrum.

Signs and symptoms

Clinical features of VCFS vary greatly among affected persons. Neonates with complex heart malformations, dysmorphic features, hypocalcemia, missing thymus, and renal anomalies represent the severe end of the VCFS clinical presentation. On the other hand, the clinical features can be so mild that an affected parent isn't identified until an offspring is diagnosed and genetic testing is subsequently done on the parents. Symptoms have been reported in the cardiac, craniofacial, neuropsychological, renal, ocular, neurologic, skeletal, endocrine, immune, and hematologic systems. The most common symptoms can be classified as cardiac, craniofacial, and neuropsychological.

Clinical studies indicate that 70% to 85% of persons with VCFS have cardiac anomalies, of which conotruncal defects (for example, tetralogy of Fallot, interrupted aortic arch, truncus arteriosis) are the most common. This incidence may decrease over time as persons with only

mild symptoms, such as learning difficulties in school or subtle dysmorphic features, are tested and found to be deletion positive.

Craniofacial features include palatal abnormalities, dysmorphic facial features, and dysphagia usually due to velopharyngeal incompetence with or without pharyngoesophageal dysmotility. Therefore, feeding problems during infancy are common. The palate may be hypotonic and hypoplastic or have a midline cleft (ranging from bifid uvula to complete clefts of the palate). Related to palate problems are speech delays and abnormalities—particularly hypernasal speech and dyspraxia. Typical dysmorphic features include malformed

ears, narrow palpebral fissures, hooded upper eyelids, ptosis, a broad square nasal root, a bulbous nasal tip (typically with a midline vertical crease), and micrognathia.

Neuropsychological symptoms are present to some degree in most persons with VCFS. Hypotonia during the neonatal stage through early childhood period has been reported in more than 75% of cases. Even as hypotonia resolves with maturation, coordination and balance remain problematic. Cognitive symptoms, which can range from learning difficulties to varying levels of mental retardation, have been reported in over 80% of persons with VCFS. Children with VCFS typically have difficulties in visual-spatial activities, planning, attention, and concentration. Their strengths tend to be in rote verbal memory skills. Reading skills usually exceed math skills; however, reading comprehension tends to be problematic. The behavior of children with VCFS can be either shy and withdrawn or disinhibited and impulsive. Thought problems can be recognized during childhood and adolescence. Adults with VCFS are at risk for psychiatric disorders, particularly schizophrenia.

Diagnosis

Fluorescence in situ hybridization (FISH) using 22q 11.2 specific and chromosome 22 control probes is the preferred diagnostic test for VCFS and DiGeorge syndrome. Chromosome analysis with high-resolution banding detects only about one-third of affected persons. However, high-resolution chromosome analysis may be ordered in conjunction with

FISH analysis for patients whose clinical presentation suggests a chromosome abnormality and 22ql 1.2 deletion is only one of several possible diagnoses in the differential.

Prenatal diagnosis is possible by performing a 22ql 1.2 FISH analysis on chorionic villi or cultured amniocytes. Prenatal diagnosis may be considered when a biologic parent is known to have a 22ql 1.2 deletion or when a level 2 prenatal ultrasound reveals anomalies that can be present in persons with VCFS. A 22ql 1.2 FISH analysis is recommended in neonates with cardiac anomalies and any one or more of the other clinical features of VCFS.

Treatment

Treatment is aimed at preventing, ameliorating, or managing symptoms.

Special considerations

- Infants with palatal abnormalities and suck and swallow coordination difficulties will likely require feeding interventions, such as the use of cleft palate nursers and, in some cases, nasogastric or gastric tube feedings.
- Infants with heart malformations may require increased caloric intake.
- Management of heart malformations ranges from careful monitoring to multiple surgical interventions.
- Repair of cleft or abnormally functioning palate may improve hypernasal speech.
- Referral of the patient to speech pathology for evaluation of language delays or speech problems can be helpful.
- Infants may require occupational and physical therapy to minimize the developmental effects of hypotonia.

PEDIATRIC TIP

Encourage the parents to have the child participate in early intervention programs and educational services to optimize learning abilities.

- Designate a case manager to optimize care given by professionals from multiple disciplines and specialty areas.
- Refer the parents of an infant diagnosed with VCFS for genetic testing and counseling services.
- When providing patient and family teaching, assess for parental cognitive impairments and adjust teaching interventions accordingly.
- Anticipate, assess, and provide support for shock, denial, anger, and guilt reactions by parents discovered to have VCFS after their child's diagnosis.
- Help parents to identify and use effective coping strategies, and make referrals to mental health professionals as needed.
- Refer parents to appropriate support groups.
- Provide anticipatory guidance related to the physical, emotional, and neuropsychological effects of VCFS.

MULTIFACTORIAL ABNORMALITIES

Neural tube defects

Neural tube defects (NTDs) are serious birth defects that involve the spine or brain; they result from failure of the neural tube to close at about 28 days after conception. The most common forms of NTDs are spina bifida (50% of cases), anencephaly (40%), and encephalocele (10%).

Spina bifida occulta is the most common and least severe spinal cord defect. It's characterized by incomplete closure of one or more vertebrae without protrusion of the spinal cord or meninges.

However, in more severe forms of spina bifida, incomplete closure of one or more vertebrae causes protrusion of the spinal contents in an external sac or cystic lesion (spina bifida cystica). *Spina bifida cystica* has two classifications: *myelomeningocele (meningomyelocele)* and *meningocele*. In myelomeningocele, the external sac contains meninges, cerebrospinal fluid (CSF), and a portion of the spinal cord or nerve roots distal to the conus medullaris. When the spinal nerve roots end at the

sac, motor and sensory functions below the sac are terminated. In meningocele, less severe than myelomeningocele, the sac contains only meninges and CSF. Meningocele may produce no neurologic symptoms. (See *Types of neural tube defects*.)

In *encephalocele*, a saclike portion of the meninges and brain protrudes through a defective opening in the skull. Usually, it's in the occipital area, but it may occur in the parietal, nasopharyngeal, or frontal area.

In *anencephaly*, the most severe form of NTD, the closure defect occurs at the cranial end of the neuroaxis and, as a result, part or the entire top of the skull is missing, severely damaging the brain. Portions of the brain stem and spinal cord may be missing. No diagnostic or therapeutic efforts are helpful; this condition is invariably fatal.

Causes and incidence

NTDs may be isolated birth defects, may result from exposure to a teratogen, or may be part of a multiple malformation syndrome (for example, chromosomal abnormalities such as trisomy 18 or 13 syndrome). Isolated NTDs (those not due to a specific teratogen or associated with other malformations) are believed to be caused by a combination of genetic and environmental factors. Although most of the specific environmental triggers are unknown, recent research has identified a lack of folic acid in the mother's diet as one of the risk factors.

The incidence of NTDs varies greatly among countries and by region in the United States. For example, the incidence is significantly higher in the British Isles and low in southern China and Japan. In the United States, North and South Carolina have at least twice the incidence of NTDs as most other parts of the country. These birth defects are also less common in blacks than in whites.

Complications

- Infection
- Paralysis
- Hydrocephalus

Signs and symptoms

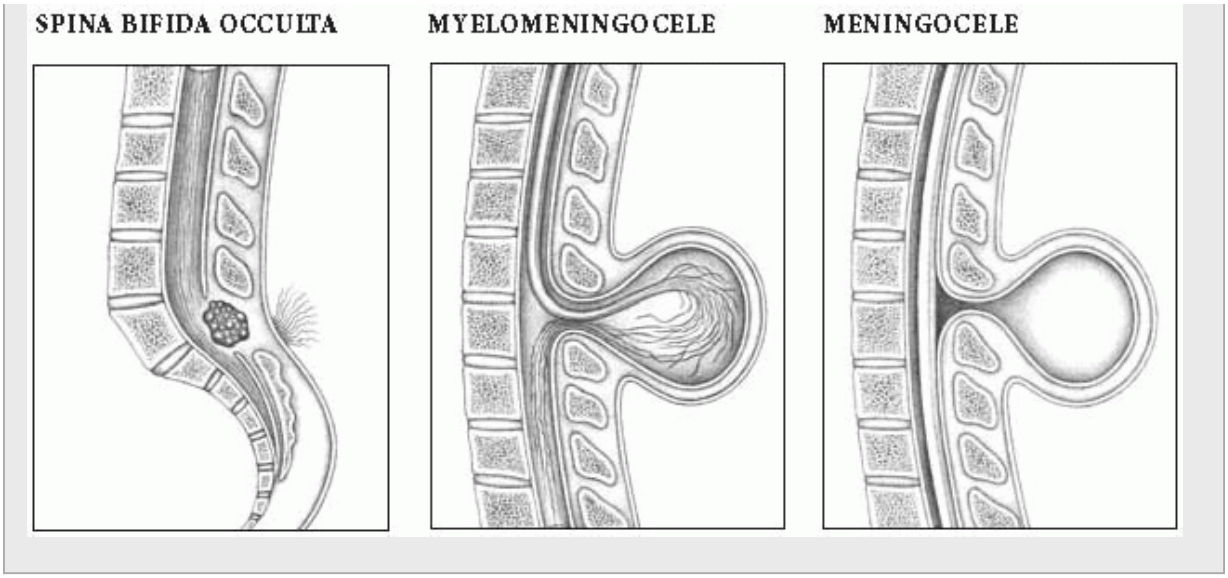
Spina bifida occulta is usually accompanied by a depression or dimple, tuft of hair, soft fatty deposits, port wine nevi, or a combination of these abnormalities on the skin over the spinal defect; however, such signs may be absent. Spina bifida occulta doesn't usually cause neurologic dysfunction but occasionally is associated with foot weakness or bowel and bladder disturbances. Such disturbances are especially likely during rapid growth phases, when the spinal cord's ascent within the vertebral column may be impaired by its abnormal adherence to other tissues.

In both myelomeningocele and meningocele, a saclike structure protrudes over the spine. Like spina bifida occulta, meningocele seldom causes neurologic deficit. But myelomeningocele, depending on the level of the defect, causes permanent neurologic dysfunction, such as flaccid

or spastic paralysis and bowel and bladder incontinence. Associated disorders include trophic skin disturbances (ulcerations, cyanosis), clubfoot, knee contractures, hydrocephalus (in about 90% of patients), and possibly mental retardation, Arnold-Chiari syndrome (in which part of the brain protrudes into the spinal canal), and curvature of the spine.

TYPES OF NEURAL TUBE DEFECTS

The three major types of neural tube defects are illustrated below. Spina bifida occulta is characterized by a depression or raised area and a tuft of hair over the defect. In myelomeningocele, an external sac contains meninges, cerebrospinal fluid (CSF), and a portion of the spinal cord or nerve roots. In meningocele, an external sac contains only meninges and CSF.



Clinical effects of encephalocele vary with the degree of tissue involvement and location of the defect. Paralysis and hydrocephalus are common. Infants with this defect have a better chance of survival than anencephalic infants and usually suffer less paralysis; however, surviving infants are usually severely mentally retarded.

Diagnosis

CONFIRMING DIAGNOSIS

Amniocentesis can detect elevated alpha fetoprotein (AFP) levels in amniotic fluid, which indicates the presence of an open NTD. Measuring acetylcholinesterase levels can confirm the diagnosis. (Biochemical testing will usually miss closed NTDs.) Because 5% to 7% of NTDs are associated with chromosomal abnormalities, a fetal karyotype should be done in addition to the biochemical tests.

Maternal serum AFP screening in combination with other serum markers, such as human chorionic gonadotropin (HCG), free beta-HCG, or unconjugated estriol, may be offered to some patients who aren't scheduled for amniocentesis, such as those with a lower risk of NTDs and those who will be younger than age 34½ at the time of delivery. Although this screening test can't diagnose either an open NTD or a

chromosomal abnormality, it can estimate a fetus's risk of such a defect. Most patients with abnormal maternal serum AFP levels won't have an affected child; however, they may be at increased risk for perinatal complications, such as premature rupture of the membranes, abruptio placentae, or fetal death.

Ultrasound may be used when the fetus has an increased risk of an open NTD based on either the family history or abnormal serum screening results; however, this test alone can't identify all open NTDs or ventral wall defects.

PREVENTION

FOLIC ACID SUPPLEMENT RECOMMENDATIONS

The following recommendations for folic acid supplement dosages have been endorsed by the Centers for Disease Control and Prevention, the American Academy of Pediatrics, and the Spina Bifida Association of America, among other groups.

All women of childbearing age

All women who can become pregnant should consume 0.4 mg of folic acid daily to reduce their risk of having a child with spina bifida or another neural tube defect (NTD).

Women at high risk

Women with a previous pregnancy affected by an NTD should:

- receive genetic counseling before their next pregnancy
- consume 0.4 mg of folic acid daily
- when actively trying to become pregnant (at least 1 month before conception), increase their intake of folic acid to 4 mg daily and continue to take 4 mg of folic acid daily through the first 3 months of pregnancy.

If the NTD isn't diagnosed before birth, other tests are used to make the diagnosis. For example, spina bifida occulta is commonly overlooked, although it's occasionally palpable and spinal X-ray can show the bone defect. Myelography can differentiate it from other spinal abnormalities, especially spinal cord tumors.

Myelomeningocele and meningocele are obvious on examination; transillumination of the protruding sac can sometimes distinguish between them. (In meningocele, it typically transilluminates; in myelomeningocele, it doesn't.) In myelomeningocele, a pinprick examination of the legs and trunk shows the level of sensory and motor involvement; skull X-rays, cephalic measurements, and computed tomography (CT) scan demonstrate associated hydrocephalus. Other appropriate laboratory tests in patients with myelomeningocele include urinalysis, urine cultures, and tests for renal function starting in the neonatal period and continuing at regular intervals.

In encephalocele, X-rays show a basilar bony skull defect. CT scan and ultrasonography further define the defect.

Treatment

Prompt neurosurgical repair and aggressive management may improve the condition of children with some NTDs, but serious and permanent disability is likely.

Spina bifida occulta usually requires no treatment. Treatment of meningocele consists of surgical closure of the protruding sac and continual assessment of growth and development. Treatment of myelomeningocele requires repair of the sac and supportive measures to promote independence and prevent further complications. Surgery doesn't reverse neurologic deficits. A shunt may be needed to relieve associated hydrocephalus.

Treatment of encephalocele includes surgery during infancy to place protruding tissues back in the skull, excise the sac, and correct associated craniofacial abnormalities.

Special considerations

- When an NTD has been diagnosed prenatally, refer the prospective parents to a genetic counselor, who can provide information and support the couple's decisions on how to manage the pregnancy.
- Recent research sponsored by the March of Dimes and others has indicated that the risk of an open NTD may be reduced 50% to 70% in pregnant women who take a daily multivitamin with folic acid. Urge all women of childbearing age to take such a vitamin supplement until menopause or the end of childbearing potential. (See *Folic acid supplement recommendations*.)

PEDIATRIC TIP

The parents of a child with an NTD will need assistance from physicians, nurses, surgeons, rehabilitation providers, and social workers. Help to coordinate such assistance as needed. Obviously, care is most complex when the neurologic deficit is severe. Immediate goals include psychological support to help parents accept the diagnosis and preoperative and postoperative care. Long-term goals include patient and family teaching, and measures to prevent contractures, pressure ulcers, urinary tract infections (UTIs), and other complications.

Before surgery:

- Prevent local infection by cleaning the defect gently with sterile saline solution or other solutions, as ordered. Inspect the defect often for signs of infection, and cover it with sterile dressings moistened with sterile saline solution. Prevent skin breakdown by placing sheepskin or a foam pad under the infant. Keep skin clean, and apply lotion to knees, elbows, chin, and other pressure areas. Give antibiotics as needed.
- Handle the infant carefully, and don't apply pressure to the defect. Usually, the infant can't wear a diaper or a shirt until after surgical correction because it will irritate the sac, so keep him warm in an

infant Isolette. Hold and cuddle the infant; on your lap, position him on his abdomen; teach parents to do the same.

- Provide adequate time for parent-child bonding if possible.
- Measure head circumference daily, and watch for signs of hydrocephalus and meningeal irritation, such as fever or nuchal rigidity. Be sure to mark the spot so you get accurate readings.
- Contractures can be minimized by passive range-of-motion exercises and casting. To prevent hip dislocation, moderately abduct hips with a pad between the knees or with sandbags and ankle rolls.
- Monitor intake and output. Watch for decreased skin turgor, dryness, or other signs of dehydration. Provide meticulous skin care to genitals and buttocks to prevent infection.
- Ensure adequate nutrition.

After surgery:

- Watch for hydrocephalus, which commonly follows surgery. Measure the infant's head circumference as indicated.
- Monitor vital signs often. Watch for signs of shock, infection, and increased intracranial pressure (ICP) such as projectile vomiting. Frequently assess the infant's fontanels. Remember that, before age 2, infants don't show typical signs of increased ICP because suture lines aren't fully closed. In infants, the most telling sign is bulging fontanels.
- Change the dressing regularly as ordered, and check for any signs of drainage, wound rupture, and infection.
- Place the infant in the prone position to protect and assess the site.
- If leg casts have been applied to treat deformities, watch for signs that the child is outgrowing the cast. Regularly check distal pulses to ensure adequate circulation.

To help parents cope with their infant's physical problems and successfully meet long-term treatment goals:

- Teach them to recognize early signs of complications, such as hydrocephalus, pressure ulcers, and UTIs.

- Provide psychological support and encourage a positive attitude. Help parents work through their feelings of guilt, anger, and helplessness.
- Encourage parents to begin training their child in a bladder routine by age 3. Emphasize the need for increased fluid intake to prevent UTIs. Teach intermittent catheterization and conduit hygiene, as ordered.
- To prevent constipation and bowel obstruction, stress the need for increased fluid intake, a high-bulk diet, exercise, and a stool softener, as ordered. If possible, teach parents to help empty their child's bowel by telling him to bear down, and giving a glycerin suppository as needed.
- Urge early recognition of developmental lags (a possible result of hydrocephalus). The child may need to attend a school with special facilities. Also, stress the need for stimulation to ensure maximum mental development. Help parents plan activities appropriate to their child's age and abilities. Refer to early intervention.
- Refer parents for genetic counseling, and suggest that parents consider an amniocentesis in future pregnancies. Also refer parents to the Spina Bifida Association of America.

Cleft lip and cleft palate

Cleft lip and cleft palate—an opening in the lip or palate—may occur separately or in combination. These deformities originate in the second month of pregnancy, when the front and sides of the face and the palatine shelves fuse imperfectly. Cleft deformities usually occur unilaterally or bilaterally, rarely midline. Only the lip may be involved, or the defect may extend into the upper jaw or nasal cavity.

Cleft lip and cleft palate occur in twice as many males as females; isolated cleft palate is more common in females.

Causes and incidence

Cleft lip or palate most commonly occurs as an isolated birth defect. Isolated cleft lip with or without cleft palate and cleft palate only are the result of a disruption in the normal development of the orofacial

structures. This disruption in development is thought to be the result of a combination of genetic and environmental factors, including drugs, viruses, and environmental toxins. Cleft lip or cleft palate may also occur as part of a chromosomal or Mendelian syndrome (cleft defects are associated with over 300 syndromes). Exposures to specific teratogens during fetal development may also produce these defects.

Cleft lip with or without cleft palate occurs in about 1 in 1,000 births among Whites; the incidence is higher in Asians (1.7 in 1,000) and Native Americans (over 3.6 in 1,000) but lower in Blacks (1 in 2,500).

A family history of cleft defects increases the risk of a couple having a child with a cleft defect. Likewise, an individual with a cleft defect is at an increased risk for having a child with a cleft defect. Children with cleft defects and their parents or adult individuals should be referred for genetic counseling for accurate diagnosis of cleft type and recurrence risk counseling. Recurrence risk information is based on family history, the presence or absence of other physical or cognitive traits within a family, and prenatal exposure information.

Signs and symptoms

Orofacial cleft defects are divided into two major groups: cleft lip with or without cleft palate or cleft palate only. Cleft of the lip may involve the alveolus (premaxilla) and may extend through the palate (hard and soft). Congenital clefts of the face occur most commonly in the upper lip. They can range from a simple notch to a complete cleft from the lip edge, through the floor of the nostril and through the alveolus. Cleft lip can occur on either or both sides of the midline but rarely along the midline itself. A cleft lip involving only one side is a *unilateral* cleft lip, and a cleft on both sides of the midline is a *bilateral* cleft lip. When a bilateral cleft lip involves clefting of the alveolus on both sides of the premaxilla, the premaxilla is separated from the maxilla into a freely moving segment.

A cleft of the palate only may be partial or complete, involving only the soft palate or extending from the soft palate completely through the hard palate. A cleft palate can occur alone or with a cleft lip. Isolated cleft palate is more commonly associated with congenital defects other than isolated cleft lip with or without cleft palate. (See *Variations of*

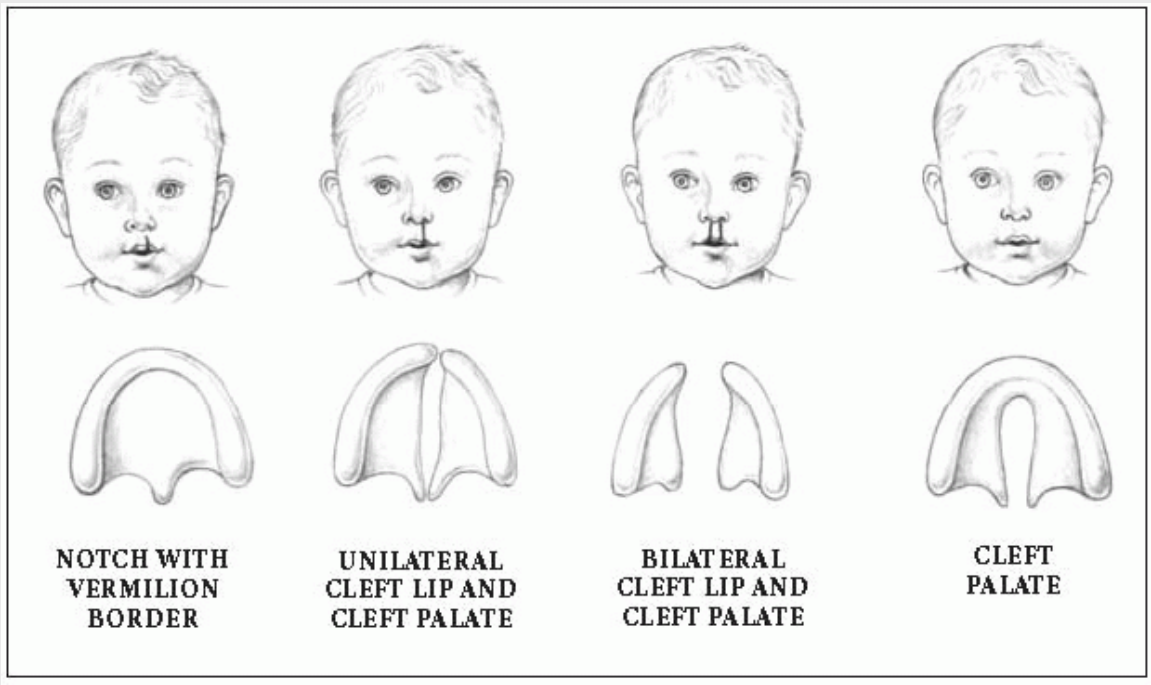
cleft lip and cleft palate.) The constellation of U-shaped cleft palate, mandibular hypoplasia, and glossoptosis is known as *Pierre Robin syndrome*, or *Robin syndrome*. Robin syndrome can occur as an isolated defect or one feature of many different syndromes; therefore, a comprehensive genetic evaluation is suggested for infants with Robin syndrome. Because of the mandibular hypoplasia and glossoptosis, careful evaluation and management of the airway are mandatory for infants with Robin syndrome.

Diagnosis

A typical clinical picture confirms the diagnosis. Cleft lip with or without cleft palate is obvious at birth; occasionally, more severe defects may be seen with diagnostic prenatal ultrasonography. Cleft palate without cleft lip may not be detected until a mouth examination is done or until feeding difficulties develop.

VARIATIONS OF CLEFT LIP AND CLEFT PALATE

The illustration below shows the four variations of cleft lip and cleft palate.



Treatment

Treatment consists of surgical correction, but the timing of surgery varies. Some plastic surgeons repair cleft lips within the first few days of life to make feeding the baby easier. However, many surgeons delay lip repairs for 8 to 10 weeks (sometimes as long as 6 to 8 months) to allow the infant to grow and mature, thereby minimizing surgical and anesthesia risks, ruling out associated congenital anomalies, and allowing time for parental bonding. Cleft palate repair is usually completed by the 12th to 18th month. Still other surgeons repair cleft palates in two steps, repairing the soft palate between ages 6 and 18 months and the hard palate as late as age 5 years. In any case, surgery is performed only after the infant is gaining weight and infection-free.

Surgery must be coupled with speech therapy. Because the palate is essential to speech formation, structural changes, even in a repaired cleft, can permanently affect speech patterns. To compound the problem, children with cleft palates commonly have hearing difficulties because of middle ear damage or infections.

Special considerations

- Recent research has indicated that ingestion of 0.4 mg of folic acid twice daily before conception may decrease the risk of isolated cleft defects.

ALERT

Never place a child with Robin syndrome on his back because his tongue could fall back and obstruct his airway. Place these infants on their side for sleeping. Most other infants with a cleft palate can sleep on their backs without difficulty.

- Maintain adequate nutrition to ensure normal growth and development. Experiment with feeding devices. A baby with a cleft palate has an excellent appetite but often has trouble feeding because of air leaks around the cleft and nasal regurgitation. He usually feeds better from a bottle and nipple designed specifically for

feeding infants with cleft defects. These bottles come with special nipples or regular nipples with enlarged holes and may be used with cleft palate bottles.

Teach the parents how best to feed the infant. Advise them to hold the infant in a near-sitting position, with the flow directed to the side or back of the baby's tongue. Tell them to burp the baby frequently because he will tend to swallow a lot of air. If the underside of the nasal septum becomes ulcerated and the child refuses to suck because of the pain, instruct the parents to direct the nipple to the side of his mouth to give the mucosa time to heal. Tell them to gently clean the palatal cleft with a cotton-tipped applicator dipped in half-strength hydrogen peroxide or water after each feeding.

- Encourage the mother of a baby with cleft lip to breast-feed if the cleft doesn't prevent effective sucking. Breast-feeding an infant with a cleft palate or one who has just had corrective surgery usually isn't possible. (Postoperatively, the infant can't suck for 6 to 10 weeks.) However, if the mother desires, suggest that she use a breast pump to express breast milk and then feed it to her baby from a bottle.
- Following surgery, record intake and output and maintain good nutrition. To prevent atelectasis and pneumonia, the physician may gently suction the nasopharynx (this may be necessary before surgery, too). Restrain the infant to prevent him from hurting himself. Elbow restraints allow the baby to move his hands while keeping them away from his mouth. When necessary, use an infant seat to keep the child in a comfortable sitting position. Hang toys within reach of restrained hands.
- Surgeons sometimes place a curved metal bow over a repaired cleft lip to minimize tension on the suture line. Remove the gauze before feedings, and replace it often. Moisten it with normal saline solution until the sutures are removed. Check your hospital policy to confirm this procedure.
- Help the parents deal with their feelings about the child's disability. Start by telling them about it and showing them their baby as soon as possible. Because society places undue importance on physical

appearance, many parents feel shock, disappointment, and guilt when they see the child. Help them by being calm and providing positive information.

Direct the parents' attention to their child's assets. Stress the fact that surgical repairs can be made. Include the parents in the care and feeding of the child right from the start to encourage normal bonding. Provide the instructions, emotional support, and reassurance that the parents will need to take proper care of the child at home.

- Refer the parents to a social worker who can guide them to community resources, if needed, and to a genetic counselor to determine the recurrence risk. Refer the family to the American Cleft Palate-Craniofacial Association for information and support.

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