## Neurofibromatosis

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.

## Osteogenesis imperfecta

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.

## Marfan syndrome

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.

## Stickler's syndrome

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.

## Cystic fibrosis

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 fatsoluble 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.

## Tay-Sachs disease

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.

## Phenylketonuria

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.

## Albinism

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.

## Sickle cell anemia

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 longterm 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).

## Hemophilia

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.

## Fragile X syndrome

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.

## Down syndrome

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.

## Trisomy 18 syndrome

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.

## Trisomy 13 syndrome

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. Microophthalmia, 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.

## Turner's syndrome

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.

## Klinefelter's syndrome

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. 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.

## Velocardiofacial syndrome

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.

## Neural tube defects

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.

## Cleft lip and cleft palate

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.