torn or scarred. Patients with classical EDS develop characteristic "cigarette-paper" scars. In vascular-type EDS, extensive scars and hyperpigmentation develop over bony prominences, and the skin may be so thin that subcutaneous blood vessels are visible. In the periodontotic type of EDS, the skin is more fragile than hyperextensible, and it heals with atrophic, pigmented scars. Easy bruisability occurs in several types of EDS.

Ligament and Joint Changes Laxity and hypermobility of joints vary from mild to unreducible dislocations of hips and other large joints. In mild forms, patients learn to avoid dislocations by limiting physical activity. In more severe forms, surgical repair may be required. Some patients have progressive difficulty with age.

Other Features Mitral valve prolapse and hernias occur, particularly with type I. Pes planus and mild to moderate scoliosis are common. Extreme joint laxity and repeated dislocations may lead to degenerative arthritis. In the ocular-scoliotic type of EDS, the eye may rupture with minimal trauma, and kyphoscoliosis can cause respiratory impairment. Also, sclerae may be blue.

Molecular Defects Subsets of patients with different types of EDS have mutations in the structural genes for collagens (Table 427-3). These include mutations in the *COL1A1* gene in a few patients with moderately severe classical EDS (type I); mutations in *COL1A2* in rare patients with an aortic valvular form of EDS; mutations in two of the three genes (*COL5A1* and *COL5A2*) for type V collagen, a minor collagen found in association with type I collagen, in about half the patients with classical EDS (types I and II); and mutations in the *COL3A1* gene for type III collagen, which is abundant in the aorta in patients with the frequently lethal vascular EDS (type IV).

Some of the type I collagen-related mutations alter processing of the protein or genes for the processing enzymes. Arthrochalasic EDS (type VII) is caused by mutations in the amino acid sequence that make type I procollagen resistant to cleavage by procollagen N-proteinase or by mutations that decrease the activity of the enzyme. The persistence of the N propeptide causes the formation of collagen fibrils that are thin and irregular. Some of the patients have fragile bones and therefore a phenotype that overlaps with OI. The ocular-scoliotic type of EDS (type VI) is caused by homozygous or compound heterozygous mutations in the *PLOD1* gene, which encodes procollagen-lysine 5-dioxygenase (lysyl hydroxylase 1), an enzyme required for formation of stable cross-links in collagen fibers.

Some patients with the hypermobile EDS (type III) and a few with mild EDS (type II) have mutations in the *TNXB* gene, which encodes tenascin X, another minor component of connective tissue that appears to regulate the assembly of collagen fibers. Mutations in proteoglycans have been found in a few patients. The progeroid form of EDS results from autosomal recessive mutations in *B4GALT7*, the gene for β-1,4-galactosyltransferase 7, a key enzyme in the addition of glycosaminoglycan chains to proteoglycans.

Diagnosis The diagnosis is based on clinical criteria and increasingly on DNA sequencing. Correlations between genotype and phenotype can be challenging, but gene or biochemical tests are particularly useful for the diagnosis of vascular type IV EDS with its dire prognosis.

As with other heritable diseases of connective tissue, there is a large degree of variability among members of the same family carrying the same mutation. Some patients have increased fractures and are difficult to distinguish from OI. A few families with heritable aortic aneurysms have mutations in the gene for type III collagen without any evidence of EDS or OI.

TREATMENT EHLERS-DANLOS SYNDROME

Surgical repair and tightening of joint ligaments require careful evaluation of individual patients, as the ligaments frequently do not hold sutures. Patients with easy bruisability should be evaluated for bleeding disorders. Patients with type IV EDS and members of their families should be evaluated at regular intervals for early detection of aneurysms, but surgical repair may be difficult because of friable tissues. Also, women with type IV EDS should be counseled about the increased risk of uterine rupture, bleeding, and other complications of pregnancy.

CHONDRODYSPLASIAS

(See also Chap. 426e) Chondrodysplasias (CDs), also referred to as skeletal dysplasias, are heritable skeletal disorders that are characterized by dwarfism and abnormal body proportions. The category also includes some individuals with normal stature and body proportions who have features such as ocular changes or cleft palate, which are common in more severe CDs. Many patients develop degenerative joint changes, and mild CD in adults may be difficult to differentiate from primary generalized osteoarthritis. An undefined number of patients have mutations in either the most abundant collagen in cartilage (type II) or the less abundant collagens (types X or XI). Other patients have mutations in genes that code for other components of cartilage or for proteins required for the embryonic development of cartilage, including a common mutation in a gene for a fibroblast growth factor receptor.

Classification Over 200 distinct types and subtypes have been defined based on criteria such as "bringing death" (thanatophoric), causing "twisted" bones (diastrophic), affecting metaphyses (metaphyseal), affecting epiphyses (epiphyseal), affecting spine (spondylo-), and producing histologic changes such as an apparent increase in the fibrous material in the epiphyses (fibrochondrogenesis). Also, a number of eponyms are based on the first or most comprehensive case reports. Severe forms of the diseases produce dwarfism with gross distortions of most cartilaginous structures and of other structures including the eye. Mild forms are more difficult to classify. Among the features are cataracts, degeneration of the vitreous, retinal detachment, high forehead hypoplastic facies, cleft palate, short extremities, and gross distortions of the epiphyses, metaphyses, and joint surfaces. Patients with Stickler's syndrome (hereditary arthro-ophthalmopathy) have been classified into three types based on a combination of the ocular phenotype and mutated genes.

INCIDENCE

The overall incidence of all forms of CD ranges from 1 per 2500 to 1 per 4000 births. Data on the frequency of individual CDs are incomplete, but the incidence of Stickler's syndrome is 1 in 10,000. Therefore, the disease is probably among the more common heritable disorders of connective tissue.

Molecular Defects Mutations in the *COL2A1* gene for the type II collagen of cartilage are found in a fraction of patients with both mild and severe CDs. For example, a mutation in the gene substituting a cysteine residue for an arginine was found in three unrelated families with spondyloepiphyseal dysplasia (SED) and precocious generalized osteoarthritis (OA). Mutations in the gene, often glycine substitution mutations with the collagen II triple helix, were also found in some lethal CDs characterized by gross deformities of bones and cartilage, such as those found in spondyloepiphyseal dysplasia congenita, spondyloepimetaphyseal dysplasia congenita, hypochondrogenesis/achondrogenesis type II, and Kniest's syndrome. The highest incidence of *COL2A1* mutations, however, occurs in patients with the distinctive features of Stickler's syndrome, which is characterized by skeletal changes, orofacial abnormalities, and auditory abnormalities. Most of the mutations in *COL2A1* are premature stop codons that produce haploinsufficiency. In addition, some patients with Stickler's syndrome or a closely related syndrome have mutations in two genes specific for type XI collagen, which is an unusual heterotrimer formed from α chains encoded by the gene for type II collagen (*COL2A1*) and two distinctive genes for type XI collagen (*COL11A1* and *COL11A2*). Mutations in the *COL11A1* gene are also found in patients with Marshall's syndrome, which is similar to classic Stickler's syndrome, but with more severe hearing loss and dysmorphic features, such as a flat or retracted midface with a flat nasal bridge, short nose, anteverted nostrils, long philtrum, and large-appearing eyes.