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RHEUMATOLOGICAL MANIFESTATIONS OF SYSTEMIC DISEASE

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M. I. V. JAYSON, *Guest Editor*

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Foreword

The first issue of this new series, *Clinics in Rheumatic Diseases*, is devoted to some unusual arthropathies and other rheumatological manifestations associated with systemic disease.

Fifty years ago, rheumatic complaints were dealt with primarily by orthopaedic surgeons as localised or traumatic lesions (and many of them are), or by Spa doctors as ill defined derangements helped by mud and water. Since the 1930s, in more sophisticated areas, rheumatology has emerged as a branch of general medicine concerned with the disorders of the locomotor system. This has led to collaboration with specialists in many related fields, particularly orthopaedic surgery, and required an understanding of problems in endocrinology, cardiology, gastroenterology, nephrology, neurology, haematology, dermatology, metabolic diseases, respiratory and infectious diseases, immunology, genetics, paediatrics and geriatrics.

In this issue, from a large number of systemic diseases with rheumatic manifestations, I have chosen a few which are either comparatively little known, or about which new data have accumulated. Since almost all diseases have some systemic manifestations, some very interesting topics and systemic diseases have had to be omitted. Throughout this book emphasis is placed on the rheumatological aspects of disease, since these aspects have often been neglected by the speciality concerned; for the same reason, the contributors are authorities on their own subject but in the main, also rheumatologists.

Most of the chapters mention genetic susceptibility. This plays a major role in classic diseases such as sickle cell anaemia and ochronosis, but its role in many other diseases, less obviously metabolic, such as ankylosing spondylitis and Reiter's disease is being actively pursued. An attempt has been made to include mention of the study of penetrance and triggering factors, of localisation and chronicity. The locomotor complications of infection have been omitted, but Whipple's disease is included, as are the results of neoplastic disease and an example of the so-called 'connective tissue diseases', systemic lupus erythematosus, where joint manifestations are often evident, if not usually severe.

I have been pleased and surprised that so many busy people have felt able

to contribute. This is I think a measure of the interest of these boundary fields to medicine. Finally, my sincere thanks are due to Mr Inglis and the editorial staff of W. B. Saunders, who by their kind, patient and expert assistance made my task much easier than I had anticipated.

E. G. L. BYWATERS

1

Rheumatic Manifestations of Heritable Disorders of Connective Tissue

M. F. KAHN
S. DE SEZE

In this chapter, we shall describe the rheumatic manifestations, essentially articular, of a certain number of diseases of connective tissue.

It is difficult to define exactly the 'heritable disorders of connective tissue'. It is worthwhile noting that authoritative authors who have studied these diseases extensively, such as MacKusick (1966), MacKusick and Scott (1971) and Beighton (1973), are very wary of giving such a definition. In 'heritable diseases of connective tissue' these authors have included not only those diseases which involve one of the basic constituents of general or of specialised connective tissue (bone or cartilage), but also disorders in which an abnormal metabolite, that does not originate from connective tissue (e.g., alkaptonuria), is deposited. Contrary to this, however, Dupuytren's contracture received little attention although it is definitely a problem of connective tissue, and seems hereditary. It is therefore to a large extent arbitrary as to whether a disease is included in 'heritable disorders of connective tissue' or not.

We would like to remind the rheumatologist here of the principal characteristics of this group of diseases, especially those which he is most likely to encounter. We have therefore selected those disorders which may clinically manifest rheumatic symptoms: the Ehlers–Danlos syndrome, Marfan's syndrome, articular hypermobility syndrome, pseudoxanthoma elasticum, achondroplasia, fibrodysplasia ossificans progressiva, mucopolysaccharidosis, multiple epiphyseal dysplasia and spondylo-epiphyseal dysplasia, Paget's disease, and Dupuytren's contracture. Some other disorders which may be of marginal interest to the rheumatologist are summarised in Table 1.

EHLERS–DANLOS SYNDROME

The term Ehlers–Danlos (ED) syndrome covers a group of disorders characterised by skin hyperelasticity and fragility, by loose-jointedness and by various visceral anomalies, all due to the insufficient tensile strength of tissues

Table 1. *Five heritable, infrequently occurring diseases involving the connective tissue and presenting rheumatological symptoms*

Disease or syndrome	General manifestations	Rheumatological manifestations	Genetic inheritance	Reference
Multiple exostosis	Multiple exostosis (osteochondromas), impaired bone growth	Limit to joint movement, irritation of tendons or bursae, nerve compressions, secondary osteoarthrosis	Autosomal-dominant	Maroteaux and Lamy (1960)
Osteogenesis imperfecta	Multiple fractures, deafness	Articular consequences of mal-repaired fractures	Autosomal-dominant, sometimes recessive	Albright and Grunt (1971)
Nail-patella syndrome	Nail atrophic dysplasia, knee dysplasia with small patella-lliac horns, nephritis	Dislocation of patella, osteoarthrosis of the knees	Autosomal-dominant	Duncan and Souter (1963)
Dyschondrosteosis	Mesomelic dwarfism, deformation of the wrist (Madelung type)	Osteoarthrosis of the wrist	Autosomal-dominant	Weil (1965)
Werner's syndrome	Scleroderma, skin ulcers, calcinosis, juvenile cataract	Scleroderma, subcutaneous calcifications, stiff joints	Autosomal-recessive	Epstein et al (1966)

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containing elastic fibres. The disease has been known for centuries. As to whether credit for the first description of the disease should be attributed to Ehlers and Danlos is debatable. The Russian, Tschernogobow, seems to have made a very complete description in 1891, but the present name of the syndrome has become fixed through usage. In our description of the syndrome we have borrowed a great deal from MacKusick's study of 30 families (1966, 1971), and from Beighton's study of 100 cases (Beighton and Horan, 1969).

General description

The skin of these patients is hyperelastic; the patients can stretch it to an astonishing length at times. Released, the skin returns to its normal position. The skin is fragile, it tears even with minimal trauma and scars slowly and poorly, especially after surgery. The scars are slack on the surface, their depth is shallow and they are often pigmented because of haemorrhagic phenomena in the area (Figure 1).

Easy bruisability is the rule. The mucous membranes of these patients bleed easily. Acrocyanosis often exists and chilblains occur frequently. At pressure points adjacent to 'papyraceous' scars and surrounding telangiectases, mollu-

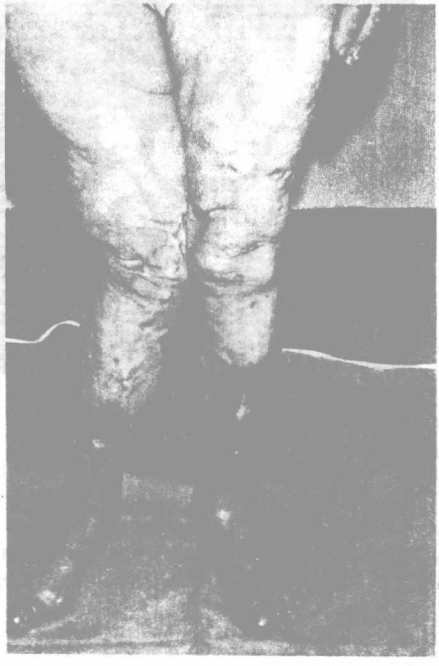

Figure 1. J.V., a 60-year-old woman. Typical appearance of lower limbs in a case of Ehlers Danlos syndrome. Notice joint hypermobility (genu valgum), skin fragility, and multiple scars and varicosities. This patient also had severe acrocyanosis. Blood coagulation was normal on an extensive study. Six other individuals known to have ED syndrome in her family. Two died of acute vascular accidents.

scoid pseudotumours can exist; they can also be found disseminated throughout the skin. These tumours are made up of fat and tend to calcify.

In addition to easy bruisability due to the fragility of the walls of small blood vessels in the skin, certain patients have various anomalies of coagulation (Beighton and Horan, 1969) which can cause, along with the vascular anomalies, internal haemorrhages.

The hyperextensibility of the joints is often spectacular, especially in young patients. They can completely hyperextend their fingers and maintain extraordinary positions ('pretzelman') with legs crossed behind the neck (Figure 2). This loose-jointedness results in effects on the locomotor apparatus that we will come to later.

Figure 2. J.B., a 51-year-old man. Extreme hypermobility in a case of ED syndrome. Skin hyperelasticity was minor. This patient had a marked pectus excavatum. He also had ankylosing spondylitis, with bilateral sacro-iliitis and typical spine lesions. He was HL-A W 27+. Nevertheless, his articular hypermobility was not complicated by coincidental arthritis.

The visceral manifestations consist of internal hernias, intestinal diverticulosis, and urinary and cardiac malformations. Dissecting aneurysms of the aorta can be found. Various ocular complications, not easily classifiable, are also possible.

Variants of the Ehlers–Danlos syndrome

Thanks to the important study made on a series of patients by Beighton et al (1969), the manifestations of the disease can be grouped into five types:

the severe type represents 32 per cent of the cases, the intermediate type, 45 per cent, the benign type, 11 per cent, the ecchymotic type, four per cent, the hereditary sex-linked type, eight per cent. The majority of orthopaedic and rheumatic complications described below are observed in the severe type. In their review of 100 cases, Beighton and Horan (1969) ascertained the frequency of these complications. Their results, summarised in Table 2, show

Table 2. *Orthopaedic and rheumatic manifestations in 100 patients with the Ehlers–Danlos syndrome*

Symptoms	Number of patients and affected site
Hypermobility	63 with 3+ criteria present[a]
Dislocations	26: fingers (7) elbows (3) shoulders (10) temporo-mandibular (2) patella (8) sterno-clavicular (7) hips (2)
Chronic hydrarthrosis	19, also hypermobility present
Joint instability	20 (15 with hypermobility)
Vertebral anomalies	20
Thoracic anomalies	22: scoliosis (18, 6 severe) pectus excavatum (8) costo-chondrial anomalies (5)
Foot deformations	59: flat-feet (52) equino-varus (7) 10 operated for hallux valgus
Muscular cramps	43
Osteoarthrosis	20

[a] See criteria for diagnosis of hypermobility, page 12.
Table reproduced from Beighton and Horan (1969) with the permission of the authors, and the Editor, *Journal of Bone and Joint Surgery.*

that, besides the purely orthopaedic problems (dislocations), the rheumatologist may be consulted for: chronic hydrarthrosis (present in 20 patients), muscular cramps (present in 43 patients), 'frequent' bursitis of the olecranon or patella, cramps and deformations of the feet (seven cases of talipes equinovarus, 52 cases of flat feet, often very marked). Painful hallux valgus was frequent, sometimes with bursitis, and was brought to surgery in ten cases. Claw toes were present in 20 cases. Of 22 patients aged over 40, 16 had modifications of one or more joints, and six were normal (all six belonged to the benign type of ED syndrome). Ten patients had knee complaints, usually unilateral (Figures 1 and 3), and five had arthrosis of both hands, involving the thumbs in particular. Two patients had painful ankles and one had bilateral arthrosis of the shoulders. Only two patients were severely invalid: one, a male of 82 years confined to a wheelchair with osteoarthrosis of the spine, the knees, the elbows and the hands; the other, a female of 63 years, especially handicapped by her shoulders. Lumbar pain was rare in this series, occurring in only six patients, although 23 had a clinically visible spinal deformation. We

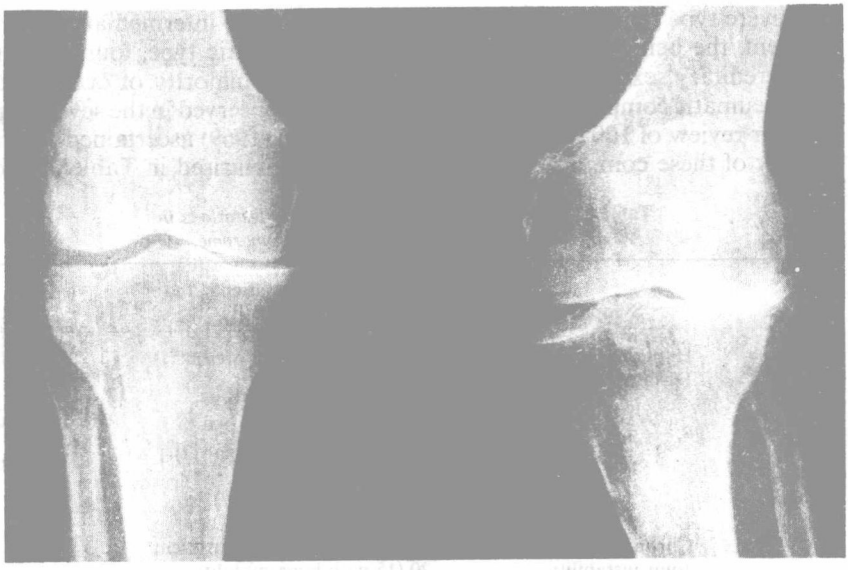

Figure 3. Same patient as Figure 2. X-rays of both knees, showing severe secondary osteoarthrosis of the left knee. Arthrosis was the presenting symptom. Wrists, fingers and feet were also affected.

must draw attention to the fact that the bone solidity of these patients did not seem to be affected at all. The authors did not note any pathological fractures.

Physiopathology and treatment

In the majority of these cases the inheritance of the ED syndrome seemed autosomal-dominant, but a sex-linked variety has been described which is characterised by a predominance of cutaneous symptoms, with the possibility of orthopaedic complications.

No abnormality, either chromosomal, biochemical, or anatomical (light or electron microscopy), has been definitely demonstrated to be the cause of the ED syndrome. Neither the study of serum elastase inhibition, or of the urinary excretion of hydroxyproline, have been fruitful.

One of the earlier hypotheses postulates that the basic cause of the syndrome is an abnormality in the interweaving of the collagen fibrils: instead of being largely anastomosed by molecular interconnections, they may be independent of each other. Certain histological results from the skin studies seem to favour this hypothesis. If the basic defect lies in the cross-linking of the collagen fibrils, we still do not know if it is due to an amino acid substitution in the polypeptide chain of the collagen molecule, or to a functional defect in the cross-linking.

In treating the orthopaedic and rheumatic manifestations an attempt must be made to avoid surgery. The difficulties of surgical intervention involve not just the tegument, but the whole ensemble of organs and tissues.

Treatment should therefore be preventive, conservative and symptomatic. Children having this syndrome should avoid violent sports, but it is not desirable to forbid all physical activity and sport. Overweight should be controlled.

The deformation of the feet can be alleviated by the use of individually adapted soft-soled shoes. One tries to promote muscular development to maintain the joints hypermöbile and prevent repeated dislocations. The treatment of juvenile scoliosis should be undertaken early enough to avoid the possible rapid development of severe changes in the spine.

If joint effusions or haemarthroses occur, rest, postural plaster casts, and anti-inflammatory drugs (salicylates and non-steroid drugs) should be used for short-term treatment.

MARFAN'S SYNDROME

This syndrome was described by Marfan in 1896, after observing just one case, a girl five years old. This child was seen to have a 'pronounced elongation of bone, with a certain degree of tapering; this deformation was more prominent at distal extremities rather than proximal'.

The frequent ocular and cardiovascular manifestations which also characterise this disease must be noted. The patients are generally thin and tall, and their limbs are elongated especially distally (dolichostenomelia). This elongation is striking in the hands and has led to the use of such names as arachnodactyly (spider fingers). The big toe is often very long. Various indices have been proposed for describing the dysmorphia in a precise fashion: the length of the longest digit is usually one and one-half times that of the corresponding metacarpal. The length of the patellar ligament is exaggerated. The most useful index according to MacKusick (1966) is the ratio of the lower segment of the body (pubic symphysis to the floor) to the upper segment. However, the indices only have a relative value. There is a considerable overlap with values for normal subjects.

In addition, a kyphoscoliosis often exists. The thoracic cage can be deformed by rib elongation, taking on the appearance of a pigeon-breast, or hollowed out as in pectus excavatum (Figure 4). The skull is dolichocephalic, the palate arched, the face narrow, and there can be prognathism. The subcutaneous fat is scarce, the musculature is underdeveloped, and a hyperlaxity of ligaments exists, consequences that we will see later on.

Thus the complete forms are easily recognisable by their very characteristic clinical aspects, but each of these characteristics may be missing in some forms, in which the visceral manifestations and hereditary character still support the authenticity.

The ocular involvement is characterised by ectopia lentis (ectopic lens), usually bilateral. This ectopia can advance to subluxation or complete dislocation. It is clinically significant in approximately two-thirds of the cases, but if one looks at incomplete forms under a slit-lamp, with maximal mydriasis, and in those cases with associated malformations of the iris, it is almost a constant feature. Other ocular findings can be present, either complications

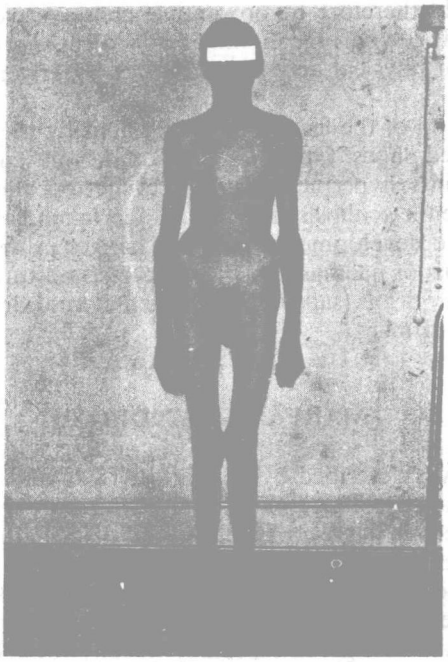

Figure 4. R.D., a 25-year-old man. Typical Marfan's syndrome with dolichostenomelia, arachnodactyly, and subluxation of both lens. Notice deformation of thorax ('pigeon breast'), of feet, and genu valgum. The presenting symptom was mechanical pain in both knees and lower back.

of the ectopic lens, or independent abnormalities involving the cornea, corneal–iris angle, or retina. They are too specialised to be discussed here.

The cardiovascular involvement is of major diagnostic importance. It is the most frequent cause of early death in these patients, and is due to degeneration of the media in the aorta and pulmonary arteries. It can become symptomatic early in life and lead to frank angina. An aneurysmal dilatation of initial intrapericardiac portions of the aorta, at the level of the sinus of Valsalva, can develop. The aortic insufficiency produced by this dilatation results in auscultatory and phonocardiographic findings.

The major, often fatal, complication is dissecting aneurysm. Certain patients do, however, survive for many years, and surgical intervention is possible. Other malformations, coarctation and aneurysms of the abdominal aorta can also be seen. Many diverse anomalies have also been described in the pulmonary arteries, the coronary arteries, the myocardium and the veins.

The skin of patients with Marfan's syndrome may show pale striae and small tumours made up of elastic fibres (elastomas).

Rheumatic manifestations

In addition to kyphoscoliosis, which can be painful, pain is principally the result of ligamentary hyperlaxity. Genu valgum or recurvatum, very

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