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VARIANTS OF THE EHLERS-DANLOS SYNDROME

CLINICAL, BIOCHEMICAL, HAEMATOLOGICAL, AND CHROMOSOMAL FEATURES OF 100 PATIENTS

BY

P. BEIGHTON,* A. PRICE, J. LORD, AND E. DICKSON

St. Thomas's Hospital, London

The Ehlers-Danlos syndrome (EDS) is an uncommon genetically-determined disorder of connective tissue. The main characteristics are joint hypermobility and skin hyperextensibility (Figs 1, 2, 3). The skin tends to split on minor trauma, with the

* Present address: Johns Hopkins Hospital, Baltimore, U.S.A.

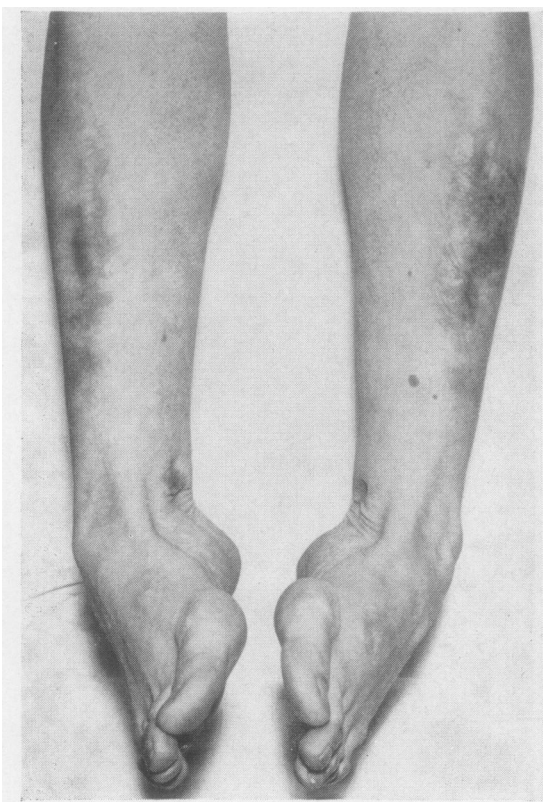

Fig. 1.—Hypermobility of ankle joints and scarring of shins.

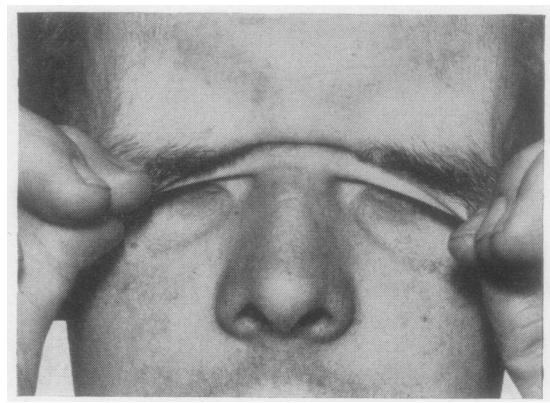

Fig. 2.—Skin hyperextensibility.

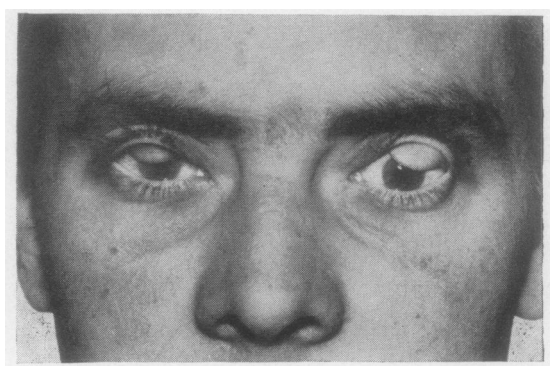

Fig. 3.—Extensibility of skin permitting ease of eversion of upper eyelid (Méténier's sign) (Méténier, 1939).

formation of thin, gaping scars (Fig. 4). The condition is usually transmitted by the autosomal dominant mode of inheritance.

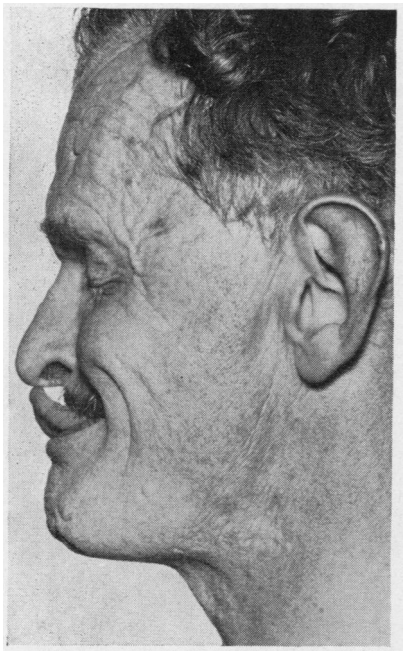

Fig. 4.—Facial scarring. The ability to touch the tip of the nose is present in 50 per cent. of patients with EDS, and only 10 per cent. of normal people (Gorlin's sign) (Gorlin and Pindborg, 1964).

A bruising tendency is frequently present and orthopaedic, cardiovascular, gastrointestinal, and ocular concomitants occur. Other features which are sometimes found are calcified subcutaneous spheroids and molluscoid pseudotumours (Fig. 5).

During a recent survey one hundred patients with the EDS were examined and investigated. It became apparent that, although the stigmata of the condition were very similar in members of the same family, there was a very wide variation between different families, to the extent that the syndrome

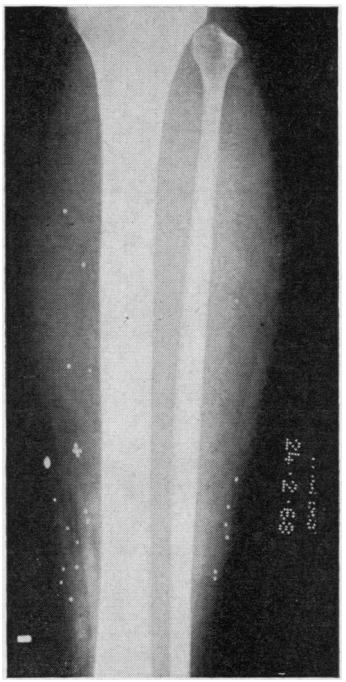

Fig. 5.—Calcified subcutaneous spheroids.

was manifestly more than one entity. On analysis of the results, five well-defined types emerged, and it is the purpose of this paper to describe the characteristics of these variants of the EDS and to present the results of biochemical, haematological, and chromosomal investigations in patients representing each of these types of the syndrome.

CLINICAL CHARACTERISTICS OF THE VARIANTS OF THE EDS

The main stigmata of the patients in the series are summarized in the Appendix. The clinical features of the various types of the EDS are shown in Table I.

TABLE I
CHARACTERISTICS OF THE VARIANTS OF THE EHLERS-DANLOS SYNDROME

Type of EDS	Skin Hyperextensibility	Joint Hypermobility	Skin Splitting	Bruising	Mode of Inheritance	Major Concomitants
Gravis	Gross	Gross	Gross	Moderate	Dominant	Musculoskeletal deformity Varicose veins Prematurity
Mitis	Moderate	Moderate	Moderate	Moderate	Dominant	
Benign Hypermobile	Variable Usually gross	Gross	Minimal	Minimal	Dominant	
Ecchymotic	Minimal	Minimal	Moderate	Gross	Dominant	Death from arterial rupture
X-linked	Moderate	Limited to digits	Minimal	Minimal	X-linked	

The proportions of the patients and kindreds with each variety of the condition are shown in Table II.

TABLE II
INCIDENCE OF VARIANTS OF THE EHLERS-DANLOS SYNDROME

Type	No. of Cases in Series	Kindreds in Series	
		No.	Per cent. of Total
Gravis	32	22	43
Mitis	45	18	35
Benign Hypermobile ..	11	6	12
Ecchymotic	4	3	6
X-Linked	8	2	4
Total	100	51	100

(1) EDS Gravis Type

This is the form of the condition which is usually recognized. Joint hypermobility is generalized and gross while skin hyperextensibility is marked. The tendency to skin splitting is severe, and the forehead, elbows, knees, and shins are frequently covered with wide gaping scars. The bruising tendency is usually of moderate degree. Molluscoid pseudotumours and subcutaneous spheroids occur in the majority of these patients, and varicose veins are very common (Fig. 6). Musculoskeletal deformity is often present, with diverse orthopaedic complications (Fig. 7). The tissues are sometimes unduly friable and difficulties have been encountered at operation. In this group of patients there is a high incidence of prematurity, due to early rupture of the foetal membranes.

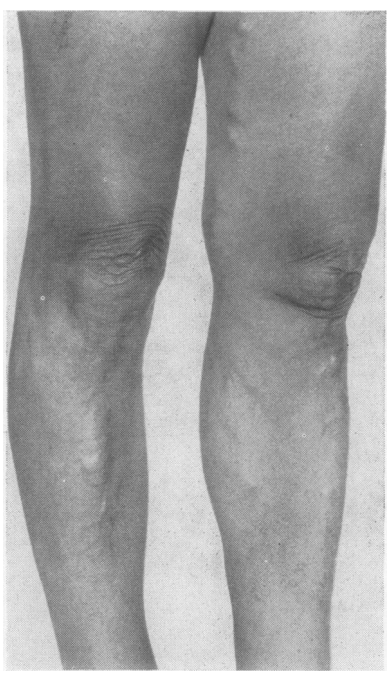

Fig. 6.—Varicose veins and scarring of knees.

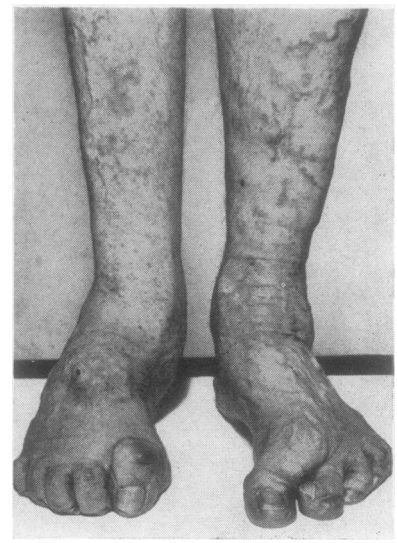

Fig. 7.—Pes cavus and deformed toes.

ILLUSTRATIVE CASE

Patient 18, a 20-year-old male (Family 11, III-5), had been born prematurely when the foetal membranes had ruptured spontaneously at the 34th week of his mother's pregnancy. He weighed 3½ lb. at birth and was late in walking. He fell frequently during childhood and developed a huge haematoma on his forehead following a fall at the age of 2½ years. Many episodes of skin splitting occurred, and the diagnosis of the EDS was made when he was 4 years old, after he had gashed his shin open on a cushion.

As he grew older lacerations, bruising, and haematomata formation continued. In adolescence he had a successful skin graft to a particularly large cut on his thigh. By the time that he had reached adult life, he had received well over one thousand stitches. Fortunately these always held well, and healing occurred quickly. He had increasing trouble with his unstable joints and had episodes of "locking" of the knees. He could spontaneously dislocate and reduce his patellae and the terminal interphalangeal joints of his thumbs, and there had been repeated effusions into the elbow and knee joints.

He was an only child and was unmarried. Neither his parents nor any of their relations had any stigmata of the EDS, and he was therefore a "sporadic" case rather

than a member of a kindred showing the true autosomal dominant mode of inheritance.

Examination.—He was of small stature and had a gross deformity of the chest. The costochondral junctions on the left side of the thorax were angulated forwards, giving a marked thoracic asymmetry.

He had the typical facies of the Gravis type of the EDS, with a scarred forehead and chin, lop ears, a bent nose, irregular teeth, and marked epicanthic folds.

His skin was hyperextensible, and could be pulled out from the ventral aspect of his forearm for 6 cm., and over his olecranon the skin could be stretched for 10 cm. On release the skin snapped back to resume its former position. The skin was pale and velvety to touch, and there were numerous thin gaping scars over all bony prominences. Subcutaneous spheroids could be palpated in the shins and forearms, and molluscoid pseudotumours were present on the elbows.

He had hypermobility of all joints, with over 100° of hyperextension of the metacarpophalangeal joints, 20° of genu recurvatum, and 15° of hyperextension of the elbow joint. There was severe static pes planus and prominent varicose veins in the legs and thighs.

Comment.—This patient had many of the typical features of the Gravis type of the EDS, with gross joint hypermobility and marked skin hyperextensibility and splitting. The musculoskeletal deformity and orthopaedic complications were typical of this entity, as were the facies, the varicose veins, and the premature birth. The apparent lack of any affected ancestors is not an uncommon feature of the EDS.

(2) EDS Mitis Type

In this variety of the EDS, the stigmata are all of minor degree, and patients may easily remain undiagnosed. Joint hypermobility is limited in degree, and may be confined to the hands and feet. The skin is less hyperextensible and does not split as readily as in the former variety, so that the resultant scarring is less marked (Fig. 8). The bruising tendency is of mild degree. Subcutaneous spheroids and molluscoid pseudotumours are less evident, and varicose veins do not occur with any frequency. Musculoskeletal deformity, if present at all, is usually slight, and orthopaedic complications are not a hazard. Tissue friability is not a problem and there is no raised incidence of prematurity.

ILLUSTRATIVE CASE

Patient 60, a 35-year-old housewife (Family 38, IV-23), was the daughter of a woman with the Mitis type of the EDS. She, herself, had been a full-term baby and her birth had been uncomplicated. She had a normal childhood but had always bruised more easily than her fellows and had a few cuts that occurred on minor trauma. Cramps in the calf muscles had been troublesome in early life, but this symptom disappeared at puberty. She had an uncomplicated mastoidectomy and an uneventful repair of a uterine prolapse. She was otherwise well, and both her pregnancies had been quite normal.

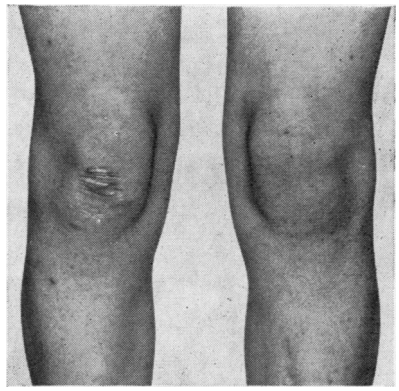

Fig. 8.—Minor degree of scarring characteristic of Mitis variety of EDS.

Her grandfather and great grandmother also had the EDS and one of her two children was also affected.

Examination.—She was pleasant and rather plump. There was no musculoskeletal deformity and she did not have varicose veins. The skin of the ventral surface of the forearm could be stretched to 4 cm. and there were a few wide scars on the knees and elbows. The metacarpophalangeal joint of the little fingers could be hyperextended to 95°, and the elbows could be extended to 10°. She had neither subcutaneous spheroids nor molluscoid pseudotumours.

Comment.—This patient's pedigree demonstrated the typical autosomal dominant mode of inheritance of the trait. All the affected members of the kindred in five generations had stigmata which were mild in degree. The condition had caused them little inconvenience, and there had been no difficulties at operation or during pregnancy.

(3) EDS Benign Hypermobile Type

In this entity joint hypermobility is generalized and gross, while skin hyperextensibility is variable and may be marked or minimal. Skin splitting is limited and there is little scarring. It is in this variety of the EDS that *formes frustes* apparently occur. Spheroids and pseudotumours are uncommon and varicose veins and prematurity are not features of this type of the condition. The bruising tendency is variable in degree but it is not usually troublesome. Musculoskeletal deformity is infrequent but orthopaedic complications occur in many of these patients.

ILLUSTRATIVE CASE

Patient 80, a 43-year-old housewife (Family 40, III-1), had loose joints and had been greatly troubled by pain in the leg muscles during childhood. The lax knee joints had "given way" on several occasions, and a cartilage had been removed. The operation was uneventful, but effusions and instability persisted. She had always been able to amuse her friends by her ability to stretch her skin. She had never had any trouble with skin splitting, but she bruised easily.

During pregnancy she had subluxed both shoulder joints and in her second labour her pubic symphysis had become distracted. Increasing deformity of the left great toe, associated with a "bunion", had necessitated a Keller operation. There had been no complications of this operation, and an appendicectomy was also uneventful.

Her mother had hypermobile joints and hyperextensible skin and a brother and sister were similarly affected, although the degree of skin hyperextensibility was much less in these two siblings. She had two sons, both of whom were very hypermobile, but one of them had virtually no skin hyperextensibility. Skin splitting did not occur in any of her relatives.

Examination.—She was a jolly woman with gross generalized joint hypermobility, including 25° genu recurvatum. The skin was moderately hyperextensible, but she had neither scars nor molluscoid pseudotumours. She had static pes planus but there was no other musculoskeletal deformity.

Comment.—This patient exhibited the characteristic features of the benign hypermobile type of the EDS, having gross joint hypermobility and moderate skin hyperextensibility, in the absence of any tendency to skin splitting. The occurrence of orthopaedic complications is also typical of this group of patients. Her pedigree demonstrated the autosomal dominant mechanism of inheritance, but the variation in the degree of skin hyperextensibility in the affected patients in this kindred could lead to them being regarded as *formes frustes* of the condition.

(4) EDS Ecchymotic Type

This uncommon entity is readily recognizable and is of paramount clinical importance. Joint hypermobility is usually limited to the digits, while the skin hyperextensibility may be minimal or absent. However, the skin is characteristically thin and pale, with a prominent venous network. The cardinal feature of this entity is the bruising tendency, which is gross. Minor trauma leads to extensive ecchymosis and the bony prominences become covered with thin, darkly-pigmented scars which are unlike those in the other types of the EDS. Musculoskeletal and orthopaedic disorders are not a feature of this condition, but cardiovascular and gastrointestinal catastrophes frequently occur. Many of the reports in the literature describing death in the EDS from arterial rupture, aortic dissection, or intestinal perforation probably pertain to patients with this variety of the syndrome.

ILLUSTRATIVE CASES

Patient 90, a 29-year-old housewife (Family 50, II-1), had had the daily activity limited by her bruising tendency. The slightest trauma caused massive ecchymoses and to give some degree of protection she constantly wore crepe bandages around her shins. She gave a vivid description of the massive haematoma that occurred when she dropped a loaf of bread on her shin, and she claimed that her housework caused bruising of her knuckles. In the past she had epistaxis, haematuria, and menorrhagia, but her teeth had been removed without undue bleeding. Her skin was fragile and lacerations were frequent. Recurrent dislocation of a finger and of the right patella had occurred.

Neither her parents nor her many siblings were affected, but the eldest of her two sons had the condition, his clinical stigmata being very similar to those of his mother.

The patient's elbows, knees, and shins were covered with atrophic, heavily-pigmented scars (Fig. 9). Her skin was transparent and the underlying venous plexus

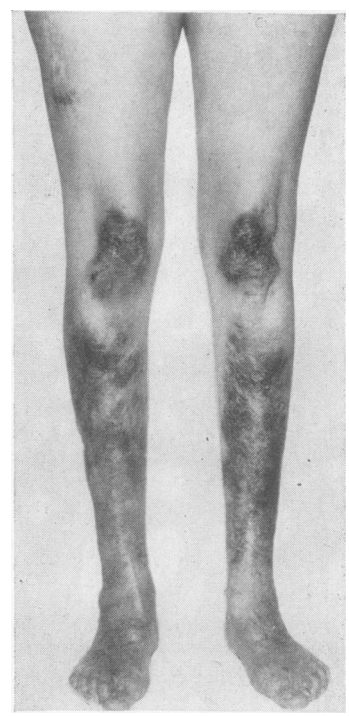

Fig. 9.—Atrophic darkly-pigmented scars. Ecchymotic variety of EDS. Patient 90.

was visible. The joints were not hypermobile and the skin was not hyperextensible. The only other abnormal findings were a mild dorsal kyphoscoliosis and a moderate degree of pes planus.

Patient 89, a 53-year-old woman (Family 49, III-2), had similar clinical features. Her father, brother, and sister had all died suddenly from arterial or gastrointestinal catastrophes.*

Comment.—The pedigrees of these patients were characteristic of an autosomal dominant mode of inheritance of the trait. The clinical features were similar in all of them, and they were so unlike those seen in patients with the other types of the EDS that this condition probably represents a completely distinct and separate entity. Sudden death from arterial rupture is an ever-present risk.

(5) EDS X-linked Type

Inheritance in the EDS is usually mediated by an autosomal dominant gene. However, a new entity in which the EDS was transmitted as an X-linked trait has recently been described (Beighton, 1968a). In this condition joint hypermobility is of limited degree, while skin hyperextensibility is very prominent (Fig. 10). The extensible fold of skin is thick, and the sensation of the skin coming away from the underlying tissues, which occurs in the Gravis variety, is not obtained (Fig. 11). Skin splitting, scarring, and bruising are of moderate degree and both spheroids and molluscoid pseudotumours are found. Orthopaedic complications are frequent in spite of the lack of joint hypermobility, and the tissues may be friable at operation.

ILLUSTRATIVE CASE

Patient 94, an 18-year-old youth (Family 53, IV-2), had had three operations for correction of squint in childhood but had been otherwise well until recent years when recurrent effusions in both knee joints had become troublesome. Skin splitting had only been a minor problem, and indeed for some years he had been a local boxing champion. Diagnosis of the EDS was made on skin biopsy appearances after it had been noted that the skin was unduly hyperextensible. When the biopsy was taken, the surgeon noticed the friability of the tissues, and remarked that closing the incision was "like sewing butter".

Review of his family revealed that his two brothers were similarly affected, as were an uncle, a great-uncle, and a male cousin. All the female members of the family were apparently perfectly normal, and the pedigree was typical of an X-linked mode of inheritance.

* Another patient, who is not included in the series, had died of a ruptured iliac artery. She also had similar clinical stigmata and she had a history of previous spontaneous bleeding, carotid-cavernous fistula, and severe haemorrhage at operation.

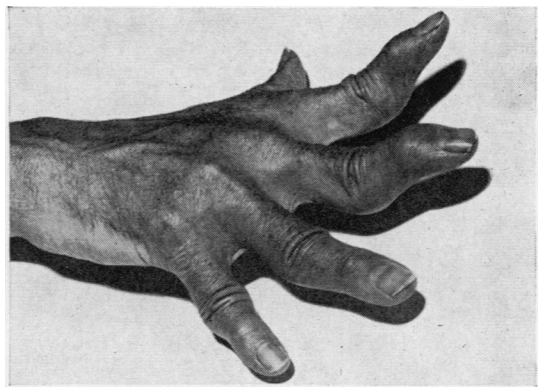

Fig. 10.—Hypermobility limited to digits. X-linked variety of EDS.

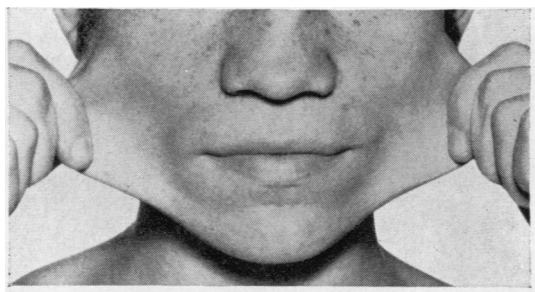

Fig. 11.—Hyperextensible skin. The skin-fold is characteristically thick in the X-linked variety of EDS.

Examination.—He was a fit, well-built young man with marked hyperextensibility of the skin. There were a few wide scars on the knees, and the finger joints were moderately hyperextensible. A molluscoid pseudotumour was present on the left knee, but no subcutaneous spheroids were found.

Two affected brothers (Cases 99 and 100) in Family 54, the other X-linked EDS family, had similar features. In addition, one of them had repeated dislocations of both shoulders while the other had several spontaneous haematomata in the muscles of his forearms and thighs.

Comment.—These patients demonstrated the marked skin hyperextensibility, minor joint hypermobility, the tendency to skin splitting, and the liability to orthopaedic complications that characterize this type of the EDS.

Discussion

McKusick (1966) suggested that the EDS might consist of more than one entity, and Barabas (1967) described three subgroups of the syndrome. Harris (1968) stated, "what are at present considered single disease entities may well be found to be due to a series of distinct and different abnormalities of a single enzyme protein". It seems likely that the five recognizable types of the EDS are separate

entities of this nature. Their clinical features are consistent and their complications are predictable.

The Gravis type has some features in common with the "classical" EDS described by Barabas (1967), while the Ecchymotic variety possibly corresponds to his "arterial" subgroup. This latter condition is so distinct, both on a basis of the clinical appearances and the very high mortality rate, that it should probably be considered to be a condition quite separate from the true EDS.

The Benign Hypermobile variety of the EDS is easily recognized, but it may be confused with familial hypermobility (Kirk, Ansell, and Bywaters, 1967) or arthrochalasis multiplex congenita (Hass and Hass, 1958): see Figs 12 and 13. However, although a mild bruising tendency sometimes occurs in patients with these latter conditions, they never have skin hyperextensibility, splitting, or scarring, and differentiation from the EDS is therefore possible (Beighton and Horan, 1968a).

There are several reasons why it is important to distinguish the various types of the EDS.

(1) *Prognosis.*—Death in youth or early adult life occurs frequently in the Ecchymotic variety and some descriptions in the literature of dissected aneurysms (McKusick, 1966) and ruptured arteries (Mories 1960; Bannerman, Graf, and Upson, 1967) probably refer to this type of the EDS. Other reports describing arterial bleeding (McFarland and Fuller, 1964) and aortic dissection (Lynch, Larsen, Wilson, and Magnuson, 1965) apparently concerned patients with the Gravis type of the syndrome (Beighton, 1968b). The other types are compatible with a comparatively normal existence within the limits imposed by skin splitting, the bruising tendency and the occurrence of orthopaedic complications.

(2) *Operative Risk.*—Friable tissues and operative difficulties due to abnormal bleeding have been reported in the Gravis and Ecchymotic types of the EDS, and death from arterial tear at angiography has been described (Schoolman and Kepes, 1967). Tissue friability is not troublesome in the other forms of the condition (Beighton and Horan, 1968b).

(3) *Obstetric Features.*—Nine of the 32 patients with the Gravis type of the EDS were born prematurely, and obstetric complications were common in this group. For these reasons delivery in hospital is preferable in these patients (Beighton, 1969).

Fig. 12.—Familial generalized hypermobility. A professional contortionist.

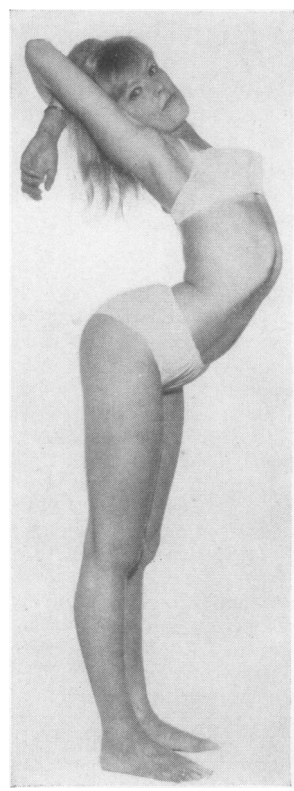

Fig. 13.—Familial generalized hypermobility. Although this is frequently confused with the EDS, the two conditions are quite separate and distinct.

(4) *Genetic Counselling.*—Apart from the X-linked variety, the other types of the EDS are all inherited as autosomal dominant traits. For this reason an affected parent has a 50 per cent. chance of producing an affected child, irrespective of sex. In the X-linked variety, the affected patients are all males, and their daughters are carriers, while their sons are unaffected.

The question of therapeutic abortion has been raised with reference to the EDS. There are strong indications for this procedure in the Ecchymotic variety, and relatively good grounds in the Gravis variety, especially if it is present in the family in a particularly severe form. In the other types of the EDS, the indications for termination are much less positive.

In the past, there have been many isolated reports of biochemical or haematological abnormalities in the EDS, while other workers have refuted or failed to confirm these findings. The subsequent sections of this paper deal with some biochemical, haematological, and chromosomal investigations in patients with variants of the EDS.

LABORATORY INVESTIGATIONS

Biochemical Investigations

Previous investigations into the chemical pathology of the EDS are few in number, and have given conflicting results, possibly because patients with different variants of the syndrome were examined. For this reason patients with each form of the EDS were investigated, and the following estimations were carried out.

(1) Urinary hydroxyproline.
(2) Plasma elastase inhibitor.
(3) Urinary mucopolysaccharides.
(4) Urinary chromatography.

(1) URINARY HYDROXYPROLINE.—The 24 hr urinary hydroxyproline excretion rate is widely used as a measure of collagen turnover, as this amino acid is restricted to that tissue. For this reason the hydroxyproline excretion rate in patients with the EDS was measured as a possible index of an abnormality of collagen metabolism.

Method.—24 hr urine samples were collected from patients, who were instructed not to eat gelatin-containing products on the day before collection. Thymol in iso-propyl alcohol was used as a urinary preservative. The analysis was carried out according to the method of Kivirikko, Laitinen, and Prockop (1967). Three estimations in duplicate were performed on each urine. These included a neat sample and mixtures with two internal standards.

The results of the estimations are shown in Table III.

TABLE III
HYDROXYPROLINE EXCRETION IN EIGHT CASES OF THE EHLERS-DANLOS SYNDROME

Case No.	Family	Type of EDS	Age (yrs)	Sex	Hydroxyproline Excretion (mg./m²/24 hrs)
1	1 III-1	Gravis	29	Male	9·0
4	2 III-3	Gravis	28	Female	25
13	6 IV-4	Gravis	30	Female	18·6
37	24 III-1	Mitis	24	Male	15
43	28 IV-9	Mitis	13	Male	47·7
93	53 IV-1	X-linked	19	Male	33
94	53 IV-2	X-linked	18	Male	25
95	53 IV-4	X-linked	11	Male	98·5

Comment.—The excretion of hydroxyproline varies with age and rate of growth (Jones, Bergman, Kittner, and Pigman, 1964) and it is highest in actively growing adolescents (Jasin, Fink, Wise, and Ziff, 1962). The results of previous work on hydroxyproline excretion in the EDS have been conflicting because of confusion over the diagnosis of the condition and uncertainty as to the normal levels of this substance in the urine. Bland, Lipson, Dunihue, Kusscrow, Clemmons, and Williams (1965) reported raised levels in four patients with the EDS, while Straus and Tejaratchi (1966) reported a raised level in one patient who, however, also had osteomalacia. Goltz and Hult (1965) found normal levels in their patients with the EDS.

The eight cases investigated had urinary 24 hr hydroxyproline excretion levels within the range of normal reported by Anderson, Bannister, and Tomlinson (1965), using the same method. There is therefore no evidence from these cases to suggest that increased turnover of collagen, as reflected by hydroxyproline excretion, occurs in the EDS.

(2) PLASMA ELASTASE INHIBITOR.—Since the discovery of pancreatic elastase and the presence of a serum inhibitor by Baló and Banga (1949), interest in these enzymes has centred in their role in the ageing process and atherosclerosis. Raised elastase inhibitor levels in patients with the EDS were first reported by Hall, Keech, Reed, Saxl, Tunbridge, and Wood (1955), and Goltz and Hult (1965) also reported raised levels in two patients.

On the other hand, Carter and Walford (1963) found normal levels in seven patients.

Method.—The determination was by the method described by Hall (1962) and Dr Hall also kindly provided the elastin and elastase for the estimations. Plasma samples were prepared from citrated blood and they were then stored in liquid nitrogen. Normal age-matched controls were estimated concurrently with the specimens from thirty EDS patients.

The mean value of the percentage inhibition of a standard mixture of elastin and elastase was 40·7 per cent. (range 33 to 53) in the patients and 38·3 per cent. (range 25 to 50) in the age-matched normal control subjects.

Comment.—Hall (1962) has shown that elastase exists in two forms with differing sensitivities to the elastase inhibitor. The preparation of enzyme and subtrate is therefore of great importance, and a comparison between the results of different workers is impossible unless methods of preparation are standardized. In the present investigation Hall's method and preparations were used. The results showed no significant difference between the controls and the patients, and are within Hall's normal range (Hall, 1968).

(3) URINARY MUCOPOLYSACCHARIDES.—Acid mucopolysaccharides form part of the ground substance of connective tissue. They are excreted in normal urine mainly as chondroitin and heparatin sulphates, and in certain connective tissue disorders their excretion rate is raised. In this investigation the urines of the patients with the EDS were screened for excess mucopolysaccharide excretion.

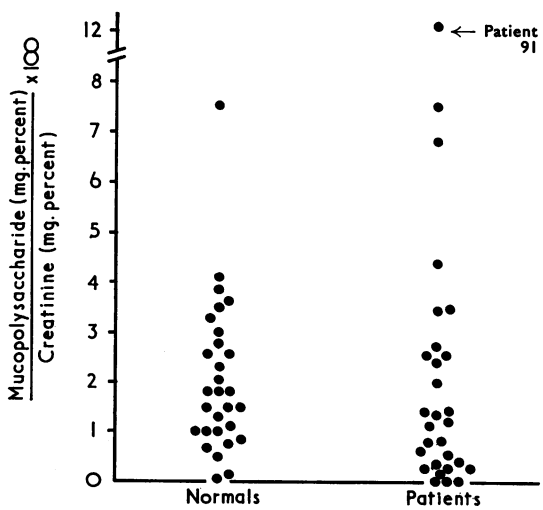

Fig. 14.—Distribution of mucopolysaccharide values in normal controls and Ehlers-Danlos patients.

Method.—Urine samples from 29 patients were examined and compared with thirty normal age-matched controls. The method was that of Levin (1968) based on the use of CTAB (cetyl trimethyl ammonium bromide). The spectrophotometer was calibrated using known solutions of chondroitin sulphate. The results are shown in Fig. 14.

Camment.—There is no statistically significant difference between the values for controls and EDS patients.

However, Levin (1968) takes a value of four as the upper limit of normal and four patients and one control had values greater than this. In particular, the level in Patient 91 was repeatedly very high. There is no obvious explanation for these high results and a more detailed investigation of these patients might be worthwhile.

(4) URINARY CHROMATOGRAPHY.—Certain genetically-determined conditions are characterized by abnormal urinary amino-acid chromatograms. As McKusick (1966) pointed out, these tend to be conditions inherited as autosomal recessive traits rather than by the autosomal dominant mode of transmission usually found in the EDS. It was thought worthwhile to examine the urinary chromatograms of the EDS patients, for the large number of apparently sporadic patients in the series might have been due to the operation of the former mechanism of inheritance.

Method.—32 one-way chromatograms and fifteen two-way chromatograms were developed. Butanol acetic acid and phenol ammonia solutions were used as solvents and colour development was with cadmium acetate/ninhydrin solution.

All the urines showed an essentially normal pattern, with well-defined spots for glycine, serine, glutamine or glutamic acid, histidine, and alanine. All the two-way chromatograms also showed a threonine spot.

Comment.—Although the threonine spot is considered an intermittent normal finding it is worthy of note, as Badanoiu and Teodoresco (1966) also found augmented levels in a serum chromatogram in a patient with the EDS.

Colour development for hydroxyproline and hydroxylysine (Smith, 1960) was negative.

Conclusions.—The failure to find any biochemical abnormalities in these investigations clarifies the field to some extent but does little to suggest where the basic lesion in the EDS might lie. Collagen turnover was normal in the series and the plasma elastase inhibitor did not seem to be responsible for any changes in elastic tissue metabolism.

There was no significant difference in the results of the biochemical investigations between patients with the various types of the EDS, and further studies are required to develop a satisfactory biochemical diagnostic indicator.

Haematological Aspects

The majority of affected patients have a bleeding diathesis. This may be mild, consisting simply of a tendency to bruise easily, or it may be severe, with the occurrence of haematoma formation and bleeding from the nose, gut, lungs, and urogenital tract.

The bleeding diathesis is quite distinct from spontaneous arterial rupture, although it is most severe in the patients with the Ecchymotic type of the EDS, who are also liable to arterial catastrophes.

Present Investigation.—Previous studies of the bleeding tendency have given contradictory results, possibly because the investigators were examining patients with different types of the EDS. For this reason the coagulation mechanisms of patients representing all the five types of the EDS were investigated. The results obtained, which were essentially normal, are shown in Table IV.

Discussion.—The cause of the bleeding in the EDS is still a matter for speculation, but capillary fragility, as demonstrated by the tourniquet test has often been described (Pascher and Kanof, 1953; Samuels, Schwartz, and Meister, 1953; Packer and Blades, 1954; Frick and Krafchuk, 1956; Rubinstein and Cohen, 1964). It has been suggested that the liability of the capillary vessels to rupture is due to a defect in the surrounding supporting connective tissue (Day and Zarafonetis, 1961). On the other hand, Wigzell and Ogston (1963) found that the capillaries of their two patients were able to withstand a negative pressure to a greater extent than a series of normal control subjects.

A defect of the coagulation mechanism may also exist, and an elevated thromboplastin generation was found in two patients by Bruno and Narasimhan (1961). Two patients with deficient plasma thromboplastin were investigated by Lisker, Noguerón, and Sánchez-Medal (1960) and, from the clinical descriptions, it is likely that they had the Ecchymotic type of the EDS. Defects in clot retraction and platelet function were demonstrated in several affected members of a kindred by Goodman, Levitsky, and Friedman (1962). The patient described by Self (1967), who had "an abnormal fibrinolytic mechanism", also possibly had the EDS. A deficiency of the Hageman factor was found in the patient described by Fantl, Morris, and Sawers (1961), but this abnormality was probably inherited independently from the EDS. Abnormal platelet structure and aggregation in patients with the EDS has been reported by Kashiwagi, Riddle, Abraham, and Frame (1965), and Worth Estes (1968) found abnormally large platelets in affected patients. However, the electron microscopic studies of the latter did not reveal any abnormality of platelet ultrastructure.

In distinction to all these findings, a comprehensive investigation into the coagulation mechanism in four affected members of a Negro kindred revealed no abnormality (Day and Zarafonetis, 1961). Normal results were also obtained by Summer (1956), Tucker, Miller, and Jacoby (1963), and Golden and Garret (1964).

Comment.—The bleeding diathesis in the EDS is probably due to a varying combination of capillary fragility, clotting mechanism defect, and platelet abnormality. The present investigation has not demonstrated any consistent abnormality in patients with the various types of the EDS.

TABLE IV
COAGULATION TESTS IN THIRTEEN CASES OF THE EHLERS-DANLOS SYNDROME

Case No.	Family	Type of EDS	Prothrombin Time Ratio (Normal = 1·0 to 1·2 sec.)	Partial Thromboplastin Time Difference (Normal = <6 sec.)
100	54, III-2	X-linked	1·1	+0·5
93	53, IV-1	X-linked	1·0	+0·8
90	50 { II-7	Ecchymotic	1·0	−13·0
91	50 { III-15	Ecchymotic	1·0	−6·0
36	24, II-1	Mitis	1·0	−3·0
41	26, III-3	Mitis	1·1	+2·2
12	5, III-1	Gravis	0·9	+1·5
21	14, II-6	Gravis	0·9	−1·2
4	2, III-3	Gravis	0·9	+2·0
13	6, IV-4	Gravis	1·1	−3·0
9	4, IV-1	Gravis	1·0	0·5
18	11, III-5	Gravis	1·1	0·0
14	7, II-2	Gravis	1·1	−4·5

Partial thromboplastin times were also carried out in 1·20 dilutions of plasma in Haemophilic and Christmas plasmas. Normal results were obtained.

Chromosome Investigation

McKusick (1964) stated: "It is possible, furthermore, that certain very rare syndromes that are transmitted in a Mendelian manner are the result of small chromosome aberrations, such as deletion or inversion, affecting the action of several genes." On this basis, chromosome analysis was carried out in the leucocytes from seventeen patients, representing each of the five types of the EDS, in an attempt to find a constant abnormality.

Method.—Leucocytes from peripheral blood samples were cultured according to the method of Moorhead, Nowell, Mellman, Battips, and Hungerford (1960) and were harvested after 3 days. The chromosomes in about fifty metaphase cells from each patient were counted to ascertain the modal number, and approximately fifteen of these cells were fully analysed. The results are shown in Table V.

Results.—The modal number in each case was 46 and in eight patients, one cell with an abnormal karyotype was found. Two of these had an extra acentric fragment, but they appeared to be otherwise normal. The abnormalities in the other six cells included translocations, a pericentric inversion, and supernumerary chromosomes.

TABLE
CHROMOSOMAL ANALYSIS IN SEVENTEEN CASES OF THE

Case No.	Family	Type of EDS	Age (yrs)	Sex	Total No. of Cells Counted	No. of Chromosomes						
						<44	44	45	46	47	48	>48
4	2, III-3	Gravis	28	F	50	1	2	3	44			
12	5, III-1	Gravis	49	M	50		1	2	46			1
13	6, IV-4	Gravis	30	F								Culture 1
21	14, II-6	Gravis	28	M	50	4	1	5	39			1
18	11, III-5	Gravis	20	M	50			2	48			
88	45, III-5	Benign	14	M	50		1	4	45			
7	3, II-3	Gravis	48	F	50			3	47			
85	42, II-4	Benign	31	F	50			1	49			
47	32, III-3	Mitis	44	F	50			3	47			
93	53, IV-1	X-linked	19	M	51			2	49			
40	26 II-1	Mitis	51	F	50		1	5	43	1		
41	26 III-3	Mitis	15	M	50	3		5	42			
100	54 III-2	X-linked	22	M	50	2		5	42			
99	54 III-1	X-linked	36	M	49			4	44			1
90	50 II-7	Ecchymotic	29	F	50	1	1	4	44			
91	50 III-15	Ecchymotic	8	M	50		2	5	43			
1	1, III-1	Gravis	29	M	51				51			
				M	50		1	5	44			
				F	50	2		1	47			
	Normal Controls (young adults)			M	50		2	4	44			
				M	50	1	1	4	44			
				M	50		2	3	45			
				M	44	2		4	38			

A fair proportion of aneuploid cells was found, particularly cells with 45 chromosomes. These were examined to rule out the possibility of mosaicism but, as they showed random loss of chromosomes, it was probable that they had occurred for technical reasons.

Six phenotypically normal people were studied as controls during the period of investigation. Again, the modal number in each case was 46 and no consistent abnormality was detected in the karyotypes.

Discussion.—There are few reports of other studies of the chromosomes in the EDS. The chromosomes of the peripheral blood of three related patients with the EDS were found to be normal by Pommerening and Antonius (1966), and in another family chromosome analysis in two related patients affected by the EDS and in a third unaffected relative did not reveal any significant abnormality (Green, Friedman-Kien, and Banfield, 1966).

Large satellites on Group D and G chromosomes were reported in two patients with Marfan's syndrome by Tjio, Puck, and Robinson (1960). However, when Handmaker (1963) found similar satellites in a normal family, it was suggested that these changes were not specifically related to Marfan's

V
EHLERS-DANLOS SYNDROME AND IN SIX NORMAL CONTROLS

Cells with Chromosomal Gaps/Breaks	No. of Cells Analysed	No. of Cells with Abnormal Karyotype	Nature of Abnormalities
	15		
1	15	1	One poorly-spread cell with 46 normal chromosomes + 3 extra acentric chromosomes
failed twice			
6	16	1	One cell with 3 No. 1 chromosomes, an extra group C and group E chromosome: a group D chromosome was missing
2	15	1	In one cell part of a group D chromosome has been translocated onto another group D
3	15		
	15		
	15		
2	15	1	Possible translocation of part of a No. 2 chromosome onto a group D chromosome in one cell
1	16		
3	16		One cell had 47 chromosomes with a supernumerary group G
3	16		
4	15	1	One cell had an extra acentric fragment which possibly constitutes part of an apparently partially deleted No. 1 chromosome
3	16	1	One cell with 46 normal chromosomes + an acentric fragment
3	16		
2	20		
2	16	1	One abnormal cell with a pericentric inversion in a No. 2 chromosome; also a group C missing and an extra chromosome resembling the No. 16s
2	15	1	In one cell a group C is partially deleted—possibly broken at the site of secondary constriction
	15		
3	15		
1	15	1	One cell had a group C chromosome missing and had an extra acentric chromosome
	15		
1	13		

syndrome. As Marfan's syndrome and the EDS are probably both related disorders of collagen tissue, the chromosomes in our series were inspected for such satellites. Those seen were considered to be within normal limits.

A case of the EDS occurring together with the *cri du chat* syndrome in a newborn male infant was reported by Vissian, Manasséro, Blaive, and Borja (1955). Chromosome analysis revealed the characteristic loss of part of the short arm of chromosome five. The authors pointed out the similarity between certain features of both these syndromes and suggested that this case might serve to locate the genes controlling mesenchyme development. The parents of the child were clinically normal and chromosome studies revealed no abnormality of their cells.

Comment.—The cases studied constituted a good clinical cross-section of the syndrome. Occasional variations and abnormalities of the chromosomes were noted. However, it is concluded that there is no *consistent* chromosomal abnormality in any of the various types of the Ehlers-Danlos syndrome.

SUMMARY

The results of an examination of one hundred patients with the Ehlers-Danlos syndrome suggest that there are five distinct and clinically recognizable varieties of the condition.

The incidence of complications differs in these variants of the syndrome. In particular, one group of patients are at great potential risk from sudden death from vascular accidents.

A form of the condition which is transmitted as an X-linked character exists. Complications are few in this variant.

The results of biochemical, haematological, and chromosomal investigations in patients with all forms of the syndrome were essentially normal.

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Les variations du syndrome de Ehlers-Danlos

RÉSUMÉ

Les résultats de l'examen de 100 malades atteints du syndrome de Ehlers-Danlos suggèrent qu'il y a cinq formes distinctes cliniquement reconnaissables de cette affection.

L'incidence des complications diffère dans chaque forme du syndrome. En particulier, un groupe de malades court un très grand risque de mort subite causée par des accidents vasculaires. Une variété de cette affection qui est transmise par un chromosome X associé existe. Les complications de cette forme sont peu nombreuses.

Les résultats des examens biochimiques, hématologiques et chromosomiques des malades atteints de toutes les formes du syndrome étaient tout a fait normaux.

Variantes del síndrome Ehlers-Danlos

SUMARIO

Los resultados de un examen de cien pacientes con el síndrome de Ehlers-Danlos sugieren que existen cinco variedades, distintas y clínicamente identificables, de esta afección.

La incidencia de las complicaciones difiere en estas variantes del síndrome. En particular, un grupo de pacientes está en riesgo de muerte repentina a causa de accidentes vasculares.

Existe una variante de esta afección que se transmite por un cromosoma X asociado. Las complicaciones son pocas en esta variante.

Los resultados de las investigaciones bioquímicas, hematológicas y cromosomales en pacientes con todas las formas del síndrome fueron fundamentalmente normales.

APPENDIX

CLINICAL CHARACTERISTICS OF 100 AFFECTED PATIENTS

Degree of severity of joint mobility, skin extensibility, scarring, and bruising tendencies are scored 0-5

EDS Gravis (Families 1-22) (Cases 1-32)

Case No.	Family	Sex	Age (yrs)	Joint Mobility	Skin Extensibility	Scarring	Bruising	Molluscoid Pseudotumours	Subcutaneous Spheroids	Prematurity	Other Features
1	1 III-1	M	29	5	4	3	3	–	–	+	Dissected aorta
2	1 IV-1	F	3	5	4	3	3	–	+	+	Inguinal hernia
3	2 II-1	F	51	5	3	2	2	–	–	–	Thoracic deformity
4	2 III-3	F	28	5	3	4	2	+	+	–	Thoracic deformity
5	2 IV-3	F	4	5	3	2	2	–	–	–	
6	2 IV-4	M	2	5	3	2	2	–	–	–	
7	3 II-3	F	48	5	3	3	3	+	–	–	Spinal deformity Arterial bleeding at operation
8	3 III-5	F	9	4	3	1	2	–	–	–	Umbilical hernia
9	4 IV-1	M	15	5	4	4	2	–	–	–	Inguinal and umbilical hernia
10	4 IV-2	F	11	4	2	2	2	+	–	–	
11	5 II-4	M	82	4	4	4	3	+	+	–	Multiple subluxed and arthritic joints Incisional hernia
12	5 III-1	M	49	4	4	4	3	+	+	–	Talipes Lumbar kyphoscoliosis
13	6, IV-4	F	30	5	3	3	3	–	+	–	Lumbar kypnosis
14	7, II-2	M	31	5	3	4	2	+	–	–	
15	8, II-8	F	31	4	4	3	2	+	+	–	Umbilical hernia
16	9, II-4	F	4	5	3	4	3	–	+	–	Congenital dislocation of hips Talipes Umbilical and inguinal hernia
17	10, II-1	F	18	5	3	3	3	+	–	–	Pectus excavatum
18	11, III-5	M	20	5	4	4	4	+	+	+	Gross thoracic deformity
19	12, III-8	M	4	5	2	2	3	–	–	–	
20	13, III-4	F	7	5	3	4	3	+	+	–	
21	14, II-6	M	28	4	5	3	2	+	–	–	
22	15, III-3	M	36	4	4	3	3	–	–	+	Deep haematomata Friable tissues at operation
23	16 III-12	F	23	5	5	3	3	–	+	+	
24	16 IV-1	M	1	5	4	0	2	–	–	–	
25	17 II-3	M	35	3	4	4	3	+	+	+	
26	17 III-1	F	8	3	4	3	3	–	–	+	
27	17 III-2	M	5	3	4	2	3	–	–	–	
28	18, II-1	M	21	5	3	5	3	–	–	+	Talipes
29	19, II-1	F	38	5	3	4	3	+	–	–	Multiple miscarriages Ante-partum haemorrhage
30	20, II-4	M	25	4	5	5	4	+	+	–	Gross lumbar kyphosis Severe facial scarring
31	21, III-1	F	35	5	5	2	1	–	+	+	Acro-osteolysis
32	22, III-4	M	28	4	4	2	2	–	–	–	Pectus excavatum

EDS Mitis (Families 23-39) (Cases 33-77)

Case No.	Family	Sex	Age (yrs)	Joint Mobility	Skin Extensibility	Scarring	Bruising	Molluscoid Pseudotumours	Subcutaneous Spheroids	Prematurity	Other Features
33	23 II-1	F	30	3	2	2	2	–	–	–	Multiple miscarriages
34	23 III-6	F	21	4	2	2	2	+	+	–	Complete heart block
35	23 III-9	F	14	4	2	2	2	+	+	–	
36	24 II-1	F	50	3	3	3	2	–	+	–	Dorsal kyphosis
37	24 III-1	M	24	3	3	2	2	+	+	–	
38	24 III-2	F	20	2	2	1	1	–	–	–	
39	25, III-2	F	28	4	2	1	1	–	–	–	Multiple miscarriages
40	26 II-1	F	51	1	3	2	2	–	–	–	Fixed flexion deformity of first metacarpophalangeal joints
41	26 III-3	M	15	1	3	1	1	–	–	–	
42	27, II-2	M	52	3	2	0	0	–	–	–	
43	28, IV-9	M	13	3	1	0	2	–	–	–	
44	29, III-4	F	19	3	3	2	2	–	–	–	
45	30, II-4	M	33	3	3	1	1	–	+	–	
46	31, II-1	F	20	3	1	1	1	+	–	–	
47	32, III-3	F	44	3	1	1	1	–	–	–	Dorsal scoliosis
48	33, III-5	M	18	1	3	3	3	+	–	–	
49	34, III-2	M	21	1	3	3	1	+	+	–	
50	35, III-4	M	23	1	1	2	1	–	–	–	Talipes Umbilical hernia
51	36, II-1	M	25	1	4	3	2	–	–	–	
52	37 II-1	M	21	2	4	2	2	+	+	–	
53	37 IV-2	F	7	3	2	2	2	–	+	–	
54	38 IV-4	F	28	0	1	2	1	–	–	–	
55	38 V-1	M	5	0	1	1	1	–	–	–	
56	38 III-16	F	48	3	1	2	1	–	–	–	
57	38 IV-21	M	28	3	1	1	2	+	+	–	
58	38 V-12	M	14	2	1	2	1	–	–	–	
59	38 V-13	F	11	3	1	1	2	+	–	–	
60	38 IV-23	F	36	3	1	1	1	–	–	–	
61	38 V-16	M	10	1	1	1	1	–	–	–	
62	38 III-2	F	59	5	1	2	1	+	–	–	
63	38 IV-19	M	37	2	2	2	1	–	–	–	
64	38 V-9	M	8	1	1	1	1	+	–	–	
65	38 V-10	M	5	0	1	0	1	+	–	–	
66	38 III-9	F	63	0	1	1	1	+	–	–	
67	38 IV-5	F	42	2	2	2	1	–	–	–	
68	39 IV-1	F	29	3	1	2	1	+	–	–	
69	39 II-15	M	84	0	1	1	3	–	–	–	
70	39 IV-10	F	32	0	1	1	1	+	–	–	
71	39 V-14	M	8	2	1	2	2	+	–	–	
72	39 IV-8	F	27	3	1	2	1	+	–	–	
73	39 V-9	M	5	0	1	2	2	–	–	–	
74	39 III-5	F	58	0	2	2	2	–	–	–	
75	39 IV-6	F	27	2	1	2	4	–	–	–	
76	39 III-3	M	62	0	1	1	1	–	–	–	
77	39 III-2	F	59	0	1	2	1	–	–	–	

EDS Benign Hypermobile (Families 40-45) (Cases 78-88)

Case No.	Family	Sex	Age (yrs)	Joint Mobility	Skin Extensibility	Scarring	Bruising	Molluscoid Pseudo-tumours	Subcutaneous Spheroids	Prematurity	Other Features
78	40 II-4	F	63	3	2	1	2	–	+	–	Incisional hernia Dislocated hip Subluxed shoulders
79	40 III-6	M	27	4	1	1	0	–	–	–	
80	40 III-1	F	43	5	2	0	1	–	–	–	
81	40 IV-1	M	22	4	0	0	0	–	–	–	
82	40 IV-2	M	20	4	2	0	0	–	–	–	
83	40 III-3	F	40	5	1	0	1	–	–	–	
84	41, II-5	F	28	5	4	0	1	–	–	–	
85	42, II-4	F	31	5	4	1	2	–	–	–	
86	43, II-4	M	41	4	3	0	0	–	–	–	Inguinal hernia
87	44, III-2	M	7	5	4	1	1	–	–	–	
88	45, III-5	M	14	4	5	1	2	+	–	–	Initially diagnosed as Oppenheim's disease

EDS Ecchymotic (Families 49-51) (Cases 89-92)

Case No.	Family	Sex	Age (yrs)	Joint Mobility	Skin Extensibility	Scarring	Bruising	Molluscoid Pseudo-tumours	Subcutaneous Spheroids	Prematurity	Other Features
89	49, III-2	F	53	0	0	2	5	+	–	–	Father, brother and sister died of arterial rupture or intestinal perforation Inguinal hernia Severe bleeding at operation
90	50 II-7	F	29	0	1	5	5	–	–	–	Gross bruising
91	50 III-15	M	8	0	1	3	4	–	–	–	
92	51, III-2	F	18	2	1	2	3	+	+	–	Menorrhagia

EDS X-linked (Families 53-54) (Cases 93-100)

Case No.	Family	Sex	Age (yrs)	Joint Mobility	Skin Extensibility	Scarring	Bruising	Molluscoid Pseudo-tumours	Subcutaneous Spheroids	Prematurity	Other Features
93	53 IV-1	M	19	1	2	1	1	+	–	–	Recurrent knee joint effusions
94	53 IV-2	M	18	0	3	1	1	+	–	–	Recurrent knee joint effusions
95	53 IV-4	M	11	0	3	1	1	–	–	–	
96	53 II-6	M	50	0	3	0	0	+	–	–	
97	53 III-5	M	25	0	3	0	0	–	–	–	
98	53 IV-3	M	14	1	2	1	0	–	–	–	
99	54 III-1	M	36	1	4	1	3	+	+	–	Deep haematomata
100	54 III-2	M	22	1	3	0	2	+	+	–	Recurrent shoulder dislocations