**Formes frustes** of Marfan's syndrome presenting with severe aortic regurgitation

*Clinicogenetic study of 18 families*


*From the National Heart Hospital and Cardiothoracic Institute, London; and Departments of Cardiology, Ophthalmology, and Biology as Applied to Medicine, The Middlesex Hospital and Medical School, London*

Eighteen patients who presented with severe aortic regurgitation and dilatation of the ascending aorta were found to be formes frustes of Marfan's syndrome and formed the basis for this clinicogenetic study. All had aortic valve replacement and reconstruction of part of the ascending aorta. The diagnosis was confirmed by histological examination of the aortic tissue.

There were 126 first degree relatives; 85 were living and 67 (78.8%) of these were examined. Limited information was available about 32 of the 41 relatives who had died. No relative had the classical clinical features of Marfan's syndrome but stigmata of the disease were found in 25 (37.3%) of the 67 first degree relatives examined. In 21, the abnormality was confined to the cardiovascular system, the skeleton, or the eye, but in 4, abnormalities involved 2 systems.

Cardiovascular abnormalities affecting the aortic valve or aortic wall were present in 6 (9.0%) of the 67 first degree relatives examined. One or more of the skeletal indices measured (height-span difference, metacarpal index, phalangeal index) was abnormal in 18 (26.9%) and ocular abnormalities were found in 5 of 31 (9.8%) examined. There were no relatives with dislocation of the lens or iridodonesis.

Using strict diagnostic criteria, a minimum of 37.3 per cent of the first degree relatives examined were affected; this involved 12 of the 18 families studied. There was nothing in our data to suggest that the formes frustes of the disease had a different mode of inheritance from the classical syndrome.

The eponym, Marfan's syndrome is used to describe a genetically determined disorder of connective tissue affecting the skeleton, cardiovascular system, and eye. The clinical picture has evolved since the original account by Marfan (1896) when he used the name 'dolichesternomelia' to describe unusually long and slender extremities. The term 'arachnodactyly' was introduced later by Achard (1902) who also noted the familial incidence. Ocular abnormalities were described by Bürger (1914) and Ormond and Williams (1924) but it was not until 1943 (Baer et al.) that the cardiovascular components of the syndrome were recognized.

Marfan's syndrome may be readily diagnosed when the classical features are present but formes frustes are difficult to detect and define. Here, a single abnormality may be present such as isolated aortic regurgitation or a dislocated ocular lens; or there may be several minor and occult defects, each of which is difficult to detect. This is particularly the case when minor abnormalities are confined to the skeletal system.

The present study was undertaken to determine the nature and frequency of the stigmata of Marfan's syndrome in first degree relatives of 18 propositions who were examples of the formes frustes, each presenting clinically with severe aortic regurgitation. The mode of inheritance in these families was also studied.

**Subjects and methods**

Eighteen patients with severe aortic regurgitation and varying degrees of dilatation of the ascending aorta seen at the National Heart Hospital and Hammersmith Hospital between November 1965...
and October 1972 form the basis of this study. All were examples of the *formes frustes* of Marfan’s syndrome. In none was the aetiopathological diagnosis made before operation though it was suspected in 7. All had aortic valve replacement (Starr-Edwards prosthesis) and reconstruction of part of the ascending aorta with ‘teflon’ or ‘dacron’ grafts. The diagnosis of Marfan’s syndrome was confirmed as a result of histological examination of the aortic tissue obtained at operation.

As in previous studies (Emanuel et al., 1968, 1971, 1975), arrangements were made to interview the propositus or a close relative at home and a family pedigree was drawn up which included all first and second degree relatives and first cousins. Relevant information when available on more distant relatives was also recorded. During the interview, specific questions were asked to ascertain whether any relative was known to have abnormalities involving the heart, skeleton, or eye.

All the propositi who were alive and all first degree relatives who were willing to co-operate were examined at either the Middlesex Hospital, National Heart Hospital, or a convenient regional hospital. This involved a physical examination, chest radiographs (PA and lateral), an electrocardiogram, ophthalmological assessment, skeletal measurements of height and span, and the necessary radiographs for the calculation of the metacarpal index (MI) and the phalangeal index (PI). Phonocardiograms and echocardiograms were also carried out in those with questionable cardiovascular abnormalities.

Measurements of the height and span were considered abnormal if the span exceeded the height by 7-6 cm or 3 inches (Pearson and Lee, 1902; Sinclair et al., 1960). The metacarpal index (the ratio between the total axial length of the second, third, fourth, and fifth metacarpals of the right hand and the total breadth of the same metacarpals at their mid points) was measured as described by Sinclair (1958) and Sinclair et al. (1960). A ratio of 8·4 or more was considered abnormal; doubtful values between 8·0 to 8·3 (Sinclair, 1958; McKusick, 1972) were excluded. The phalangeal index (the ratio of the length of the proximal phalanx of the right ring finger and its minimum width) was considered abnormal if in excess of 4·6 for men and 5·6 for women (Parish et al., 1960). In order to decrease observer error, the metacarpal and phalangeal indices were calculated independently by 2 of us, and where differences existed after a second assessment, an average was taken.

The following skeletal features known to be associated with Marfan’s syndrome were also noted but were not considered diagnostic: kyphoscoliosis, vertebral abnormalities, long ribs, clavicles, and toes, pectus excavatum, pectus carinatum, and the straight back syndrome (Twigg et al., 1967).

**Results**

(a) **PROPOSITI**

Of the 18 propositi, 16 were men and 2 were women, their ages ranging from 28 to 61 years, with a mean of 44·7 years. The clinical features and operative details are summarised in Table 1.

<table>
<thead>
<tr>
<th>Pedigree no.</th>
<th>Sex</th>
<th>Age (y)</th>
<th>Surgical findings* in addition to AR and dil. asc. ao.</th>
<th>Wt (kg)</th>
<th>Ht (cm)</th>
<th>Span (cm)</th>
<th>Ht-span difference (cm)</th>
<th>MI</th>
<th>PI</th>
<th>Ocular syndrome</th>
<th>Date of op.</th>
<th>Date of death</th>
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<td>BAV</td>
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<td>173</td>
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<td>156</td>
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<td>4·3</td>
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<td>13.4.72</td>
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<td>Aneu. des. ao.</td>
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<td>167·5</td>
<td>177·8</td>
<td>-10·3‡</td>
<td>7·5</td>
<td>4·3</td>
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<td></td>
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<td>NAD</td>
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<td>169</td>
<td>176·5</td>
<td>+2·5</td>
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<td>3·9</td>
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<td>BAV</td>
<td>83·9</td>
<td>179·8</td>
<td>190·5</td>
<td>-10·7†</td>
<td>7·5</td>
<td>4·3</td>
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<td>MR</td>
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<td>4·3</td>
<td>NAD</td>
<td>7.4.70</td>
<td>13.4.72</td>
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</tbody>
</table>

*All had aortic Starr valve replacement and ‘teflon’/‘dacron’ grafts. †Stigma of Marfan’s syndrome.

AR, aortic regurgitation; DIS. asc. ao., dilated ascending aorta; MI, metacarpal index; PI, phalangeal index; BAV, bicuspid aortic valve; Coarct., coarctation of aorta; ASOV, aneurysm of sinus of Valsalva; Aneu. des. ao., aneurysm of descending aorta; DIS. asc. ao., dissection of descending aorta; MB, mitral regurgitation; NAD, nothing abnormal (pertaining to Marfan’s syndrome) detected.
At the time this study started, 11 propositi were living and 7 were dead; 3 died during the study so that at the time of writing 8 were alive with a postoperative follow-up which varied from 3.4 to 9.8 years, with a mean of 5.5 years. Of the 10 who died, there were 2 operative deaths (within 1 month of operation) and 8 late deaths with an average survival of 4.3 years.

In addition to severe aortic regurgitation and varying degrees of dilatation of the ascending aorta, 5 of the propositi had a bicuspid aortic valve, 2 had aneurysms of the sinuses of Valsalva, and 2 had coarctation of the aorta; there was also a single example of each of the following: dissecting aneurysm of the ascending aorta, aneurysm of the abdominal aorta, and mitral regurgitation.

Information about the skeletal and ocular abnormalities among the propositi was incomplete. Limited skeletal data were available in 11. Height and span measurements were obtained in 10 and were abnormal in 5. The metacarpal index was measured in 10 and was abnormal in 1. The phalangeal index was measured in 8 and was normal in all. Thus, there was a single abnormal skeletal index in 6 of the 11 propositi examined.

The 11 propositi alive at the beginning of the study had a detailed ophthalmological assessment, and no ocular abnormality relevant to Marfan’s syndrome was found (Table 1).

(b) FIRST DEGREE RELATIVES
In the 18 families, there were 126 first degree relatives (36 parents, 57 sibs, 33 children), 85 of whom were living and 67 (76.8%) of these were examined (4 parents, 34 sibs, and 29 children). Limited information was available on 32 of the 41 who had died. In 12 of the 18 families there was more than one affected member (Table 2).

One or more of the stigmata of Marfan’s syndrome was present in 25 (37.3%) of the 67 living first degree relatives examined (3 parents, 10 sibs, and 12 children).

In 21 of these relatives, the abnormality was confined to the cardiovascular system, the skeleton, or the eye, but in 4, abnormalities involved two or more of these systems. None of the relatives examined had the classical features of Marfan’s syndrome.

(i) Cardiovascular abnormalities (Table 2)
Abnormalities in the cardiovascular system compatible with Marfan’s syndrome were found in 8 first degree relatives (6 living, 2 dead). Six showed dilatation of the ascending aorta on chest radiograph; 2 of these had additional aortic regurgitation and 1 a bicuspid aortic valve on clinical grounds. The seventh died from a dissecting aneurysm of the ascending aorta which was confirmed at necropsy and the eighth who was reported to have died from aortic regurgitation was a member of a family in which 3 more distant relatives had aortic aneurysms. Two of these 8 relatives had additional skeletal abnormalities (Table 2, Pedigree No. 13; III. 4, and IV. 8).

In addition to these 8, there were 5 with cardiovascular signs of doubtful significance. Four had an isolated ejection murmur, either aortic or pulmonary, without a preceding ejection sound and one a late apical systolic murmur. All 5 had phonocardiograms and echocardiograms but in none was there confirmatory evidence of either bicuspid aortic valve or prolapse of the mitral valve. Investigations involving invasive techniques were considered unjustified. In 2 of these 5 relatives however, there were skeletal abnormalities compatible with Marfan’s syndrome (Table 2 Pedigree No. 13, IV. 7; Pedigree No. 17, III. 13).

A further 3 first degree relatives had cardiovascular disease of uncertain aetiology, 2 had died and there was no necropsy, the third who was living and had cardiac failure refused detailed examination (see Fig. Pedigree Nos. 11:II. 7; 15:II. 6; 15:III. 5).

(ii) Skeletal abnormalities (Table 2)
Sixty-seven first degree relatives had skeletal surveys. The height-span measurement was obtained in all 67 and was abnormal in 12 (17·9%). The metacarpal index and phalangeal index were measured in 53 relatives. The metacarpal index was abnormal in 9 (17·0%) and the phalangeal index in 5 (9.4%).

Eighteen first degree relatives showed one or more skeletal abnormality. A single abnormal skeletal index was present in 11 (height-span difference in 7; metacarpal index in 2; phalangeal index in 2), 2 abnormal indices were present in 6, and all 3 skeletal indices were abnormal in 1. Of these 18 relatives with skeletal abnormalities, 2 had associated cardiovascular abnormalities (Table 2 Pedigree No. 13: III.4, and IV.8) and a further 2 had ocular defects (Table 2, Pedigree No. 8: IV.3 and No. 13: IV 6). An additional 8 first degree relatives had a MI between 8.0 and 8.3, not in itself diagnostic, but as 2 had additional ocular abnormalities they were probably examples of Marfan’s syndrome (Table 2, Pedigree No. 9: II.10, No. 16: IV.4).

Other less specific and less objective skeletal features found in 24 (35.8%) relatives included mild scoliosis in 8, unduly long slender ribs and clavicles in 6, long toes (especially the great toe) in 5, pectus excavatum in 3, and a straight back in 2.
Formes frustes of Marfan's syndrome

Fig. Pedigrees of the first degree relatives in the 12 affected families. The numbering takes into account the existence of more distant relatives who have not been included in this study.
(iii) **Ocular abnormalities (Table 2)**

A total of 51 first degree relatives had a detailed ophthalmological assessment by one of us (P.A. MacF.). Abnormalities compatible with Marfan's syndrome were found in 5 and included a single example of each of the following: spherophakia with severe myopia, hypoplasia of the iris, bilateral retinal detachment with severe myopia, bilateral ciliary degeneration, and peripheral retinal degeneration with myopia. Of these 5 cases, 2 had

<table>
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<tr>
<th>Pedigree no.</th>
<th>Sex</th>
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<th>Cardiovascular abnormalities</th>
<th>Musculoskeletal abnormalities</th>
<th>Additional abnormalities</th>
<th>Ocular abnormalities</th>
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<td>73.7</td>
<td>—</td>
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</tr>
<tr>
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<td>—</td>
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<td>NAD</td>
<td>34.7</td>
<td>137.3</td>
<td>NAD</td>
</tr>
<tr>
<td>17:IV.4</td>
<td>F</td>
<td>9</td>
<td>NAD</td>
<td>30.8</td>
<td>134.5</td>
<td>NAD</td>
</tr>
<tr>
<td>18:III.6</td>
<td>M</td>
<td>45</td>
<td>Rupt. asc. ao. an. (PM)†</td>
<td>—</td>
<td>—</td>
<td>NAD</td>
</tr>
<tr>
<td>18:IV.9</td>
<td>M</td>
<td>28</td>
<td>NAD</td>
<td>67.9</td>
<td>186.8</td>
<td>NAD</td>
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<tr>
<td>18:IV.12</td>
<td>M</td>
<td>14</td>
<td>NAD</td>
<td>46</td>
<td>166.5</td>
<td>NAD</td>
</tr>
</tbody>
</table>

**General:** MI, metacarpal index; PI, phalangeal index; NAD, nothing abnormal (pertaining to Marfan's syndrome) detected; †, dead relative; *second or third degree relative; otherwise first degree; ‡, stigma of Marfan's syndrome; clav., clavicles.

**Cardiovascular:** Dil. asc. ao., dilated ascending aorta; Rupt. abd. ao. an., ruptured abdominal aortic aneurysm; AR, aortic regurgitation; Ao. ESM, aortic ejection systolic murmur; Rupt. ao. arch an., ruptured aortic arch aneurysm; PM, post mortem; DC, death certificate; BAV, bicuspid aortic valve.

**Ocular:** Bil. cyst. deg., bilateral ciliary degeneration of retina; peri. ret. deg., peripheral retinal degeneration; Bil. ret. det., bilateral retinal detachment.
additional cardiovascular or skeletal abnormalities (Table 2 Pedigree No. 8:IV.3; and No. 13:IV.6).

A further 17 had ocular defects that were not specifically related to Marfan's syndrome, such as simple refractive errors, cataracts (congenital and acquired), and fundal abnormalities. Two of these relatives had scattered dot opacities in their lenses. There were no relatives with dislocation of the lens or iridodonesis.

(c) Second and third degree relatives (Table 2)

Information about these more distant relatives was fragmentary, but 4 were considered to have cardiovascular evidence of Marfan's syndrome. Three died of ruptured aneurysms (2 dissecting aneurysms of ascending aorta, 1 ruptured descending aorta), and all had necropsies. The fourth had an abdominal aortic aneurysm and was treated surgically.

Discussion

The term formes frustes implies that either all the classical features which include abnormalities of the skeleton, cardiovascular system, and eye are not present, or if they are, they are in a minor or subtle form not easily detected. The term is, therefore, imprecise and to some extent dependent on the awareness of the clinician who uses it. Some authors have confined the diagnosis of Marfan's syndrome to patients with 2 or more of the classical features (Wilmer and Finby, 1964; Hirst and Gore, 1973). Bowers (1969) considered that the manifestations of Marfan's syndrome could be divided into major and minor features, the former being disorders of the ocular lens and a positive family history and the latter skeletal stigmata, cardiovascular abnormalities, and an increased excretion of urinary hydroxyproline. He restricted the term Marfan's syndrome to those patients who had at least one major and one minor manifestation of the disease.

Cardiovascular manifestations of the formes frustes are commonly aortic regurgitation with or without dilatation or dissection of the ascending aorta. Less common cardiovascular abnormalities include coarctation of the aorta (Eldridge, 1964b), dilatation or aneurysm of the sinuses of Valsalva (Tobin et al., 1947; Steinberg et al., 1957; Papioannou et al., 1961), bicuspid aortic valve (Soman et al., 1974), abnormalities of the mitral and tricuspid valves (Shankar et al., 1967; McKusick, 1972), including the floppy valve syndrome (Read et al., 1965; Sherman et al., 1970; McKusick, 1976), and the systolic click-late systolic murmur syndrome (Salomon et al., 1975; Bon Tempo et al., 1975). Atrial and ventricular septal defects (Ellis, 1940; Tolbert and Birchall, 1956), persistent ductus arteriosus (Anderson and Pratt-Thomas, 1953), Fallot's tetralogy (McKusick, 1955), aneurysm of the pulmonary artery (Lillian, 1949; Simon et al., 1965), and coronary artery involvement (Becker and Van Mamtgem, 1975) have also been described. The frequency of bicuspid aortic valve in Marfan's disease is unknown, which is in part because of the difficulty in making a clinical diagnosis even after angiocardioangiography and echocardiography (Feizi and Ruzic, 1976). In this series, 5 of the 18 propositi (27·8%) had a bicuspid valve, an unusually high incidence which may well reflect the mode of selection of the propositi, for all had severe aortic regurgitation requiring surgery, thus allowing inspection of the aortic valve in each case.

The practical importance of recognizing Marfan's syndrome presenting with isolated aortic regurgitation is threefold. First, progressive dilatation of the ascending aorta with or without dissection is common whereas it is rare in aortic regurgitation from other causes. Secondly, if aortic valve replacement is required, there are special hazards relating to the lack of connective tissue support; these include excessive haemorrhage, rupture of the aortic suture lines and secondary dehiscence of the inserted valve (Symbas et al., 1970; Nasrallah et al., 1975). Thirdly, it has been suggested that propranolol (Halpern et al., 1971; McKusick, 1976) or reserpine (Wheat et al., 1965; Murdoch et al., 1972), if used sufficiently early, may delay progressive dilatation of the aortic root. In cases of aortic regurgitation of doubtful aetiology, measurement of simple skeletal indices such as height span difference, metacarpal and phalangeal indices, and an ophthalmic examination may be helpful and lead to the correct aetiologic diagnosis. This was done retrospectively in 11 of the propositi after the diagnosis had been confirmed from histological examination of the aorta, and in 6 (54-5%) one of the skeletal indices was abnormal but none had ocular defects. Early recognition of the correct diagnosis may also be important when the skeleton is involved, for McKusick (1972) has raised the possibility of initiating puberty early in girls with oestrogen-progesterone treatment in order to control adult height and minimize the risk of severe scoliosis in later life.

None of the propositi or affected first degree relatives had the classical musculoskeletal features of Marfan's syndrome which again emphasizes the importance of looking for the less obvious stigmata and, if possible, establishing an objective method of
measuring them. Skeletal indices are prone to observer error, which is minimized when measurements are obtained from radiographs, as with the metacarpal and phalangeal indices: the former is probably the most reliable skeletal index (Eldridge, 1964a) particularly if the stricter criteria of ratios in excess of 8:4 are used. Parish et al. (1960) however considered the phalangeal index more specific, but this is not universally accepted (Eldridge, 1964a; McKusick, 1972). Direct clinical measurements of the height, span, and upper and lower body segments are more subjective; this is particularly so in respect of the last and is the reason for its omission in the present study. The reliability of the height span difference has been claimed by some authors (Pearson and Lee, 1902) but others have reservations unless it is used in conjunction with additional indices as in this study (Sinclair et al., 1960). In this context, age is important, for both the height span difference and the ratio of the upper and lower body segments are less reliable during the growing period and after middle life when degrees of kyphoscoliosis tend to distort measurements. The importance of measuring several skeletal indices is well illustrated in this series, for of the 18 first degree relatives with skeletal abnormalities only 7 (38:9\%) had more than one abnormal index.

The classical ocular abnormalities in Marfan's syndrome include a characteristic pattern of dislocation of the lens, which is typically small and globular (spherophakia) and may be associated with coloboma and localized nonprogressive dot opacities, iridodonesis, hypoplasia of the iris, poor dilatation of the pupils, secondary glaucoma from persistence of mesodermal elements in the draining angle of the anterior chamber, and various forms of peripheral degeneration and detachment of the retina (Duke-Elder, 1964).

In this study, 5 (9:8\%) relatives had ocular defects which were thought to be directly related to Marfan's syndrome. This excluded 2 relatives with scattered dot opacities of the lens, a feature occasionally associated with the syndrome (Duke-Elder, 1964). A further 17 relatives had ocular defects which were considered unrelated, which included 7 with myopia, 5 with hypermetropia, and astigmatism, 3 with lenticular abnormalities (including the 2 with scattered dot opacities), 1 with optic disc abnormalities, and 1 with hypertensive retinopathy. Seven of these 17 (41:2\%) relatives, however, had cardiovascular or skeletal abnormalities of the formes frustes of Marfan's syndrome, but these did not include the 2 relatives with scattered dot opacities of the lens. Once again this draws attention to the difficulty of interpreting isolated ocular abnormalities in the formes frustes of the disease.

Genetic implications and Conclusions

Marfan's syndrome is a congenital disorder of connective tissue transmitted as an autosomal dominant. The fact that only 25 (37:3\%) of the 67 living first degree relatives who were examined were affected rather than the expected 50 per cent may be the result of a number of factors, the most relevant probably being underdiagnosis of the less evident manifestations and the strict criteria used in this study. For example, if a metacarpal index of 8:0 rather than 8:4 had been accepted as it is by some authors, a further 6 relatives would have been included, and if the ocular abnormality of scattered lenticular dot opacities had also been considered compatible with Marfan's syndrome a further 2 would have been accepted bringing the total of affected first degree relatives to 33 (49:3\%). Another factor accounting for the limited number of first degree relatives affected could be the early deaths of those with Marfan's syndrome, as our information about the 41 who had died was incomplete. Furthermore, the appearance of some clinical abnormalities in the cardiovascular system and eye are age related in spite of being genetically determined. In some of the younger first degree relatives, therefore, abnormalities may have been present but undetected. Finally, Bowers (1959) suggested that the fertility rate and ability to transmit the disease differed in the two sexes; affected males averaged only 1/11 as many children and 1/23 as many affected offspring as affected females. If this is correct, it may be relevant to the present study as 16 of the propositi were males and only 2 females.

There was nothing in our clinical data to suggest that the formes frustes had a different mode of inheritance from the classical syndrome. However, it is probable that we are looking at some of the pleiotropic effects of a single gene. Until the biochemical lesion has been determined, which may be in collagen or elastin biosynthesis, it is impossible to discuss the pleiotrophy in realistic terms as has been done for other collagen disorders such as the Ehlers-Danlos syndrome and osteogenesis imperfecta (McKusick, 1976).

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Formes frustes of Marfan's syndrome


Requests for reprints to Dr. R. Emanuel, Cardiothoracic Institute, 2 Beaumont Street, London W1N 2DX.
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R Emanuel, R A Ng, J Marcomichelakis, E C Moores, K E Jefferson, P A MacFaul and R Withers

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