Ocular Features Upward displacement of the lens is common. It is usually not progressive but may contribute to the formation of cataracts. The ocular globe is frequently elongated, and most patients are myopic, but with adequate vision. Retinal detachment can occur.

Other Features Striae may occur over the shoulders and buttocks. A number of patients develop spontaneous pneumothorax. Inguinal and incisional hernias are common. Patients are typically thin with little subcutaneous fat, but adults may develop centripetal obesity.

Molecular Defects More than 90% of patients clinically classified as having MFS by the "Ghent criteria" have a mutation in the gene for fibrillin-1 (*FBN1*). Mutations in the same gene are found in a few patients who do not meet the Ghent criteria. Also, a few MFS patients without mutations in the *FBN1* gene have mutations in the gene for TGF-β receptor 2 (*TGFBR2*). In addition, mutations in either *TGFBR2* or *TGFBR1* are found in the related Loeys-Dietz syndrome, which is characterized by aortic aneurysms, cleft palate, and hypertelorism. Mutations in the *FBN2* gene, which is structurally similar to the *FBN1* gene, are found in patients with MFS-like syndrome of congenital contractual arachnodactyly.

FBN1 gene mutations are scattered throughout its 65 coding exons. Most are private mutations, but about 10% are recurrent new mutations that are largely located in CpG sequences known to be "hot spots." Most severe mutations are located in the central codons (24–32). About one-third of the mutations introduce premature termination codons, and about two-thirds are missense mutations that alter calcium-binding domains in the repetitive epidermal growth factor–like domains of the protein. Rarer mutations alter the processing of the protein. As in many genetic diseases, the severity of the phenotype cannot be predicted from the nature of the mutation.

The discovery that syndromes similar to MFS are caused by mutations in *TGFBR1* and *TGFBR2* refocused attention on structural similarity between fibrillin-1 and TGF-β binding proteins that sequester TGF-β in the extracellular matrix. As a result, some of the manifestations of MFS have been shown to arise from alterations in binding sites that modulate TGF-β bioavailability during development of the skeleton and other tissues. Likewise, *TGFBR1* and *TGFBR2* mutations in Loeys-Dietz syndrome alter TGF-β signaling. In both MFS and Loeys-Dietz syndrome, the pathogenic mechanisms involve increased TGF-β signaling, which contributes to aneurysm formation.

Diagnosis All patients with a suspected diagnosis of MFS should have a slit-lamp examination and an echocardiogram. Also, homocystinuria should be ruled out by amino acid analysis of plasma (Chap. 434e). The diagnosis of MFS according to the international Ghent standards places emphasis on major criteria that include presence of at least four skeletal abnormalities: ectopia lentis; dilation of the ascending aorta with or without dissection; dural ectasia; and a blood relative who meets the same criteria, with or without a DNA diagnosis. A final diagnosis is based on a balanced assessment of the major criteria together with several minor criteria. The absence of ocular changes suggests the Loeys-Dietz syndrome, and the presence of contractures with some of the signs of OI suggests congenital contractual arachnodactyly.

Diagnostic tests based on gene sequencing or detection of protein defects are available. These results are unlikely to alter the treatment or prognosis but are helpful to inform the patients and families and to rapidly exclude the diagnosis in unaffected family members.

TREATMENT MARFAN'S SYNDROME

Propranolol or other β-adrenergic blocking agents are used to lower blood pressure and thereby delay or prevent aortic dilation. Surgical correction of the aorta, aortic valve, and mitral valve has been successful in many patients, but tissues are frequently friable. Patients should be advised that the risks are increased by severe physical exertion, emotional stress, and pregnancy.

The scoliosis tends to be progressive and should be treated by mechanical bracing and physical therapy if >20° or by surgery if it progresses to >45°. Dislocated lenses rarely require surgical removal, but patients should be followed closely for retinal detachment. The finding that MFS pathophysiology involves alterations in TGF-β signaling has raised the possibility of new therapeutic strategies. Attenuation of TGF-β signaling with agents such as angiotensin II receptor blockers (e.g., losartan) was effective in animal studies and has been very promising in small observational studies on MFS patients, significantly reducing progressive aortic enlargement. Based on these results, large randomized clinical trials of angiotensin receptor blockers in MFS are under way.

ELASTIN-RELATED DISEASES

Mutations in the elastin gene (*ELN*) have been found in patients with supravalvular aortic stenosis and skin that hangs in loose and redundant folds (cutis laxa). As indicated in Table 427-3, patients with several forms of EDS have similar changes in skin that were initially thought to reflect changes in elastin.

EPIDERMOLYSIS BULLOSA (EB)

EB has been defined as the category of heritable disorders involving skin that is specifically characterized by blistering as a result of friction. Using this criterion, it was possible to define subtypes by the ultrastructural layer of skin in which the cleavage and blistering occurred. These functional and anatomical criteria made it possible to establish that most patients with a specific subtype have mutations in genes coding for a structural protein, or a cell adherence protein, expressed in the corresponding layer of skin.

Classification and Incidence The four major types of EB are: (1) EB simplex in which cleavage occurs within the epidermis, (2) junctional EB in which cleavage occurs within the lamina lucida, (3) dystrophic EB in which cleavage occurs within the sublamina densa, and (4) Kindler's syndrome with a mixed level of cleavage in different layers. Patients are then separated into major and minor subtypes based on clinical features and analysis of mutations.

The incidence of EB in the United States is about 1 in 50,000.

Molecular Defects The distinctive anatomic locations in skin have made it possible to relate the clinical subtypes of EB to mutations for specific components. In EB simplex, mutations are found primarily in the genes for the major keratins of basal epithelial cells (keratins 5 and 14) and the cell adhesion proteins plectin, α6β4 integrin, plakophilin-1, and desmoplakin. Patients with the related syndrome, epidermolytic ichthyosis, have mutations in keratin 1 and keratin 10. In junctional EB, mutations occur in type XVII collagen, a laminin (laminin-332), and α6β4 integrin. In the severe syndrome of dystrophic EB, mutations are found in the gene that codes for type VII collagen, which forms long loops anchoring the epidermis to the dermis. Patients with more complex features of what is classified as Kindler's syndrome have mutations in kindlin-1, a focal adhesion protein involved in integrin activation.

Diagnosis and Treatment The diagnosis is based on skin that readily breaks and forms blisters from minor trauma. EB simplex is generally milder than junctional EB or dystrophic EB. Dystrophic EB variants usually have large and prominent scars. Precise classification within subtypes usually requires immunofluorescent mapping. DNA diagnostic tests have been developed as research tools but are not widely available. The treatment is symptomatic. Novel therapeutic approaches such as gene therapy, protein replacement therapy, and cell therapy are being explored.

ALPORT'S SYNDROME (AS)

AS is an inherited disorder characterized by hematuria and several associated features. It was not initially considered as a disorder of connective tissue. However, the search for mutations in the genes coding for the collagen found that most patients had mutations in collagen found in basement membranes (type IV). Four forms of AS are now recognized: (1) classic AS, which is inherited as an X-linked disorder with hematuria, sensorineural deafness, and conical deformation of