density are consistently seen in patients. Some clinical trials observed improvements in bone pain and fracture incidence; however, there are still unresolved questions about the best delivery protocols and the risks associated with long-term use in OI patients. For these reasons, the current consensus is that bisphosphonate therapy should be restricted to moderate to severe OI, where the possible benefits outweigh risks. Also, a clinical trial was performed in which patients were treated by intravenous infusion of cells from bone marrow referred to as mesenchymal stem cells, or multipotential stromal cells (MSCs; see Chap. 90e). Promising results were obtained, but the trial required a prior bone marrow transplant with marrow from a normal donor who subsequently was used as a source of normal MSCs. As a result, the procedure has not been widely adopted. However, the results raise the possibility that it may be possible in the future to develop effective stem cell therapies for OI.

Counseling and emotional support are important for patients and their parents; lay organizations in some countries provide help in these areas. Prenatal ultrasonography will detect severely affected fetuses at about 16 weeks of pregnancy. Diagnosis is routinely performed on DNA from blood.

EHLERS-DANLOS SYNDROME

EDS is characterized by hyperextensible skin and hypermobile joints, but the category includes rare patients with other distinctive features. Mutations in different types of collagen are found in many patients, but other genes are at fault in rare forms. Contrary to initial expectations, no patients have been found with mutations in the gene for elastin in EDS.

Classification Several types of EDS have been defined, based on the extent to which the skin, joints, and other tissues are involved, mode of inheritance, and molecular and biochemical analysis (Table 427-3). Classical EDS includes a severe form of the disease (type I) and a milder form (type II), both characterized by joint hypermobility and skin that is velvety in texture, hyperextensible, and easily scarred. In hypermobile EDS (type III), joint hypermobility is more prominent than skin changes. In vascular-type EDS (type IV), the skin changes are more prominent than joint changes, and the patients are predisposed to sudden death from rupture of large blood vessels or other hollow organs. EDS type V is similar to EDS type II but is inherited as an X-linked trait. The ocular-scoliotic type of EDS (type VI) is characterized by scoliosis, ocular fragility, and a cone-shaped deformity of the cornea (keratoconus). The arthrochalasic type of EDS (type VIIA and VIIB) is characterized by marked joint hypermobility that is difficult to distinguish from EDS III except by the specific molecular defects in the processing of type I procollagen to collagen. The periodontotic-type EDS (type VIII) is distinguished by prominent periodontal changes. EDS types IX, X, and XI were defined on the basis of preliminary biochemical and clinical data. EDS due to tenascin X deficiency has not been assigned a type; it is an autosomal recessive form of the syndrome similar to EDS II. The cardiac valvular form of EDS has similar features to EDS II, but also involves severe changes to the aorta. The progeroid form of EDS displays features of both EDS and progeria. Because of overlapping signs and symptoms, many patients and families with some of the features of EDS cannot be assigned to any of the defined types.

Incidence The overall incidence of EDS is about 1 in 5000 births, with a higher rate for blacks. Classical and hypermobile types of EDS are the most common. Patients with milder forms frequently do not seek medical attention.

Skin Skin changes vary from thin and velvety to skin that is either dramatically hyperextensible ("rubber person" syndrome) or easily

TABLE 427-3 DIFFERENT FORMS OF EHLERS-DANLOS SYNDROME

Type	Typical Features	Inheritance	Gene Defect	Protein Defect
Classic (EDS I—severe and EDS II—mild)	Skin hyperextensibility and fragility, joint hypermobility, tissue fragility manifested by widened atrophic scarring	AD	*COL5A1* *COL5A2*	Collagen V
		AD	*COL1A1*	Proα1 (I) and proα2 (I) chains of procollagen I
		AD, AR	*COL1A2*	
Hypermobile (EDS III)	Joint hypermobility, moderate skin involvement, absence of tissue fragility	AD	*TNXB*	Tenascin X
Vascular (EDS IV)	Markedly reduced life span due to spontaneous rupture of internal organs such as arteries and intestines; skin is thin, translucent, and fragile, with extensive bruising; hypermobile minor joints; characteristic facial appearance	AD	*COL3A1*	Collagen III
X-linked EDS (EDS V)	Similar to classic type	X-linked recessive	Unknown	Unknown
Ocular-scoliotic EDS VI (EDS VIA and EDS VIB)	Features of classic EDS as well as severe muscular hypotonia after birth, progressive kyphoscoliosis, a Marfanoid habitus, osteopenia, occasionally rupture of the eye globe and great arteries	AR	*PLOD1* Unknown for EDS VIB	Deficiency of procollagen-lysine 5-dioxygenase activity (EDS VIA) Unknown for EDS VIB
Arthrochalasic EDS VII (EDS VIIA and EDS VIIB)	Congenital bilateral hip dislocation, hypermobile joints, moderate skin involvement, osteopenia	AD	*COL1A1* *COL1A2*	Mutations that prevent cleavage of the N propeptides
Dermatosparactic EDS VII C	Redundant and fragile skin, prominent hernias, joint laxity, dysmorphic features	AR	*ADAMTS2*	Deficiency of procollagen I N-terminal proteinase
Periodontotic EDS VIII	Absorptive periodontosis with premature loss of permanent teeth, fragility of the skin, skin lesions	AD	Unknown	Unknown
EDS due to tenascin X deficiency	Similar to EDS II	AR	*TNXB*	Tenascin X
EDS, progeroid form		AR?	*B4GALT7*	Deficiency of galactosyltransferase 7 (defective synthesis of dermatan sulfate proteoglycans)

Abbreviations: AD, autosomal dominant; AR, autosomal recessive.