Symptomatic Valvular Myxomatous Transformation
(The Floppy Valve Syndrome)

A Possible Forme Fruste of the Marfan Syndrome

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VALVULAR insufficiency in the young patient is commonly labeled rheumatic even though all too frequently little specific supporting evidence is available. This problem of differential diagnosis has interested a number of clinicians1–3 and was brought to our attention recently when we encountered patients suffering from valvular incompetence who, either at surgery or autopsy, demonstrated myxomatous transformation of the aortic and mitral valves. Evidence to be presented suggests that this valvular degeneration results in loss of substance and prolapse of the leaflets. Moreover, there is a peculiar predisposition to bacterial endocarditis, which in itself tends to suggest previous rheumatic disease. The lesion may be congenital and possibly represents a forme fruste of the Marfan syndrome. In addition, in a case of idiopathic dilatation of the ascending aorta that came to surgery the accompanying aortic insufficiency was the result of myxomatous transformation of the cusps rather than the aneurysmal involvement of the aortic root.

Case Reports

Mitral Insufficiency with Myxomatous Valvular Transformation

The three women in this category presented with the classical signs and symptoms of mitral insufficiency, which was also demonstrated by angiocardiography. Each suffered from pulmonary hypertension with recurrent congestive failure. They had become refractory to digitalis, diuretics, and low-salt regimens. None showed evidence of mitral stenosis or intracardiac calcification. Electrocardiographic findings were nonspecific, indicating primarily both left atrial and left ventricular dilatation and hypertrophy. Studies of the aortic valve and coronary circulation revealed no abnormality. There was no history of rheumatic fever and laboratory tests for both rheumatic and syphilitic activity were negative. The cardiovascular findings are summarized in table 1. The operative details and their postoperative courses are described below.

Case 1

L.J. (no. 506304) a middle-aged Negro woman was chronologically the last of the series. The diagnosis of uncomplicated floppy valve syndrome was suspected, on the basis of exclusion, despite her normal appearance. Cardiac output was markedly diminished, and angiographic dye persisted long after the usual disappearance time in the left atrium and aorta. Open-heart surgery revealed grossly normal mitral leaflets, which, however, had drooped into the ventricular cavity as if by their own weight. When lifted up with forceps there was more than enough substance for coaptation. The chordae were intact, delicate, and of normal length. The cusps were thicker than usual with a cartilagenous translucency. There was neither calcification nor fibrosis. Both leaflets were excised, and a no.-3 Starr-Edwards ball valve was inserted. Stitches tended to tear out of the annulus, which was not dilated. Her postoperative course was initially satisfactory but 5 weeks following surgery she suddenly developed acute congestive failure and died. Autopsy revealed dehiscence of the prosthesis for one third of its circumference. Microscopic examination of the excised leaflets demonstrated myxomatous transformation (figs. 1 and 2). Femoral artery biopsy showed arteriosclerosis.

Case 2

E.H. (no. 343669) (fig. 3) a waitress, was
Skeletal Measurements in Patients with Myxomatous Valvular Transformation

<table>
<thead>
<tr>
<th>Patient</th>
<th>Race &amp; sex</th>
<th>Age</th>
<th>Cranial index</th>
<th>P*</th>
<th>Palate*</th>
<th>Patellar lig. (in.)</th>
<th>Actual wt. (lb.)</th>
<th>Predicted wt. (lb.)</th>
<th>Ht. (in.)</th>
<th>Span (in.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. (L.J.)</td>
<td>N.F.</td>
<td>48</td>
<td>79</td>
<td>—</td>
<td>HA</td>
<td>3½</td>
<td>172</td>
<td>160</td>
<td>67</td>
<td>68</td>
</tr>
<tr>
<td>2. (E.H.)</td>
<td>N.F.</td>
<td>35</td>
<td>85</td>
<td>—</td>
<td>N</td>
<td>2½</td>
<td>95</td>
<td>120</td>
<td>64</td>
<td>65½</td>
</tr>
<tr>
<td>3. (G.T.)</td>
<td>N.F.</td>
<td>17</td>
<td></td>
<td></td>
<td></td>
<td>95</td>
<td>110</td>
<td>63</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4. (B.M.)</td>
<td>N.F.</td>
<td>15</td>
<td>78</td>
<td>—</td>
<td>HA</td>
<td>2</td>
<td>104</td>
<td>115</td>
<td>64½</td>
<td>62</td>
</tr>
<tr>
<td>5. (T.J.)</td>
<td>N.F.</td>
<td>23</td>
<td>75</td>
<td>+</td>
<td>HA</td>
<td>2</td>
<td>98</td>
<td>113</td>
<td>64</td>
<td>68</td>
</tr>
<tr>
<td>6. (W.K.)</td>
<td>N.M.</td>
<td>18</td>
<td>70</td>
<td>—</td>
<td>HA</td>
<td>2½</td>
<td>164</td>
<td>158</td>
<td>71</td>
<td>71</td>
</tr>
<tr>
<td>7. (R.S.)</td>
<td>W.M.</td>
<td>40</td>
<td>84</td>
<td>—</td>
<td>HA</td>
<td>3</td>
<td>141</td>
<td>166</td>
<td>72</td>
<td>74½</td>
</tr>
<tr>
<td>8. (H.L.)</td>
<td>N.M.</td>
<td>39</td>
<td>75</td>
<td>—</td>
<td>HA</td>
<td>3</td>
<td>176</td>
<td>180</td>
<td>72½</td>
<td>78</td>
</tr>
<tr>
<td>9. (O.W.)</td>
<td>N.M.</td>
<td>49</td>
<td></td>
<td></td>
<td></td>
<td>208</td>
<td>199</td>
<td>75</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Normal range: 75 > 2

*Prognathism and palatal arching determined subjectively. Normal range according to Sinclair et al., P, prognathism; N, normal; HA, high arched; MI, metacarpal index; PI, phalangeal index.

also well until adult life. Second to the last to be seen, her gracile appearance, pectus deformity, scoliosis, and joint hypermobility suggested, in the absence of other diseases, the possibility of myxomatous valvular transformation. The findings at operation, performed November 12, 1964, were similar to those in case 1. Diaphanous, normally contoured, mitral leaflets had prolapsed into the ventricle with some shortening of the chordae. Microscopically the cusps were infiltrated with fibromyxoid tissue (fig. 2). No arterial biopsy was obtained. A ball-valve prosthesis was inserted with some difficulty, since the annulus and left atrium tore easily. Her postoperative course was satisfactory.

Case 3

G.T. (no. 336150) was considered to have congenital heart disease because of the early onset of cardiac abnormality. After cardiac catheterization indicated isolated mitral insufficiency, her diagnosis was changed to rheumatic disease despite a lack of supporting evidence. Operation was performed on January 3, 1963, as a desperate measure. The mitral valve was represented by a few fragments of diaphanous tissue. The annulus and surrounding atrium held sutures poorly. A Starr-Edwards ball valve was inserted. She died 8 hours later. Autopsy revealed a 2-cm. aneurysm

Figure 1A

Photomicrograph, × 90, of the anterior leaflet of the mitral valve excised at the original operation in case 4. Note replacement of the normal architecture with myxoid material and some fibroblastic proliferation. A similar picture was seen in cases 1, 2, 3, and 5.
of the membranous septum. The aortic and mitral valve rings were normal in size, and the coronary ostia were in their usual position. The aortic cusps were attenuated. Both mitral and aortic leaflets were myxomatous without evidence of inflammation (figs. 1 and 2). Toluidine-blue stains showed an increase in mucopolysaccharide. Aortic and femoral artery walls were normal on section.

**Mitral Insufficiency, Myxomatous Valvular Transformation, and Bacterial Endocarditis**

The two young women in this group resembled those in the preceding category in that they also presented with the classical signs and symptoms of severe isolated mitral insufficiency. They also suffered from pulmonary hypertension with recurrent attacks of congestive failure. Similarly neither showed intracardiac calcification or evidence for a rheumatic etiology. However, although each was known to have a heart murmur in childhood, their cardiac symptomatology began at 7 and 23 years with attacks of pneumococcal and streptococcal endocarditis. Their clinical findings are summarized in table 1. The operative and pathologic details are described below.

**Case 4**

B.M. (no. 163482) (fig. 1), a high-school girl, underwent open-heart surgery on January 7, 1964. It was not until operation that any diagnosis other than postendocarditic change was considered. The left atrial endocardium was thickened. The chordae had disappeared from the central portion of the anterior leaflet, which was translucent in some areas. There was no fibrosis or calcification. The remaining chordae were of normal length and thickness. Microscopically, it was obvious that most of the collagenous structure of the cusps had been replaced with basophilic-staining mucoid material containing stellate fibroblasts (figs. 1 and 2).

### Table 1

<table>
<thead>
<tr>
<th>Span ht. (in.)</th>
<th>Upper segment (in.)</th>
<th>Lower segment (in.)</th>
<th>Lower segment - U segment (in.)</th>
<th>MI (av.)</th>
<th>PI (av.)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>34½</td>
<td>32½</td>
<td>2</td>
<td>7.7</td>
<td>4.6</td>
<td>Hypermobility of joints. No family history</td>
</tr>
<tr>
<td>1½</td>
<td>31½</td>
<td>32½</td>
<td>-1</td>
<td>7.5</td>
<td>4.8</td>
<td>Scoliosis, funnel chest, joint hypermobility, scant fat</td>
</tr>
<tr>
<td>-2½</td>
<td>33½</td>
<td>31½</td>
<td>-2</td>
<td>7.0</td>
<td>4.7</td>
<td>Normal appearance</td>
</tr>
<tr>
<td>4</td>
<td>30</td>
<td>34</td>
<td>4</td>
<td>9.75</td>
<td>6.7</td>
<td>Mod. hypermobility of joints, scoliosis</td>
</tr>
<tr>
<td>0</td>
<td>34½</td>
<td>36½</td>
<td>2</td>
<td>7.6</td>
<td>4.1</td>
<td>Well-developed muscles, athletic build</td>
</tr>
<tr>
<td>2½</td>
<td>34</td>
<td>38</td>
<td>4</td>
<td>8.3</td>
<td>4.5</td>
<td>Bluish sclerae, hyperextensibility of joints, pigeon chest, lack of subcutaneous fat</td>
</tr>
<tr>
<td>5½</td>
<td>34</td>
<td>38½</td>
<td>4½</td>
<td>7.6</td>
<td>5.1</td>
<td>Slight joint hypermobility</td>
</tr>
<tr>
<td>&lt; 2</td>
<td>&lt; 2</td>
<td>&lt; 7.9</td>
<td>&lt; 4.6 M</td>
<td>&lt; 5.6 F</td>
<td></td>
<td>Died before need for appropriate measurements was realized</td>
</tr>
</tbody>
</table>

Normal anterior leaflet mitral valve for contrast with figure 1A.
Special stain revealed an increase in mucopolysaccharide. Her postoperative course was satisfactory, with a reduction in heart size; however, 6 weeks later she suddenly developed dyspnea. Examination revealed the return of a marked precordial, pansystolic murmur. Chest x-rays showed cardiomegaly. On March 12, 1964, she was reoperated upon for recurrent mitral insufficiency. On opening the left atrium it was obvious that the valve had torn away from the mitral annulus anteriorly leaving a large defect measuring 2 by 2% cm. This was repaired and the second postoperative course was benign. Six months later she was doing well, had some fatigue after dancing or heavy exercise, but was much improved. The femoral artery biopsy was normal. Examination on January 6, 1965, however, revealed a new precordial systolic murmur suggesting the possibility of a second dehiscence. The patient has refused further investigation, as she has only minimal symptoms at this time.

Case 5
T.J. (no. 486348) was operated upon on June 10, 1964, under cardiopulmonary bypass. Incision of the left atrium revealed two ruptured chordae without fibrosis or calcification. The endocardium was thickened, and the mitral leaflets sagged into the ventricle and appeared translucent. They were excised, and a Starr-Edwards valve was inserted. Pathologic studies of the leaflets showed the remaining chordae to be normal in length, thickness, and insertion. The majority of the collagenous tissue was replaced by basophilic mucoid material with some thickening of the leaflet. Stellate

Figure 2A
Cystic changes in the excised mitral leaflet of case 5. No evidence of inflammation. Picture similar to cystic medial necrosis.

Figure 1C
Photomicrograph, × 90, chordae tendineae of case 1 to show myxomatous replacement.

Figure 1D
Normal chordae tendineae for contrast with figure 1C.
fibroblasts were present (figs. 1 and 2). Periodic acid-Schiff and toluidine-blue stains demonstrated an increase in mucopolysaccharide. The femoral artery biopsy showed that the media contained a considerable amount of basophilic mucoid substance in microcystic areas. Biopsy of the left atrium indicated that the thickening evident grossly resulted from myxomatous degeneration of the subendocardial tissue with an increase in mucopolysaccharide in this layer.

Aortic Insufficiency with Myxomatous Valvular Transformation

The three men in this category experienced the insidious onset of the classical signs and symptoms of aortic insufficiency in adolescence (W.K.) or adult life (R.S.), (H.L.). They had all been athletic and again had no previous rheumatic or other serious diseases. Their serology was negative. In each case, angiocardiography revealed marked aortic incompetence but a normal coronary circulation. There was no demonstrated abnormality in their mitral valves. Angina developed within a year or two after the diagnosis of aortic valve disease was made, and surgery was subsequently performed. Their clinical findings are listed in table 1, and the results of surgery are described below.

Case 6

W.K. (no. 94583) (fig. 3) is the counterpart in the aortic area to case 1. He was well developed, and his diagnosis was not suspected until the valve was seen at surgery. He was operated upon on September 24, 1963. There was slight narrowing of the ascending aorta 5 cm. above the valve. On opening the aorta, the aortic leaflets were seen to be of normal contour, but diaphanous and attenuated without dilatation of the annulus. There was no commissural fusion, calcification, or fibrosis. The coronary vessels arose normally. There was some beginning dilatation of the left sinus of Valsalva. Insufficiency appeared to be the result of prolapse of the leaflets, which were floppy and lacked their normal form rigidity. A Starr-Edward’s prosthesis was inserted. The postoperative course was satisfactory, and he was discharged 4 weeks later. Pathologic examination of the excised leaflets demonstrated myxomatous transformation without inflammation. The only collagenous tissue remaining was a thin, subendocardial zone (fig. 4). Histochemical technics indicated an increase in mucopolysaccharide.

Three months later he developed recurrent signs of aortic insufficiency. Angiography showed loosening of the prosthesis. This diagnosis was confirmed at the second operation on March 10, 1964, (6 months after the original procedure), when a new valve was substituted, the previous prosthesis having torn loose from the annulus in the acoronary quadrant. He became asymptomatic after this latter procedure, his heart returning to normal size. Aortic and femoral biopsies taken at this operation demonstrated Erdheim’s cystic medial necrosis (fig. 4). However, he suddenly redeveloped the signs and symptoms of aortic insufficiency during the first week of January 1965. Retrograde aortic angiography demonstrated dehiscence of the prosthesis in the region of the left coronary commissure with free regurgitation into the ventricle through that area. At the second reoperation on January 29, 1965, (9 months following the first reoperation) these roentgenographic observations were confirmed. The prosthesis had separated from the annulus for a distance of about a third of the circumference in the region of the left coronary orifice. There was a remarkable absence of fibrosis. The stitches were intact, but they had torn out. The valve was quite easily cut out from the attached circumference, and a MacGovern prosthesis was inserted without difficulty by coronary perfusion and cardiopulmonary bypass. The patient’s postoperative course was remarkably benign, and he again appears to have recovered without complication. An interesting addendum is that his midline scar was found at the last operation to be 2 inches wide. He had had no infection or other reason for the scar to be...
Case 7

R.S.’s (no. 502755) (fig. 3) bluish sclerae and his gracile appearance with thin long extremities made myxoid valvular disease a distinct possibility preoperatively, especially as there was no other reason for aortic incompetence. He was operated upon on October 22, 1964. The ascending aorta, which was normal in size, was opened under cardiopulmonary bypass. There was no dilatation of the sinuses of Valsalva or the aortic annulus. The coronary orifices arose normally. The cusps were wrinkled and prolapsed but when drawn together adequately filled the aortic orifice. They appeared to lack their usual rigidity and as a result of rolling and folding left a central defect. They were excised under coronary perfusion. Postoperative recovery was uncomplicated. Histologic examination of the valve leaflets demonstrated myxomatous degeneration. Both the aortic and femoral artery biopsies showed Erdheim’s necrosis (fig. 4).

Case 8

H.L. (no. 504160) (fig. 3) differed in one important characteristic from the preceding two members of this category. Fluoroscopy had revealed an aneurysm at the base of the aorta, and preoperatively this was considered to be the cause of his valvular incompetence. At surgery, however, although the femoral artery was twice its normal size and a fusiform aneurysm of the ascending aorta extended to the innominate artery, it did not involve the valve ring. Similarly, the sinuses of Valsalva were unaffected and the coronary arteries arose normally. The first inch of aorta remained undilated. The valve cusps were crinkled and curled, tending to retract and prolapse, leaving a central defect. Nevertheless, when approximated, they were normal in contour and there seemed to be more than the usual expanse of tissue. The valvular tissue was excised, a Starr-Edwards prosthesis inserted, and the aneurysmal portion of the aorta resected and replaced with a Dacron prosthesis. The patient recovered after an uncomplicated postoperative course. Histologic examination demonstrated myxomatous infiltration of the aortic valve leaflets (fig. 4) and

Figure 3

This picture portrays the six surviving members of the original group of nine patients who were demonstrated either at surgery or autopsy to have myxomatous transformation of the aortic or mitral valves. From left to right: case 2 (E.H.), case 4 (B.M.), case 5 (T.J.), case 6 (W.K.), case 7 (R.S.), case 8 (H.L.). The three women underwent mitral replacement; the men had aortic surgery. Note pectus excavatum in E.H., long extremities in T.J. and H.L., arachnodactyly in T.J., and the widened midsternal scar in W.K. The general appearance of these patients is obviously not characteristic of a mesodermal dystrophy.

so stretched. The sternum was strongly healed. This response of the skin wound seems to be a reflection of the mesodermal fault in this patient.
VALVULAR MYXOMATOUS TRANSFORMATION

Figure 4A
Myxomatous aortic cusp from case 6, × 90.
Erdheim’s medial necrosis of the ascending aorta and femoral artery.

Asymptomatic Myxomatous Transformation of the Aortic and Mitral Valves with Arterial and Aortic Aneurysms
Case 9
O.W. (no. 68961). This patient who has been previously reported, was included in the present study because autopsy revealed myxomatous change in the leaflets of both the aortic and mitral valves, which, however, during life had not been known to be incompetent. There was no dilatation of the aortic ring, the coronary orifices arose in normal position, and apart from the aortic rupture, which was responsible for the man’s death, there was no dilatation of the ascending aorta. Cystic medial necrosis was disseminated throughout the arterial tree. He had experienced four spontaneous ruptures of large arteries over the 15 months preceding his demise. His serology was negative. This man, the oldest of the whole series, differed in having no evident cardiac symptoms. Nevertheless he gave us the first indication that an individual without obvious mesodermal dystrophy could not only demonstrate a widely disseminated form of the Erdheim’s arterial lesion described in cases 5, 6, 7, and 8, but, in addition, demonstrate myxomatous valvular transformation.

Signs of the Marfan Syndrome
None of the nine patients had the typical

Figure 4B
Normal aortic leaflet for contrast with figure 4A.

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Figure 4C
Erdheim’s medial cystic necrosis in aortic wall, case 6, × 135.

Figure 4D
Femoral artery biopsy showing Erdheim’s necrosis in case 7.
### Table 2

**Cardiovascular Lesions in Patients with Myxomatous Valvular Transformation**

<table>
<thead>
<tr>
<th>Patient</th>
<th>Race &amp; sex</th>
<th>Age</th>
<th>Signs &amp; symptoms</th>
<th>Roentgenography</th>
<th>ECG</th>
<th>Cardiovascular abnormality</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. (L.J.)</td>
<td>N.F.</td>
<td>48</td>
<td>Ligature, PDA at age 42; subsequent dyspnea, hemoptysis, recurrent congestive failure, cardiomegaly, apical systolic murmur, gallop rhythm, pulmonary hypertension, chest pain</td>
<td>LVH, LA enlargement, massive MI</td>
<td>LBBB, LVH</td>
<td>Myxomatous transformation mitral valve</td>
</tr>
<tr>
<td>2. (E.H.)</td>
<td>N.F.</td>
<td>35</td>
<td>Murmur age 25. Congestive failure, fatigue, chest pain, systolic apical murmur</td>
<td>LA enlargement, massive MI</td>
<td>LAH, LV strain</td>
<td>Myxomatous transformation mitral valve</td>
</tr>
<tr>
<td>3. (G.T.)</td>
<td>N.F.</td>
<td>17</td>
<td>Murmur age 3; recurrent arrhythmia, congestive failure, chest pain, cardiomegaly, apical systolic and diastolic murmur</td>
<td>LVH, Giant LA, massive MI</td>
<td>AF, LVH</td>
<td>Myxomatous transformation mitral and aortic valves, aneurysm membranous septum</td>
</tr>
<tr>
<td>4. (B.M.)</td>
<td>N.F.</td>
<td>15</td>
<td>Murmur and cardiomegaly after bacterial endocarditis age 8. Congestive failure, chest pain, apical systolic murmur</td>
<td>LVH, LA enlargement, massive MI</td>
<td>LAH, LVH</td>
<td>Myxomatous transformation mitral valve, ruptured chordae and thickened endocardium. Re-op. at 9 weeks—disruption from annulus</td>
</tr>
<tr>
<td>6. (W.K.)</td>
<td>N.M.</td>
<td>19</td>
<td>Murmur age 7, syncope, fatigue, age 15. Angina, orthopnea, cardiomegaly, murmurs of AI and AS, dyspnea, age 17</td>
<td>LVH, massive AI</td>
<td>LVH</td>
<td>Myxomatous transformation aortic valve, dilated sinus of Valsalva, Erdheim's necrosis aorta and femoral artery. Re-ops., 6 months and 16 months due to disruption from annulus</td>
</tr>
<tr>
<td>7. (R.S.)</td>
<td>W.M.</td>
<td>40</td>
<td>Eighteen-month history dyspnea, angina, palpitation, cardiomegaly, murmurs AI and AS</td>
<td>LVH, massive AI</td>
<td>LVH</td>
<td>Myxomatous transformation aortic valve, Erdheim's necrosis femoral artery and aorta</td>
</tr>
<tr>
<td>8. (H.L.)</td>
<td>N.M.</td>
<td>39</td>
<td>Six-month history dyspnea, congestive failure, angina, cardiomegaly, murmurs AI and AS</td>
<td>LVH, dilatation, ascending aorta</td>
<td>LVH</td>
<td>Myxomatous transformation aortic valve, fusiform aneurysm ascending aorta, Erdheim's necrosis aorta and femoral artery</td>
</tr>
<tr>
<td>9. (O.W.)</td>
<td>N.M.</td>
<td>49</td>
<td>One-year history recurrent aneurysms of peripheral vessels, dissecting aneurysm ascending aorta</td>
<td>Normal</td>
<td>Normal</td>
<td>Asymptomatic myxomatous transformation aortic and mitral valves. Erdheim's necrosis of small, medium, and large arteries. Dissecting aneurysm ascending aorta</td>
</tr>
</tbody>
</table>
appearance of the Marfan syndrome (table 2). None was unusually tall, and ectopia lentis was absent. Case 5, however, did have spidery fingers and her metacarpal and phalangeal indices were in the abnormally high range seen in the Marfan syndrome, whereas the values in cases 7 and 8 were borderline, being still within the normal range. These three patients did, however, have elongated lower body segments and extended arm spans. Cases 1, 7, and 8 had unusually long patellar ligaments but these, especially in men, can in our experience be attributed to athletic development. Cases 5, 6, and 8 showed either borderline or abnormal cranial indices suggesting the long narrow heads seen in the Marfan syndrome but only case 5 was prognathic. Finally, the commonest stigma present in six of the seven patients examined was palatal arching. Miscellaneous signs, such as scoliosis, pectus carinatum or excavatum, joint hypermobility, scant fat, and bluish sclerae, were present in cases 1, 2, 5, 7, and 8, but not in cases 4 or 6. Cases 3 and 9 also had no noticeable stigmata but they died before we realized the need for appropriate measurements. Nearly all of the series were thin, weighing less than their height would predict. It was possible to evaluate the immediate families in six of the nine patients. The mother and brother of case 2 were tall, with increased span and lower body segments. Each had a heart murmur, clino- dactyly, and slight pectus excavatum. The family of case 4 showed, like her, no significant musculoskeletal abnormalities. The father and two siblings of case 5 resembled her in having spidery fingers, dolichocephaly, and stenomelia; three other siblings were unaffected. Although case 6 had practically no musculoskeletal evidence of the Marfan syndrome, his mother and two sisters exhibited a positive cephalic index, metacarpal index (9.13), and an increased body segment, height/span ratio. They also had kyphosis, high-arched palate, and long patellar ligaments. A brother had no apparent musculoskeletal defect. The mother of case 7 had a positive metacarpal index (9.7) and elongated extremities. Seven of the nine children of case 8 exhibited positive signs of the Marfan syndrome. Six had high-arched palates; and seven, long patellar ligaments; span exceeded height and lower segment, upper in four; and the metacarpal index was greater than 7.9 in five. The number of positive measurements decreased with decreasing age.

Discussion

These nine patients have in common an unusual histologic appearance of their aortic or mitral valve leaflets. Varying degrees of hyalinization, disruption, and loss of the normal connective-tissue architecture was accompanied by an increase in ground substances and, in some instances, fibrosis. There was a remarkable absence of the usual signs of inflammation. The picture is that of myxomatous valvular transformation. This lesion has been described previously either as a rare pathologic curiosity in stillborn infants, babies with congenital cardiovascular anomalies and fibroelastosis, or more frequently at all ages in the Marfan syndrome.

In 1912 Salle, in the first autopsied case of arachnodactyly, described wrinkled mitral leaflets with translucent thickening. Later, Weill, Giraud, and others made similar observations. Microscopic studies by Olcott in 1940, Tobin and associates in 1947, and more recently Tung and Liebow, Austin and Schaeffer, Berenson and Greer, and Bolande supported Baer, Taussig, and Oppenheimer's impression that the lesion was not a rheumatic valvulitis, as many had thought previously. During the 1950's valvular thickening, rolling, fenestration, redundancy, wrinkling, ballooning, and nodularity with shortening or rupture of chordae tendineae were reported as incidental findings in Marfan patients dying from aortic aneurysm.

Until quite recently, myxomatous valvular transformation was generally considered to be clinically insignificant, since, by itself, it was not thought to cause insufficiency. Case 3 partially and case 9 completely support this concept. When incompetence was known to be present, it was thought to arise from either dilatation of the annulus, superimposed valvu-
litis, or an associated aneurysmal change at the base of the aorta. In the past 2 or 3 years, however, case reports with limited pathologic data have suggested that mitral valvular insufficiency may appear as an isolated cardiovascular manifestation of the Marfan syndrome.\(^{12, 38}\) The patients described above are therefore of special interest for two reasons: (1) in eight of the nine cases myxomatous valvular transformation seemed to play the leading role in the development of congestive heart failure, which in five women presented as isolated symptomatic mitral insufficiency, and in three men as aortic incompetence without dilatation of the aortic ring; (2) this structural change was discovered by surgical biopsy in young adults showing little or no external evidence of a mesodermal dystrophy.

Our experience suggests that there are at least six ways whereby this type of valvular change can cause incompetence. In its simplest form, as demonstrated by cases 1, 2, 3, 6, and 7, the mitral or aortic cusps appeared so weakened that they no longer retained enough rigidity to prevent stretching, rolling, wrinkling, retraction, inversion, and, finally, prolapse into the left ventricle (floppy valve). Weaver et al.\(^{39}\) advanced a similar explanation for their findings in a case of idiopathic dilatation of the aorta with insufficiency but later dismissed it in favor of the dilated annulus theory. Darvill\(^{40}\) reported that the senile arteriosclerotic leaflet may lose part of its integrity in this way, thereby producing incompetence (baggy valve). The second mechanism of valve failure is really an extension of the first; whereas in the latter the contour of the cusps remains normal, degeneration may progress to actual loss of substance leaving a defect (case 3) through which regurgitation can occur. A similar finding has been described by Edynak and Rawson.\(^{41}\) In their case myxomatous degeneration resulted in aneurysmal dilatation of the valve and subsequent rupture. Clinically this type of destruction can easily be mistaken for the ravages of endocarditis, which even before the antibiotic era was known to heal pathologically without a trace,\(^{42}\) as in our cases 4 and 5. The third possibility is mitral insufficiency resulting from rupture of chordae tendineae as a result of myxomatous degeneration. We have no conclusive evidence of this phenomenon occurring, since in the two cases (3 and 4) in which ruptured chordae were found, there was a history of complicating endocarditis. However, such a change has been described in the Marfan syndrome\(^{43}\) and we have histologic evidence of myxomatous involvement of these structures (fig. 1). Thickening and contraction of the chordae tendineae presumably from later fibrosis is the fourth reason for valvular insufficiency. This may have been a factor operating in case 3 as well as in previously described cases of the Marfan syndrome.\(^{24, 26, 37, 43}\) A fifth mechanism is interference with coaptation resulting from the nodular nature of the fibromyxoid change (fig. 2) with hypertrophy of the corpora Arantii and papillary vegetations.\(^{44}\) Superimposed infection is the sixth way whereby myxomatous transformation can lead to valvular incompetence. It has been recognized for some time that individuals suffering from a mesodermal dystrophy are prone to develop endocarditis.\(^{12, 13, 15, 25, 32, 45–51}\)

It is therefore of interest that two of our patients presented with this complication. This tendency to valvulitis is a further indication of a basic abnormality in valve structure.

Since myxomatous transformation of the cardiac valves has in the past\(^{12, 17}\) been considered to be, in all probability, pathognomonic of the Marfan syndrome, and certain of the musculoskeletal stigmata of this condition were present either in our patients or their immediate families, the question can be raised whether they all do not belong with this entity. Certainly our patients are not representative of the complete syndrome, since there were no ocular signs, the typical "basketball player habitus" was not present, and in the six families available for investigation no florid example of the Marfan syndrome was found. Certain features described above, however, suggest a possible relationship to the much more common forme fruste. Thus, arachnodactyly as documented by both the metacar-
pal criteria and the body/span, body/segment measurements of Sinclair et al.,50 was present in case 5 and, in addition, at least one affected relative was detected in the immediate families. Evidence of Erdheim’s cystic medial necrosis was found in the aorta or femoral artery biopsy in five of the nine cases (table 1). This disease of the arterial tree is characteristic of the Marfan syndrome, but it may also occur in pregnancy,52 senility,53 hypertension,64 coarctation,55 and as a cause of idiopathic dilatation, aneurysm, dissection, or rupture of the aorta.66 It can even occur in the absence of an obvious disease.57 Where this aortic medial change appears in association with any of the known cardiac manifestations of the Marfan syndrome, Weaver et al.50 and others59,44,58-60 have suggested that the patient should be considered a forme fruste of the Marfan syndrome. Case 9 fits these criteria. The emphasis in this patient on medial disease with only incidental valvular pathology is, of course, the usually described cardiovascular manifestation in the Marfan syndrome. Similarly, case 8 had idiopathic dilatation of the aorta and case 6 aneurysmal dilatation of a sinus of Valsalva with stenosis of the ascending aorta. Uyeyama et al.61 have reported the latter lesion in a patient with the Marfan syndrome. Case 3 showed at autopsy an aneurysm of the membranous septum, which has also been described previously in the Marfan syndrome.44 The lesion of Erdheim’s necrosis was also found in cases 5 and 7 but only as an asymptomatic histologic finding. Another cardiac stigma was found in one of the five cases in which it was looked for, namely, subendocardial myxomatous infiltration without fibroelastosis. There seems little doubt that this patient (case 5) is an example of the forme fruste of the Marfan syndrome. The final arbitration whether the other cases, 1, 2, and 4, should go into the Marfan category becomes a semantic problem, since Marfan62 originally described musculoskeletal changes, and our patients had essentially none of these. Recently, however, emphasis has been placed on the cardiovascular stigmata, since these are the principal causes of morbidity and mortality. Our cases resemble those of Whittacker and Sheehan63 with a cardiovascular forme fruste of the Marfan syndrome. An argument has continued in the literature regarding the relationship between patients having idiopathic dilatation of the aorta with Erdheim’s necrosis and those with the Marfan syndrome.29,44,64 In the present situation, we have perhaps idiopathic myxomatous transformation of the valve leaflets as opposed to the Marfan syndrome. Regardless, the important implications of these studies are that myxomatous valvular transformation must be considered in the differential diagnosis of valvular insufficiency arising not only in patients known to have the Marfan syndrome or its various forms frustes but also as an isolated idiopathic lesion in individuals not to be distinguished by external appearance from the normal population. It is thus possible that many patients now considered to be suffering from the after effects of rheumatic disease are actually examples of another entity the etiology of which is probably related more to an inborn defect in metabolism than to inflammation. We, unlike Bowers,65 found the electrocardiographic changes to be nondiagnostic.

The question of differential diagnosis is important to the surgeon because these individuals seem to share with Marfan patients a tendency to disruption of suture lines with displacement of prostheses. Dehiscence of aortic cusps has been described in the Marfan syndrome66-68 and our problem with loosening of prosthetic valves in both the aortic and mitral areas is perhaps comparable. Our operative experience with these individuals emphasizes that the annulus, even though not enlarged may be similarly involved with myxoid change. Sutures tear out, normal scar tissue does not develop, and some progressive dilatation may later take place. Finally, in cases of aneurysm affecting the ascending aorta, it can no longer be assumed that accompanying insufficiency results necessarily from stretching of the annulus or the valve ring. Our experience suggests that an associated defect in valvular tissue has to be considered, especially when the dilatation does not actually extend.
to the origin of the aorta, which Bahnson and Spencer have shown is not infrequent.

Summary

The clinical course of nine patients, aged 14 to 49, who either at surgery or autopsy demonstrated myxomatous valvular transformation, has been described. Five females presented with asymptomatic mitral insufficiency. Two of them had had endocarditis whereas in the others a heart murmur was detected during childhood. Three of the four men had a recent onset of aortic insufficiency associated in one case with aneurysm of the ascending aorta. The fourth experienced sequential arterial rupture and finally aortic dissection, his asymptomatic valvular lesion becoming manifest only at autopsy.

The electrocardiographic, roentgenographic, angiographic, and catheterization findings resembled those seen in rheumatic heart disease, except that neither fibrosis, calcification, nor stenosis was found. The histologic appearance of the valve leaflets was identical to that which has been described, primarily as an incidental lesion, in the Marfan syndrome. Only one of the nine patients, however, demonstrated arachnodactyly. Skeletal mensuration in the remainder revealed a scattering of the many stigmata known to be associated with the Marfan syndrome. Nevertheless, arachnodactyly was diagnosed in at least one member of each of the six families available for investigation, although we did not encounter dislocation of the lens or an example of a complete Marfan syndrome. Erdheim's necrosis of the aortic or arterial media was described in four of the eight cases in which vascular biopsies were obtained. Prosthetic replacement in either the aortic or mitral area was carried out in the eight patients with signs of valvular insufficiency. There was one immediate and one late death. Reoperation was necessary in another case for dehiscence from the mitral annulus and twice in one more patient for the same complication at the aortic area. None demonstrated annular dilatation but isolated aneurysmal enlargement of either the ascending aorta, the membranous septum, or the sinus of Valsalva was encountered.

Insufficiency apparently resulted because of valve prolapse from either structural fatigue, ruptured chordae, loss of substance, interference with coaptation, or supervening endocarditis. Myxomatous change may involve not only the chordae and the valve leaflets but also the annulus, since four prosthetic dehiscences occurred either in the early or late postoperative period in three of the eight operated upon. Experience with the one patient who showed aortic insufficiency and aneurysm of the ascending aorta suggests that valvular transformation may be the cause of incompetence in some of these cases rather than extension of the dilatation to the aortic ring.

These studies indicate that myxomatous valvular transformation must be considered in the differential diagnosis of valvular insufficiency not only in patients known to have the Marfan syndrome or its various formes frustes, but also as an isolated idiopathic lesion in individuals not distinguishable by external appearance from the normal population. At the present time myxomatous valvular transformation can be suspected to be the cause of isolated valvular insufficiency if evidence for a rheumatic etiology is lacking, musculoskeletal signs of the Marfan syndrome are present, or Erdheim's necrosis is found in the arterial biopsy. There is a characteristic appearance at operation (floppy valve) but the presence of the lesion can only be established by histologic examination of the leaflets.

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