CONGENITAL POLYVALVULAR DISEASE

By Saroja Bharati, M.D., and Maurice Lev, M.D.

SUMMARY
Thirty-six hearts were studied in which all valves were involved in a dysplastic process. This consisted of an increase in spongiosa with vacuolar and lacunar degeneration, and a distinct lack of elastic tissue in the proximalis and in the spongiosa. This process was similar to, but more marked than that seen in a case of a single dysplastic valve as in bicuspid aortic valve. It was completely different from that seen in hemodynamic change. These cases clinically were often associated with trisomy 18 or trisomy 13-15, and called congenital polyvalvular disease. This disease may bear some relationship to Marfan's disease and the "floppy valve".

Additional Indexing Words:
Dysplastic valve  Polyvalvular disease  Floppy valve  Acid mucopolysaccharides

IN THE PAST 15 years, among the 3,550 congenitally abnormal hearts examined at the Congenital Heart Disease Research and Training Center, we have found 36 hearts, which we believe fall into a special category which we have called congenital polyvalvular disease. In this entity, all the valves were involved in a similar pathologic process, the aortic valve being least involved. Clinical and pathologic appraisal indicated that this disease was most often associated with a chromosomal abnormality.

Gross Examination

Valves
The AV valve leaflets grossly, after fixation, were redundant, irregularly thickened, with nodular formations present in various parts, or concentrated mostly in the peripheral portions (fig. 1). Occasional blood cysts were present. The chordae in some cases were thickened, at times shortened, with an irregular distribution, and in some cases they were focally covered by nodular formations. The papillary muscles in an occasional case had an abnormal architecture.
The semilunar valves were likewise irregularly thickened throughout with smaller nodular formations than those found in the AV valves. The edges were in some cases rolled, the commissures were thickened, the supravalvular ridges were more prominent than usual, with slight aneurysmal dilatation of the sinuses of Valsalva. There was an abnormality in the number of cusps in many cases as indicated in table 1.

Associated Abnormalities
There were three cases without a shunt or an obstruction, 16 cases with a shunt, five cases with an intracardiac obstruction, and 12 cases with a combination of obstruction and shunt. The types of shunts, obstructions, and combinations of obstructions and shunts, and the age and sex of the individual cases are given in tables 2, 3, and 4, respectively. The details of the cases without shunts and obstructions are given in table 5.

Coronary Distribution
In two cases the left coronary and in one case the right coronary ostium emerged above the sinuses of Valsalva. The coronary distribution was normal except in two cases. In one case the left circumflex emerged from the right coronary artery, and in one case both coronary ostia emerged from the left coronary sinus of Valsalva.

Microscopic Examination

Methods
In eight cases of all ages and groups (shunts and obstructions) all four valves were studied. The sections included the adjacent atrium and ventricle, the annulus...
fibrous, the entire valve, the chordae, and in some cases the papillary muscles. In 17 other cases (of all ages and groups) the mitral and tricuspid valves only were studied with the associated myocardium and coronaries. The ascending aorta was separately studied in 15 cases, all groups (obstructions and shunts) and all ages being represented. All valves and other structures of the polyvalvular group were compared with normal valves and structures of the same age.

Sections of the abnormal valves, as well as the controls, were stained with hematoxylin-eosin stain, Weigert-van Gieson stain, Alcian blue, and Hotchkiss-PAS stains. A few sections in addition were stained with a combination of Alcian blue and PAS, Rinehart and Abul-Haj modification of the Hale stain for colloidal iron, and Masson stains.

A comparison was then made (a) between the aortic and pulmonic valves of cases of polyvalvular disease and a bicuspid aortic and a bicuspid pulmonic valve in a case of fetal (preductal) coarctation with aortic stenosis; (b) between the pulmonic valves of cases of polyvalvular disease and the bicuspid pulmonic valve in a case of tetralogy; and (c) between all the valves of cases of polyvalvular disease and the valves in a case of patent ductus arteriosus and ventricular septal defect. The comparison in all cases was between valves of the same age. The purpose of these studies was to compare the valve in polyvalvular disease to that in congenital univalvular disease and to the hemodynamically altered valve.

**Findings**

The terminology used here for the normal valvular architecture is that of Gross and Kugel.1 Each valve cusp or leaflet has four main layers as follows (fig. 2): (a) *Fibrosa*. This is a thick collagenous layer forming the backbone of the valve and is most prominent in the proximal 2/3 of the cusp or leaflet. (b) *Spongiosa*. This layer consists of more loosely arranged delicate connective tissue fibers and is most prominent in the annulus and in the peripheral portion of the valve. It is also situated in the ventricular aspect of the semilunar valves, and on the atrial aspect of the AV valves, and is more sharply defined as a layer in the former. (c) *Proximalis*. This is an elastic layer lying superficial to the spongiosa on the proximal surface of the semilunar and atroventricular valves, respectively. (d) *Distalis*. This is a thin elastic layer lying on the distal surface of the semilunar and atroventricular valves. Each cusp or leaflet is attached to the annulus fibrosus. The valve ring constitutes the proximal end of the cusp or leaflet and includes part of the base of the valve and the adjacent portion of the annulus. The terms basal and peripheral are used to indicate that part of the valve close to the annulus and that part away from it, respectively.

All valves in our cases of polyvalvular disease showed (figs. 3, 4): (1) proliferation of the spongiosa either diffuse or localized, often at the expense of the fibrosa, with vacuolar and lacunar degeneration; (2) a distinctive lack of elastic tissue in the proximalis and in the spongiosa; (3) in many cases there was disruption of architecture, with the fibrosa and spongiosa intermingled and the spongiosa loosened (fig. 2); (4) the proximalis was often replaced by spongiosa. Acid mucopolysaccharides (AMPS) were copiously present throughout the valves (fig. 5). These findings were the same whether there was an obstruction or a shunt or a

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**Table 1**

<table>
<thead>
<tr>
<th>Abnormality</th>
<th>Cases (no.)</th>
</tr>
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<tbody>
<tr>
<td>Bicuspid aortic valve</td>
<td>5</td>
</tr>
<tr>
<td>Bicuspid pulmonic valve</td>
<td>4</td>
</tr>
<tr>
<td>Unicuspid pulmonic valve</td>
<td>3</td>
</tr>
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<td>Bicuspid aortic and pulmonic valves</td>
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</table>

**Table 2**

<table>
<thead>
<tr>
<th>Type</th>
<th>Cases (no.)</th>
<th>Age</th>
<th>Sex</th>
</tr>
</thead>
<tbody>
<tr>
<td>ASD</td>
<td>1</td>
<td>6 mos</td>
<td>F</td>
</tr>
<tr>
<td>VSD</td>
<td>1</td>
<td>36 hrs</td>
<td>F</td>
</tr>
<tr>
<td>ASD and PDA</td>
<td>2</td>
<td>3 mos</td>
<td>M</td>
</tr>
<tr>
<td>VSD and PDA</td>
<td>3</td>
<td>5 days</td>
<td>M</td>
</tr>
<tr>
<td>ASD and VSD</td>
<td>2</td>
<td>17 yrs</td>
<td>M</td>
</tr>
<tr>
<td>ASD, VSD, and PDA</td>
<td>4</td>
<td>1½ mos</td>
<td>F</td>
</tr>
<tr>
<td>ASD, VSD, and PDA with fetal (preductal) coarctation</td>
<td>3</td>
<td>6 wks</td>
<td>M</td>
</tr>
<tr>
<td></td>
<td></td>
<td>26 days</td>
<td>F</td>
</tr>
<tr>
<td></td>
<td></td>
<td>24 hrs</td>
<td>F</td>
</tr>
</tbody>
</table>

Abbreviations: ASD = atrial septal defect; PDA = patent ductus arteriosus; VSD = ventricular septal defect.

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**Figure 1**

Gross appearance of valves in congenital polyvalvular disease in a case of ASD, VSD, tricuspid, pulmonary, mitral, and aortic stenosis, 3 years 4 months old. (Top, left) Tricuspid valve. (Top, right) Pulmonic valve. (Bottom, left) Mitral valve. (Bottom, right) Aortic valve. RA = right atrium; RV = right ventricle; ASD = atrial septal defect; VSD = ventricular septal defect; FT = pulmonary trunk; LA = left atrium; LV = left ventricle; A = aorta; TV = tricuspid valve; PV = pulmonic valve; MV = mitral valve; AV = aortic valve.

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combination of these. Likewise these findings were the same in all age groups.

When compared to the bicuspid aortic or pulmonic valve found in preductal coarctation with aortic stenosis and in tetralogy respectively, there was a difference only in degree (fig. 6). There was an increase in spongiosa and hypoeelastification. The fibrosa and spongiosa were distinctly demarcated, and acid mucopolysaccharides were abundant in the univalvular disease. The architecture was not as disturbed as in most cases of polyvalvular disease. When compared to the hemodynamically altered valves, the latter showed a normal architecture and normal or slightly increased elastification of the proximalis and the spongiosa (figs. 2 and 7).

A fine increase in connective tissue was present throughout the myocardium as well as perivascularly in our cases of polyvalvular disease. This was associated with early necrosis of the papillary muscles of the left ventricle in some cases and fibrosis, degenerative changes, and calcification of the papillary muscles of the right ventricle in others. The intima of the extramycocardial coronary arteries was proliferated beyond the normal, but there were no obstructions to the lumen. The aorta showed no remarkable changes.

Pertinent Clinical Data

There were seven cases of trisomy 17-18, one case of mosaic trisomy 18, and two cases of trisomy 13-15. In 17 cases there were multiple extracardiac abnormalities such as: low-set ears, peculiar facies, micrognathia, high-arched palate, webbed neck, shield chest, hip contractures, clinodactyly, rocker-bottom feet, genitourinary abnormalities, and gastrointestinal, central nervous system, and other abnormalities. However, no chromosomal studies were done in the latter cases. In four cases there were only a few associated extracardiac abnormalities, and in three cases no such abnormalities were present. In two cases no data were available.

Nineteen cases were male and 17 were female. Twenty-seven were white, eight were black (data were not present in one case). The age ranged from stillbirth to 19 years, the average age being 2 years 2 weeks. The mother's age was above 35 years in 10 cases. Two mothers were diabetic; one mother had German measles in early pregnancy, and another rheumatic fever.

The infants had low birth weights and did not thrive. Only four patients showed deformed thickened valves on cineangiogram. Seven infants died in the catheterization room or shortly thereafter. In the three cases without shunt or obstruction, only one case had a Grade III systolic murmur, which might have indicated valvular dysfunction. At autopsy, in this case, all chambers of the heart were hypertrophied and enlarged, and hence it cannot be stated which valve or valves might have been the seat of dysfunction.

Table 3

<table>
<thead>
<tr>
<th>Types of Intracardiac Obstruction</th>
<th>Cases (no.)</th>
<th>Age</th>
<th>Sex</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pulmonary valvular and infundibular stenosis</td>
<td>1</td>
<td>19 yrs</td>
<td>F</td>
</tr>
<tr>
<td>Pulmonary valvular and infundibular, aortic, and tricuspid stenosis, and adult (segmental) coarctation</td>
<td>1</td>
<td>15 yrs</td>
<td>M</td>
</tr>
<tr>
<td>Pulmonary valvular, tricuspid, and subaortic stenosis</td>
<td>1</td>
<td>7 wks</td>
<td>M</td>
</tr>
<tr>
<td>Pulmonary valvular and tricuspid, mitral, and aortic stenosis</td>
<td>2</td>
<td>3 yrs</td>
<td>M</td>
</tr>
<tr>
<td></td>
<td></td>
<td>4 days</td>
<td>F</td>
</tr>
</tbody>
</table>

Table 4

<table>
<thead>
<tr>
<th>Types of Combined Obstruction and Shunt</th>
<th>Cases (no.)</th>
<th>Age</th>
<th>Sex</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pulmonary stenosis with VSD</td>
<td>1</td>
<td>1 mo</td>
<td>F</td>
</tr>
<tr>
<td>Tricuspid stenosis with ASD, VSD, and PDA</td>
<td>1</td>
<td>2 mos</td>
<td>M</td>
</tr>
<tr>
<td>Coarctation, aortic stenosis, VSD, and PDA</td>
<td>1</td>
<td>5 days</td>
<td>F</td>
</tr>
<tr>
<td>Pulmonary, tricuspid, and subaortic stenosis and ASD</td>
<td>1</td>
<td>2 mos</td>
<td>M</td>
</tr>
<tr>
<td>Pulmonary, tricuspid, aortic and subaortic stenosis, ASD and PDA</td>
<td>1</td>
<td>1 wk</td>
<td>M</td>
</tr>
<tr>
<td>Pulmonary and tricuspid stenosis, ASD and PDA</td>
<td>1</td>
<td>48 hrs</td>
<td>M</td>
</tr>
<tr>
<td>Tricuspid, pulmonic and aortic stenosis and PDA</td>
<td>1</td>
<td>6 yrs</td>
<td>F</td>
</tr>
<tr>
<td>Tricuspid stenosis, ASD and PDA</td>
<td>1</td>
<td>18 days</td>
<td>M</td>
</tr>
<tr>
<td>Tricuspid, pulmonic, mitral and aortic stenosis, ASD and PDA</td>
<td>2</td>
<td>7 mos</td>
<td>M</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1 yr 8 mos</td>
<td>M</td>
</tr>
<tr>
<td>Partial transposition with pulmonary atresia and ASD</td>
<td>1</td>
<td>27 days</td>
<td>F</td>
</tr>
<tr>
<td>Tetralogy, ASD, and PDA</td>
<td>1</td>
<td>36 hrs</td>
<td>F</td>
</tr>
</tbody>
</table>

Abbreviations: ASD = atrial septal defect; PDA = patent ductus arteriosus; VSD = ventricular septal defect.
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Table 5
Cases without Obstruction and Shunt

<table>
<thead>
<tr>
<th>Age</th>
<th>Sex</th>
<th>Heart findings at autopsy</th>
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</thead>
<tbody>
<tr>
<td>1 day</td>
<td>M</td>
<td>Right ventricular hypertrophy</td>
</tr>
<tr>
<td>5 yrs 7 wks</td>
<td>M</td>
<td>All chambers normal</td>
</tr>
<tr>
<td>10 mos</td>
<td>M</td>
<td>Hypertrophy and enlargement of all chambers</td>
</tr>
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</table>

Discussion

The concept of individual "dysplastic" valves which have the gross and microscopic characteristics of our cases is old in the literature. This literature has been reviewed by Hyams and Manion. However, the concept of congenital involvement of all the valves in a single heart in a dysplastic process is of more recent vintage and has not yet been crystallized in the literature. Thus, in a case of trisomy 13-15 Koenig et al. described many small grapelike clusters of myxomatous material on the valves and chordae tendineae. Gottlieb et al. in two cases of trisomy-17 described the valves as showing multiple fleshy nodular thickenings. Smith et al. in a case of trisomy-18 described involvement of the three valves in such a process. Hecht et al., in a case of trisomy-17-18, found fine beads on all valves which were histologically identical to the valves. Way, in a case of rubella syndrome, found all the valves in a fresh state to be thick, opaque, and ruby red with nodular formations on some. Hyams and Manion mentioned one case of involvement of all the valves in a dystrophic process similar to that in our cases. Simpson et al. found "valvular sclerosis" involving all valves in five infants. In three of these, the lesions were associated...
with the rubella syndrome and Turner’s phenotype.

In our cases grossly, all the valves showed irregular thickening with nodular formations. Histologically, there was proliferation of the spongiosa and hypoelastification and in many cases disruption of architecture. These findings were associated with trisomy-18 or 13-15, or with multiple abnormalities characteristic of these trisomies in the vast majority of cases. In one case the mother had German measles in early pregnancy. Thus, from our findings

Figure 3

Microscopic appearance of valves in congenital polyvalvular disease. Weigert-van Gieson Stain. (Top) Tricuspid valve in ASD, VSD, and PDA complex, 41 days old; ×17. (Bottom) Pulmonic valve in a case of pulmonary, tricuspid, and mitral stenosis, 3 years old; ×15. F = fibrosa; S = spongiosa; B = blood cyst; M = myocardium.
and from those in the literature, there is a distinct entity, which we are calling congenital polyvalvular disease, which is usually associated with chromosomal abnormality, but which in some cases may be related to rubella, and in which, in a few instances, no etiologic agent is evident at the present time.

The valvular pathology in our cases was associated with other cardiac complexes typical of those...
described in trisomies-18 and 13-15,4, 5, 9-26 Thus various single and combined shunts, bicuspid aortic, and pulmonic valves, and various stenoses have been documented in the literature.

Our findings indicate that the histologic process in the valves in congenital polyvalvular disease differs only in intensity from that of congenital univalvular disease such as bicuspid aortic or pulmonic valve. There is not as much disruption of architecture in the latter, but the increase in spongiosa with AMPS and hypoelastification is present. The descriptions in the literature also indicate that a single dysplastic valve may be present instead of multiple-valve involvement in the trisomies with a similar histologic picture as found in polyvalvular disease. Furthermore the AV valves of common AV orifice, and the truncus communis valve may be identical to those in our cases.

The valvular changes in our cases are not related to hemodynamic change. One of us (M.L.)27, 28 and others2, 29, 30 have previously investigated hemodynamic changes in valves as found in aging, increased flow, and pressure. Hemodynamic change is manifested by elastosis of the proximalis and of the spongiosa with, in some cases, an increase in the fibrosa. Each individual layer of the valve remains distinct, although altered. To add to the documentation of this point, in this work we examined the valves in a case of left-to-right shunt at the ventricular and ductus level in a case of the same age as several of our cases of polyvalvular disease. There was a distinct lack of elastosis in the polyvalvular cases as compared to the hemodynamically altered, normally developed valve. Furthermore the lack of elastosis up to the age of 19 in our cases of polyvalvular disease indicates a lack of physiologically normal hemodynamic change associated with aging.
What is the relationship of the dystrophic valve in Marfan's disease to that in congenital polyvalvular disease? In the former there is so called "myxomatous" degeneration with an increase in AMPS.31-36 Only Crocker36 mentions hypoelastification. No one mentions complete disruption in architecture in these cases. If Crocker's findings should be confirmed then there might be some similarity between congenital polyvalvular disease and Marfan's disease. In our cases we studied the aorta specifically to see if it showed the cystic degeneration of Marfan's. This was not the case. However, we are left with the vague possibility that our cases are similar to a forme fruste of Marfan's in which the aorta may not be involved.

What is the relationship of the "floppy valve" to congenital polyvalvular disease? The histologic process in the "floppy valve" is said to be "myxomatous" degeneration with an increase in AMPS.37-48 There is a difference of opinion as to elastification. According to Pomerance46 there is also fibroelastosis of the endocardial lining of the valve. According to O'Brien et al.49 there is hypoelastification. Here, again, no mention is made as to the loss of architecture found in our cases. Thus, not enough work has been done on the "floppy valve" to answer the question posed.

What is the relationship of the valve changes in endocardial fibroelastosis, not associated with other abnormalities, to those in polyvalvular disease? According to Rosahn,49 Prior and Wyatt,50 Cowing,51 and Hyams and Manion5 there is an increase in spongiosa with a notable decrease in elastic tissue. According to Kelley and Andersen58 the microscopic picture of the valves is similar to the endocardium—an increase in fibrous and elastic tissue in the valve. Here again we are left without an answer to the question because of divergent findings.

Figure 6
Bicuspid aortic valve in a case of fetal (preductal) coarctation, with aortic stenosis, 3 days old. (Left) Weigert-van Gieson stain; × 31. (Right) Alcian blue stain; × 36. Lighter stained areas in valve at right represent acid mucopolysaccharides. S = spongiosa; F = fibrosa.
There is obviously no relationship between the valves in Hurler's disease, Ehler-Danlos disease, and those in polyvalvular disease. In Hurler's disease we are dealing with a disease of the fibrosa and annulus with an infiltration of Gargoyle cells. In Ehler-Danlos disease, there is a difference of opinion as to elastification of the valves in this disease. According to Green et al. there is an increase in elastic tissue, but according to Madison et al. there is no undue elastification. In either case no mention is made of loss of elastic tissue and disruption of architecture. In serotonism the architecture of the valves is not disturbed even though there is a fibrous coating on the valves.

As pointed out by Pomerance, it is likely that the increase in AMPS in various valvular diseases, congenital and acquired, is a nonspecific finding. One may extend this to say that it is true of the increase in spongiosa. Therefore, these findings do not constitute evidence of a congenitally dysplastic valve. We may consider that a congenitally dysplastic process in a valve exists where there is hypoeostiffication and where there is marked disruption of architecture with fibrosa and spongiosa not demarcated, as previously pointed out by Hyams and Manion. Then we may assume that there has ensued a congenital incomplete differentiation of the valve tissue in fetal life.

The papillary muscle changes noted in some of our cases may be related to the abnormality of function of the valves or to a basic myocardial disease in trisomy-18 or 13-15. The fibrosis of the myocardium may be related to the left-to-right shunts or obstructions or again may be a part of a basic myocardial disease in the trisomies.

We do not know the cause of the intimal proliferation of the coronary arteries. Changes in the arteries generally have been described in trisomies.

Figure 7

Tricuspid valve in a case of VSD and PDA complex, age 7 weeks. Weigert-van Gieson Stain; × 12. F = fibrosa; S = spongiosa; P = proximalis.
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