CDs are also caused by mutations in the less abundant collagens found in cartilage. For example, patients with Schmid metaphyseal CD have mutations in the gene for type X collagen, a short, network-forming collagen found in the hypertrophic zone of endochondral cartilage. The syndrome is characterized by short stature, coxa vara, flaring metaphyses, and waddling gait. As with other collagen genes, the most common mutations are of two types: nonsense mutations that lead to haploinsufficiency and structural mutations that compromise collagen assembly. In type X collagen, all the structural mutations detected occur in the C-terminal NC1 domain that coordinates the formation of the trimers. This NC1 domain is functionally equivalent to the C-propeptide of the fibrillar collagens. These mutations disturb the structure of the NC1 domain, leading to misfolding and initiation of cellular ER stress via the unfolded protein response (UPR). While the UPR evolved to allow cells to adjust their ER folding capacity to differing protein folding loads, it is deployed by cells when mutant misfolded proteins accumulate in the ER. Activation of the UPR attenuates protein translation and activates mutant protein degradation pathways such as ER-associated degradation. If these strategies do not sufficiently reduce the stress response, cell death may occur. In Schmid metaphyseal CD, mutant misfolded type X collagen induces the UPR, resulting in downstream consequences that contribute to the pathophysiology. This general mechanism may also contribute to pathology in other CDs (and in other connective tissues disorders) where gene mutations lead to protein structural abnormalities.

Some patients have mutations in genes for proteins that interact with collagens. Patients with pseudoachondroplasia or autosomal dominant multiple epiphyseal dysplasia have mutations in the gene for the cartilage oligomeric matrix protein (*COMP*), a protein that interacts with both collagens and proteoglycans in cartilage. However, some families with multiple epiphyseal dysplasia have a defect in one of the three genes for type IX collagen (*COL9A1*, *COL9A2*, and *COL9A3*) or in matrilin-3, another extracellular protein found in cartilage. With misfolding mutations in *COMP* and matrilin-3, the activation of the UPR has been described, providing further evidence that the UPR is a component of pathology of these conditions.

Some CDs are caused by mutations in genes that affect early development of cartilage and related structures. The most common form of short-limbed dwarfism, achondroplasia, is caused by mutations in the gene for a receptor for a fibroblastic growth factor (*FGFR3*). The mutations in the *FGFR3* gene causing achondroplasias are unusual in several respects. The same single-base mutation in the gene that converts glycine to arginine at position 380 in the *FGFR3* gene is present in over 90% of patients. Most patients harbor sporadic new mutations, and therefore, this nucleotide change must be one of the most common recurring mutations in the human genome. The mutation causes unregulated signal transduction through the receptor and inappropriate development of cartilage. Mutations that alter other domains of *FGFR3* have been found in patients with the more severe disorders of hypochondroplasia and thanatophoric dysplasia and in a few families with a variant of craniosynostosis. However, most patients with craniosynostosis appear to have mutations in the related *FGFR2* gene. The similarities between the phenotypes produced by mutations in genes for FGF receptors and mutations in structural proteins of cartilage are probably explained by the observation that the activity of FGFs is regulated in part by binding of FGFs to proteins sequestered in the extracellular matrix. Therefore, the situation parallels the interactions between transforming growth factors (TGFs) and fibrillin in MFS (see below).

Other mutations involve the proteoglycans of cartilage, aggrecan (*AGC1*), and perlecan (*HSPG2*) and the proteoglycan posttranslational sulphation pathway (DTDST, *PAPSS2*, and *CHST3*). Mutations in more than 45 other genes have been defined in chondrodysplasias.

Diagnosis The diagnosis of CDs is made on the basis of the physical appearance, slit-lamp eye examinations, x-ray findings, histologic changes, and clinical course. Evaluation of patients by specialists in the field is usually required for a diagnosis. Targeted gene and exome sequencing or more global sequencing strategies are used for molecular diagnosis. Given the wide spectrum of CD phenotypes, these gene tests are becoming critical diagnostic tools. For Stickler's syndrome, more precise diagnostic criteria have made it possible to identify type I variants with mutations in the *COL2A1* gene with a high degree of accuracy. It has been suggested that the type II variant with mutations in the *COL11A1* gene can be identified on the basis of a "beaded" vitreous phenotype, and the type III variant with mutations in the *COL11A2* gene can be identified on the basis of the characteristic systemic features without the ocular involvement. Prenatal diagnosis based on analysis of DNA obtained from chorionic villus or amniotic fluid is possible.

TREATMENT CHONDRODYSPLASIAS

The treatment is symptomatic and is directed to secondary features such as degenerative arthritis. Many patients require joint replacement surgery and corrective surgery for cleft palate. The eyes should be monitored carefully for the development of cataracts and the need for laser therapy to prevent retinal detachment. In general, patients should be advised to avoid obesity and contact sports. Counseling for the psychological problems of short stature is critical, and support groups have formed in many countries.

MARFAN'S SYNDROME (MFS)

MFS includes features that primarily affect the skeleton, the cardiovascular system, and the eyes. Most patients have mutations in the gene for fibrillin-1.

Classification MFS was initially characterized by a triad of features: (1) skeletal changes that include long, thin extremities, frequently associated with loose joints; (2) reduced vision as the result of dislocations of the lenses (ectopia lentis); and (3) aortic aneurysms. An international panel has developed a series of revised "Ghent criteria" that are useful in classifying patients.

Incidence and Inheritance The incidence of MFS is among the highest of any heritable disorder: about 1 in 3000/5000 births in most racial and ethnic groups. The related syndromes are less common. Mutations are generally inherited as autosomal dominant traits, but about one-fourth of patients have sporadic new mutations.

Skeletal Effects Patients have long limbs and are usually tall compared to other members of the same family. The ratio of the upper segment (top of the head to the top of the pubic ramus) to the lower segment (top of the pubic ramus to the floor) is usually two standard deviations below mean for age, race, and sex. The fingers and hands are long and slender and have a spider-like appearance (arachnodactyly). Many patients have severe chest deformities, including depression (pectus excavatum), protrusion (pectus carinatum), or asymmetry. Scoliosis is frequent and usually accompanied by kyphosis. High-arched palate and high pedal arches or pes planus are common. A few patients have severe joint hypermobility similar to EDS. Computed tomography or magnetic resonance imaging examinations of the lumbar sacral region frequently reveal enlargement of the neural canal, thinning of the pedicles and laminae, widening of the foramina, or anterior meningocele (dural ectasia).

Cardiovascular Features Cardiovascular abnormalities are the major source of morbidity and mortality (Chap. 301). Mitral valve prolapse develops early in life and progresses to mitral valve regurgitation of increasing severity in about one-quarter of patients. Dilation of the root of the aorta and the sinuses of Valsalva are characteristic and ominous features of the disease that can develop at any age. The rate of dilation is unpredictable, but it can lead to aortic regurgitation, dissection of the aorta, and rupture. Dilation is probably accelerated by physical and emotional stress, as well as by pregnancy. Patients usually differ from those with familial aortic aneurysms who tend to develop aneurysms in the abdominal aorta. The location of the aneurysms, however, is somewhat variable, and the high incidence of aortic aneurysms in the general population (1 in 100) makes the differential diagnosis difficult unless other features of MFS are clearly present.