Natural History of Adults With Congenitally Malformed Aortic Valves (Unicuspid or Bicuspid)

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Abstract: Appreciation of the frequency of the congenitally malformed aortic valve has come about during the last 50 years, a period during which aortic valve replacement became a predictably successful operation. Study of patients at necropsy with either a congenitally unicuspid (1 true commissure) or bicuspid (2 true commissures) valve in whom no aortic valve operation has been performed has not been conducted during these 50 years, to our knowledge. We studied 218 patients at necropsy with congenitally malformed aortic valves: 28 (13%) had a unicuspid valve and 190 (87%), a bicuspid valve. Their ages at death ranged from 21 to 89 years (mean, 55 yr), and 80% were men. Of the 218 adults, the aortic valve functioned normally during life in 54 (25%) and abnormally in 164 (75%): aortic stenosis in 142 (65%), pure aortic regurgitation without superimposed infective endocarditis (IE) in 2 (1%), and IE superimposed on a previously normally functioning aortic valve in 20 (9%). IE occurred in a total of 31 (14%) of the 218 patients: involving a previously normally functioning valve in 20 (65%) and a previously stenotic valve in 11 (35%). Of the 218 patients, at least 141 (65%) died as a consequence of aortic valve disease (124 patients) or ascending aortic tears with or without dissection (17 patients). An estimated 1% of the population, maybe higher in men, has a congenitally malformed aortic valve. Data from this study suggest that about 75% of them will develop a major complication. Conversely, and encouragingly, about 25% will go through life without a complication.

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Abbreviations: AR = aortic regurgitation, AS = aortic stenosis, CABG = coronary artery bypass grafting, IE = infective endocarditis, NHLBI = National Heart, Lung, and Blood Institute.

INTRODUCTION

The frequency of the congenitally malformed aortic valve at birth remains unclear but the best estimates are that it is present in 1% of live births,[22,50,58] probably a bit higher in males. That frequency translates into 3,130,000 persons in the United States having a congenitally malformed aortic valve. If systemic hypertension is excluded, complications of the malformation of this valve may be the second most common cardiac cause of death (after coronary heart disease) if untreated.

The frequency of the malformed aortic valve has not been properly appreciated until relatively recent decades. Paul Dudley White, the most prominent cardiologist in the United States in the first half of the 20th century, wrote in the 4th edition (1951) of his book *Heart Disease*, "Serious congenital aortic valve lesions, stenosis and atresia, are very rare, but congenital bicuspid aortic valves are found occasionally and are likely to be the site of subacute bacterial endocarditis…".[101] Paul Wood, the most prominent cardiologist in the United Kingdom during his lifetime, wrote in the 3rd edition (1968) of his book *Diseases of the Heart and Circulation*, "Apart from its association with [aortic] coarctation, bicuspid aortic valve is clinically important for four reasons: 1) it may leak spontaneously or as a result of acquired hypertension; 2) about one-quarter of all cases become infected sooner or later; 3) an associated weakness of the sinuses of Valsalva may lead to aneurysmal dilatation or rupture; 4) an insidious sclerosing process may lead to calcified aortic stenosis in middle age…".[103] And in the 3rd edition (1968) of *Pathology of the Heart and Blood Vessels* edited by S. E. Gould, only 2 of 1162 pages were devoted to aortic stenosis (AS), and bicuspid aortic valve was mentioned in only 1 of 9 paragraphs.[28] It is notable that successful aortic valve replacement had been a reality for 8 years, since 1960.[48]

The congenitally bicuspid aortic valve has captured the interest of many prominent physicians and one illustrious artist.[98,99] Leonardo da Vinci (1452–1519) appears to have been the first to draw and publish a congenitally bicuspid aortic valve and indeed to appreciate its clear difference from a tricuspid aortic valve.[34] Sir James Paget (1814–1899) described at necropsy 3 patients with stenotic bicuspid aortic valves.[52] Sir Thomas Peacock (1812–1882) also described and illustrated 3 patients studied at necropsy with stenotic congenitally bicuspid aortic valves.[54] A number of reports followed (Table 1), describing mainly patients studied at necropsy with valvular AS.[1,2,6,7,9,10,12–15,17,18,20,24,25,29,31,33,35,37–41,47,50,52,54,56,57,91,92,100] Many authors considered the AS to be the result of rheumatic heart disease,[2,7,9,13–15,17,18,29,31,33,37,57] but several authors provided illustrations of the stenotic aortic valve showing it clearly to be a congenitally bicuspid valve.[2,6,7,9,12,14,18,20,24,33,40,54,91,92] Roberts in 1970 provided a strong case against a rheumatic etiology for AS in patients with anatomically normal mitral valves.[59,60] Maude Abbott (1868–1940) demonstrated that most patients (about 75%) with coarctation of the aorta have congenitally bicuspid aortic valves,[1] and many authors later supported that view.[6,26,57,58,92] Roberts and colleagues[82] opined that 100% of patients with complete interruption of the aortic arch have bicuspid aortic valves. Authors after 1950 describing patients with AS commonly described and illustrated underlying congenitally bicuspid valves (see Table 1).[6,10–12,20,24,32,36,49,55,58–61,64,92]

Although Carl Rokitansky (1804–1878) had earlier identified bacteria in vegetations in patients with infective endocarditis (IE), Osler (1849–1919) in his 1885 Gulstonian Lectures[51] called

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TABLE 1. Reported Necropsy Cases (Before 1970) of Aortic Stenosis and/or Bicuspid Aortic Valves in Adults Without Anatomic Disease of the Mitral Valve

Year of Publication	Author(s) (Reference)	Number of Cases						Etiology of Aortic Valve Disease
		Total	Bicuspid Aortic Valve	Aortic Stenosis	Infective Endocarditis	Coarctation of Aorta	Photos (BAV)*	
1844	Paget[52]	6	3	3	0	0	0	C
1865	Peacock[54]	3	3	3	0	0	+(3/3)†	C
1886	Osler[50]	18	18	6‡	8	0	0	C
1904	Mönckeberg[47]	32	0	32	0	0	0	D
1923	Lewis, Grant[39]	13	13	0	13	0	0	C
1926	Cabot[9]	28	2	23	5	0	+(2/3)	R
1926	Clawson, Bell, Hartzell[14]	13	—	13	6	0	+(1/1)	R
1928	Wauchope[100]	52	52	0	7	2	0	C
1928	Abbott[1]	200	51	0	13	200§	0	C
1931	Christian[13]	21	0	21	0	0	0	R
1931	Margolis, Ziellessen, Barnes[40]	42	20	42	0	0	+(3/4)¶	U
1933	Laws, Levine[37]	11	—	11	2	0	0	R
1934	McGinn, White[41]	35	4	35	1	0	0	U
1934	Bishop, Bishop, Trubek[7]	9	9	2	1	1	+(2/2)	R
1935	Gibbs[25]	12	0	12	0	0	0	A
1936	Sohval, Gross**[24,91]	15	1	15	0	0	+(1/4)	NR
1937	Gross[29]	16	2	16	—	—	+	R
1938	Lesnick, Schlesinger[38]	17	0	17	0	0	0	NR
1938	Clawson, Noble, Lufkin[15]	132	0	97	0	0	0	R
1939	Dry, Willius[18]	15	1	15	0	0	+(2/4)	R
1940	Cohen, Gray, Nash, Fink[17]	7	1	7	0	0	0	R
1941	Koletsky[35]	7	7	4	1	1	0	C
1945	Reich[56]	22	0	22	0	0	0	—
1947	Karsner, Koletsky[33]	119	16	119	0	0	+(2/8)	R
1947	Reifenstein, Levine, Gross[57]	104	58	11	23	104	0	C, R
1948	Horan, Barnes[31]	100	—	100	6	0	0	R
1952	Anderson, Kelsey, Edwards[2]	49	—	49	0	0	+(2/4)‖	C, R
1953	1953 Campbell, Kauntze[12]	4	4	4	0	0	+(4/4)#	C
1955	Smith, Matthews[92]	27	20	27	0	7	+(2/2)	C
1959	Bacon, Matthews[6]	28	28	19	0	4	+(6/6)	C
1961	Edwards[20]	10	8	9	0	0	+(8/10)	C
1968	Campbell[10]	46	16	46	0	0	0	C

Abbreviations: A = atherosclerotic, C = congenital, D = degenerative, NR = non-rheumatic, R = rheumatic, U = uncertain.

*The second number in this vertical column represents the number of gross illustrations of the aortic valve.

†Drawings.

‡Osler described only 1 of these 6 cases as having aortic stenosis ("The two segments from their position obstruct and narrow the orifice") but the description of the valves make it likely that the orifices were stenotic.

§Rupture of ascending aorta in 33 and cerebral hemorrhage in 25.

‖One of the 2 is unicuspid.

¶One of the 3 is unicuspid.

#Three of the 4 are unicuspid. All are drawings.

**Clinical features in the cases were reported by Friedberg and Sohval.

attention to the congenitally bicuspid aortic valve's extreme propensity to be the site of IE. Whether Osler realized that stenosis was also a complication of the bicuspid condition is less clear; if he did, he did not write about that possibility. Mensah and Friesinger[44] believed that Osler missed entirely "the link" between the bicuspid valve and AS. The reason they suggested was that the average age of death in the United States in 1900 was 47 years, and most patients with stenosis superimposed on a bicuspid aortic valve are older than that. Osler described 18 patients with congenitally bicuspid aortic valves that he studied at autopsy, and although the aortic valve "was invariably thickened and the seat of sclerotic changes," clear AS was seen in only 1 of the 18 patients. During the 20th century a number of other authors stressed the frequent connection between IE and the congenitally malformed aortic valve.[3–5,8,22,23,58,63]

That pure aortic regurgitation (AR) without superimposed IE may be a consequence of the bicuspid condition was not

reported, to our knowledge, until 1981 when Roberts and colleagues[83] described 13 such patients who had undergone aortic valve replacement. Today, the bicuspid valve without superimposed IE is recognized as one of the most common causes of pure (no element of stenosis) AR severe enough to warrant aortic valve replacement.[65,80,83,88]

An association between aortic valve disease and "cystic medial necrosis" of the ascending aorta appears to have been first described by McKusick (1921–2008) and colleagues[43] in 1957. Although the structure of the valve was not known in their 4 cases, the severity of stenosis and the lack of associated mitral valve disease makes congenital malformation of the aortic valve highly likely, and that association has been reported often since then.[30,42,86,88,95,97,104] Not only is the ascending aorta dilated in patients with stenotic and/or purely regurgitant congenitally bicuspid aortic valves, but tears in the ascending aorta with or without dissection also is a recognized complication.[86,88] Roberts and Roberts[86] found aortic dissection to be 5 times more frequent in patients with bicuspid compared to those with tricuspid aortic valves. Although the ascending aorta may be dilated in patients with AS or pure AR, Roberts and associates[88] found that aortic-medial-elastic-fiber loss was absent or minimal in 90% of their patients undergoing aortic valve replacement for stenotic unicuspid or bicuspid aortic valves, but in only

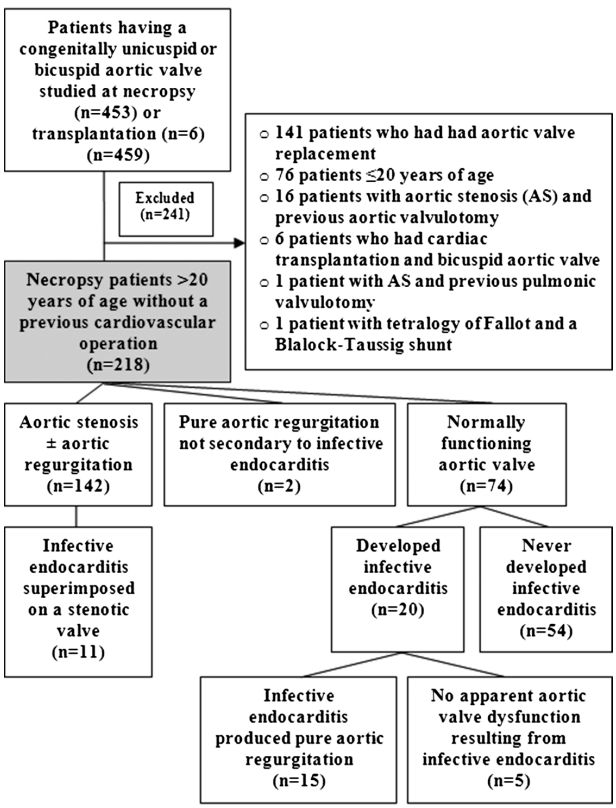

FIGURE 1. Flow chart showing our experience with patients having a congenitally malformed aortic valve. Of the total 453 patients with unicuspid or bicuspid aortic valves studied at necropsy, 241 (53%) were eliminated from this analysis mainly because of an operative intervention on the aortic valve. (In addition, we have examined 276 operatively excised congenitally unicuspid and 1330 operatively excised congenitally bicuspid aortic valves, but these 1606 cases were not included in the present analysis.)

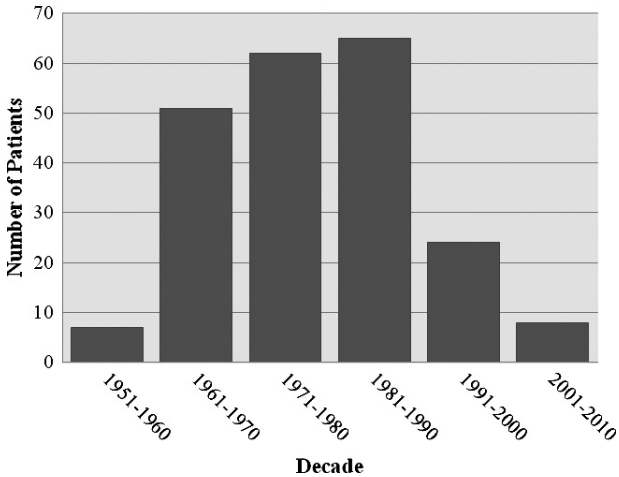

FIGURE 2. Decades during which the 218 patients were studied.

50% of patients with purely regurgitant bicuspid aortic valves. This observation suggests that the type of aortic valve dysfunction may be a major determinant of whether the ascending aorta needs to be resected at the time of aortic valve replacement, an occurrence that has become quite common in the last 2 decades.[95,96,104]

To our knowledge, the concept of the unicuspid aortic valve was first proposed by Edwards[19] (1911–2008) in 1958. He described a unicuspid unicommissural stenotic aortic valve as having only 1 true commissure and a slit-like orifice resembling an exclamation point. He opined that the unicuspid unicommissural aortic valve was stenotic from the time of birth, and that this valve structure was the structure most commonly seen in infants and very young children with severe AS. In contrast, he believed that the bicuspid aortic valve was not stenotic at birth but became so as fibrous tissue and calcific deposits developed on its cusps. Several reports on consequences of the unicuspid unicommissural aortic valve followed.[21,70,78,81,88] Probably most surgeons and pathologists call the unicuspid unicommissural aortic valve a congenitally bicuspid valve.[87] In 2007, Roberts and associates[71] described 4 patients whose operatively excised stenotic aortic valves had no true commissures and similar degrees of "commissural" fusion resulting in a central symmetrical triangular-shaped orifice. The authors called the valve congenitally unicuspid acommissural.

In the last 20 years most morphologic studies of stenotic, purely regurgitant, and infected congenitally malformed aortic valves have been of operatively excised valves, because the frequency of autopsy in patients dying in hospitals in the United States has dropped to <10% in most institutions, and operative intervention is now common and usually successful.[48,53,66–80,88,90,93,94] Nevertheless, multiple studies of operatively excised valves have demonstrated that the unicuspid ones contain the most calcium and therefore are the heaviest and the most stenotic,[69] that the bicuspid valves are the next most calcified, and that the stenotic tricuspid valves have the least calcific deposits and therefore are the lightest and the least stenotic.[66,69,70,72,78,84] Additionally, these studies have shown that men have significantly heavier valves than women, and that the stenotic valves are far heavier than the purely regurgitant valves with or without superimposed active IE.[66,69,70,72,78,80,88]

Although the natural history of patients having congenitally unicuspid or bicuspid aortic valves has received attention during the last 50 years, most reports included some patients

TABLE 2. Comparison of Various Variables Among Patients With Unicuspid vs Bicuspid Aortic Valves (n = 218)

		Aortic Valve Structure	
Variable	**Total, n = 218 (100%)**	**Unicuspid, n = 28 (13%)**	**Bicuspid, n = 190 (87%)**
Age at death (years)			
Mean ± SD [median]	55 ± 15 [57]	48 ± 15 [53]*	56 ± 15 [57]*
(Range)	(21–89)	(25–77)	(21–89)
Gender†			
Men	169 (80%)	26 (93%)	143 (78%)
Women	43 (20%)	2 (7%)	41 (22%)
Aortic valve function (before infective endocarditis)			
Normal	74 (34%)	0	74 (39%)
Stenosis	142 (65%)	27 (96%)	115 (61%)
Pure regurgitation	2 (1%)	1 (4%)	1 (<1%)
Infective endocarditis‡			
Active	25 (11%)	2 (7%)	23 (12%)
Healed	6 (3%)	1 (4%)	5 (3%)
Infective endocarditis superimposed on a:			
Previously normally functioning valve	20 (9%)	0	20 (11%)
Previously stenotic valve	11 (5%)	3 (11%)	8 (4%)
Previously purely regurgitant valve	0	0	0
Heart weight (g)			
Mean ± SD [median]	558 ± 162 [530]	603 ± 143 [605]§	551 ± 164 [520]§
(Range)	(170–1050)	(320–880)	(170–1050)

*-*p - value = 0.0109.

†Data missing on 6 patients.

‡Of the 25 patients with active infective endocarditis, 16 had a normally functioning aortic valve prior to infection and 9 had a previously stenotic valve; of the 6 patients with healed infective endocarditits, 4 had a previously normal aortic valve and 2 had infection superimposed onto a stenotic valve.

§-§p - value = 0.1428.

TABLE 3. Comparison of Various Variables According to Type of Function of the Congenitally Malformed Aortic Valve (n = 218)

	Aortic Valve Function Prior to Infective Endocarditis		
Variable	**Normal, n = 74 (34%)**	**Stenosis, n = 142 (65%)**	**Pure Regurgitation, n = 2 (1%)**
Age at death (years)			
Mean ± SD [median]	48 ± 16 [48]*	59 ± 14 [59]*	32, 42
(Range)	(21–82)	(23–89)	
Gender†			
Men	57 (78%)	110 (80%)	2
Women	16 (22%)	27 (20%)	0
Valve structure			
Unicuspid	0	27 (19%)	1
Bicuspid	74	115 (81%)	1
Infective endocarditis			
Active	16 (22%)	9 (6%)	0
Healed	4 (5%)	2 (1%)	0
Aortic valve orientation			
Anterior/posterior	43/63 (68%)	62/89 (70%)	1
Right/left	20/63 (32%)	27/89 (30%)	0
Raphe present	46/57 (81%)	66/78 (85%)	1
Heart weight (g)			
Mean ± SD [median]	477 ± 148 [450]‡	598 ± 152 [573]‡	470, 920
(Range)	(170–1010)	(300–1050)	

-, ‡-‡p - value = <0.0001.

†Data missing on 6 patients.

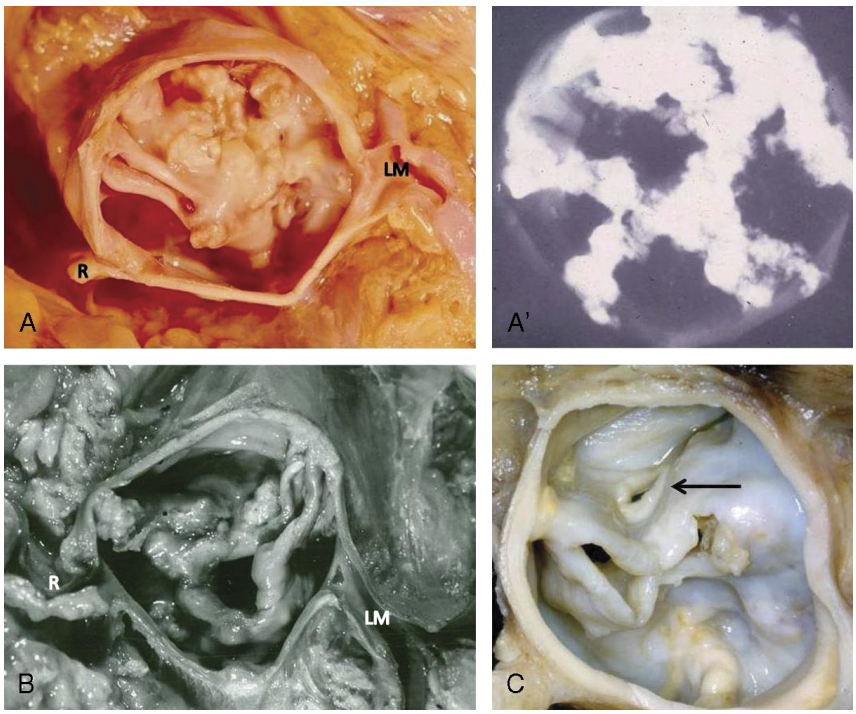

FIGURE 3. Unicuspid aortic valves in 3 patients. A and A′ (radiograph), Valve of a 48-year-old man who had been well until 5 months before death when signs and symptoms of heart failure began and progressed. Terminally, he developed pneumonia, which prevented cardiac catheterization and cardiac valve replacement. The heart weighed 750 g. LM = left main coronary artery; R = right coronary artery. B, Valve of a 31-year-old man who had been a splendid 3-letter athlete and had won his country club golf championship several days before dying quickly of severe acute heart failure. The heart failure was the first he had ever had. The peak systolic pressure difference between left ventricle and aorta was 11 mm Hg. The patient also had considerable AR with similar diastolic pressures in both left ventricle and aorta (50 and 60 mm Hg respectively). He was deemed too sick to undergo aortic valve replacement in 1969. His heart at necropsy weighed 880 g. C, Valve of a 26-year-old man who died suddenly while dancing in a disco. According to some friends, he had no known medical ailments and was not taking any medications. Prior to the sudden collapse there were apparently no complaints of feeling ill. The heart weighed 760 g. A cuspal perforation (arrow) is present, suggesting previous IE that had healed.

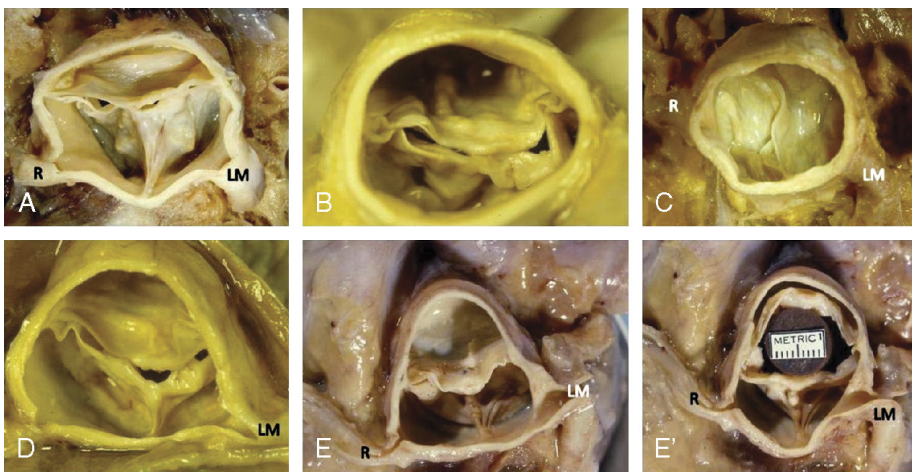

FIGURE 4. Congenitally bicuspid normally functioning aortic valves in 5 different patients, none of whom had clinical evidence of aortic valve disease. In 4 of the 5 patients the cusps are situated anterior-to-posterior, and in 1 patient (C), right-to-left. A, Valve in a 36-year-old man who died suddenly while watching television. He was a habitual alcoholic and he had a fatty liver that weighed 2900 g. The heart weighed 405 g and the coronary arteries were clean. The right coronary artery was dominant. He was found dead by fellow residents in a shelter home. LM = left main coronary artery; R = right coronary artery. B, Valve in a 63-year-old man who had undergone 2 coronary bypass grafting operations. The second operation was performed 17 days before death. The heart weighed 590 g. There are a few calcific deposits on each cusp but each cusp was freely mobile. C, Valve in a 60-year-old man who died of cancer of the pancreas. His heart weighed 470 g and he had systemic hypertension. D, Valve in a 71-year-old woman who died from Parkinson disease. She was cachexic. The heart weighed 290 g. E and E′, Valve shown in both ventricular diastole (E) and ventricular systole (E′) in a 72-year-old woman who died after a fall. The heart weighed 300 g. Small calcific deposits were present in each cusp.

who also had aortic valve replacement or repair, and thus their "natural history" was interrupted by this therapeutic event, or they included only children or young adults, or patients were followed not until death, but just for a few years.[11,16,22,32,45,46,55,89] In the present report we focus on 218 patients with congenitally malformed aortic valves all studied at necropsy by the same investigator (WCR) during the last 50 years. Our purpose is to determine the natural history of patients with this valvular abnormality without operative intervention on the aortic valve at any time.

METHODS

The cases included in the current study came from 37 different institutions including 34 cases from the National Heart, Lung, and Blood Institute (NHLBI), Bethesda, MD; 133 cases from 12 different hospitals in the Washington, DC, area, including 31 from Georgetown University Hospital; 27 from medical institutions in Dallas, TX, and the remaining 24 from 22 different medical centers excluding those in the Washington, DC, and Dallas, TX, areas. The cases from the Washington, DC, area were obtained as follows: WCR gave a conference for nearly 25 years on cardiovascular pathology at 11 or 12 hospitals each month (at Georgetown University Hospital weekly) and after conference the specimens were brought to the Pathology Branch, NHLBI, and described and photographed. Both the reports and photographs were sent to the submitting institutions. Some specimens were received via mail from more distant institutions. All hearts were examined and classified by WCR, and most were photographed or drawn or both.

The clinical records were provided by the Clinical Center of the National Institutes of Health (34 cases) or Baylor University Medical Center at Dallas (16 cases) or by the submitting hospital. Cardiac catheterization and echocardiographic data were sought in all patients. The symptomatic status of each patient was determined from the clinical records. The severity of the aortic valve dysfunction, if present, was determined by the cardiac catheterization reports for patients having that procedure. For the few cases with echocardiograms, we used that examination to determine severity, and if a patient had both an echocardiogram and a left-sided cardiac catheterization, we used the catheterization data. Photographs of stenotic aortic valves in patients in whom cardiac catheterization had been performed were compared to valves in patients in whom no cardiac catheterization was performed to show that the degrees of severity by anatomic examination were similar. All patients included were aged >20 years at the time of death. We excluded patients who had undergone aortic valvulotomy, aortic valve replacement, or replacement of another cardiac valve. Additionally, patients with mitral stenosis irrespective of the structure of the aortic valve were excluded. Patients with diffuse fibrous thickening of the mitral valve leaflets irrespective of the function of the mitral valve

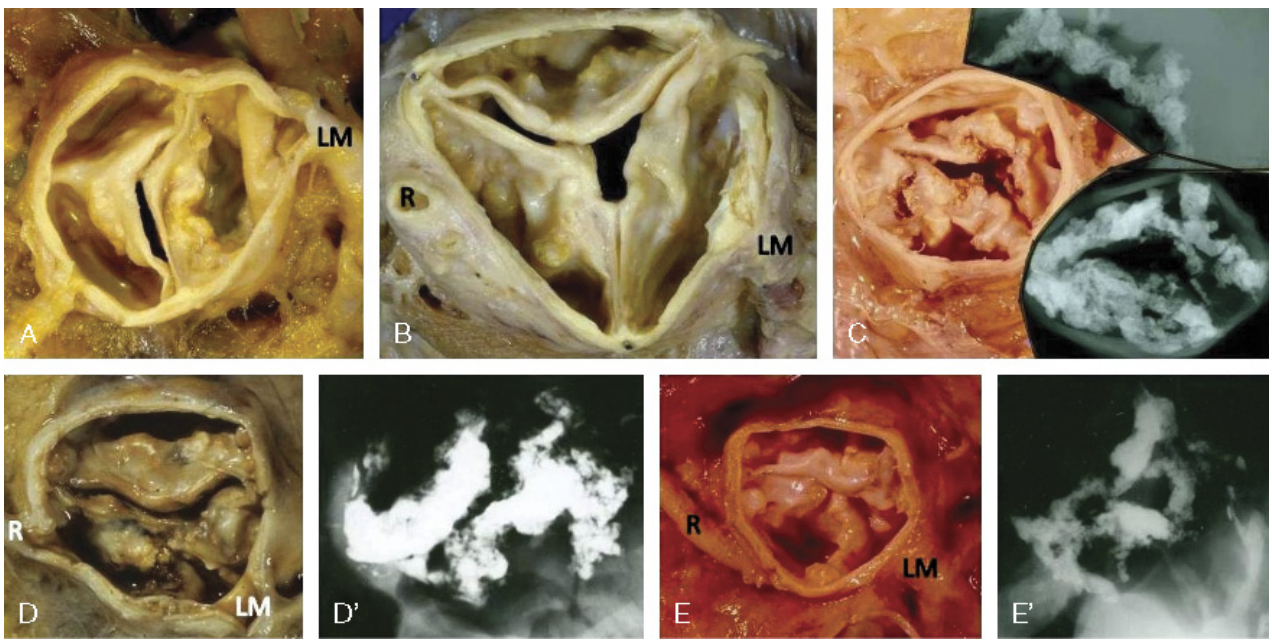

FIGURE 5. Stenotic bicuspid aortic valves in 5 patients, all of whom had undergone cardiac catheterization. The 2 cusps in the valve shown in (A) are located right and left, and all of the others are located anterior and posterior. Heavy calcific deposits are present in each valve. A, Valve belonging to a 65-year-old woman who died from cancer of the breast. She never had evidence of cardiac dysfunction. The heart at necropsy weighed 410 g. The transvalvular peak systolic pressure gradient was 25 mm Hg. LM = left main coronary artery. B, Valve in a 77-year-old man who had evidence of severe heart failure. The peak transvalvular systolic pressure gradient was 50 mm Hg. The left main coronary artery was severely narrowed, and the left ventricular ejection fraction was 40%. The heart weighed 570 g and the left ventricular wall was free of foci of necrosis and fibrosis. R = right coronary artery. C, Valve in a 37-year-old man who died suddenly in a cardiac clinic of a major hospital. He had periodic chest pain and exertional dyspnea for nearly 2 years. The peak transvalvular systolic pressure gradient was 50 mm Hg. Not only was the aortic valve heavily calcified, but also the mitral annulus was as well. The coronary arteries were insignificantly narrowed. D and D′, Heavily calcified aortic valve in a 67-year-old man who had severe angina pectoris and a 72 mm Hg peak systolic pressure gradient across the aortic valve. He had cardiac arrest the night before planned aortic valve replacement. At necropsy, the heart weighed 680 g and the heart was devoid of foci of necrosis and fibrosis. E and E′, Heavily calcified valve in a 61-year-old man who died suddenly. Earlier, the peak transvalvular systolic pressure gradient was 100 mm Hg. The heart weighed 530 g.

also were excluded. The origin of the 218 patients included in the present study is shown in the flow chart of Figure 1. The decades in which the patients were studied at necropsy are shown in Figure 2.

Means, standard deviations, and percentages were calculated to describe the study cohort. Differences in demographic, clinical, and morphologic details were tested using a 2-tailed t-test with equal variance in Microsoft Excel 2007 (Microsoft, Redmond, WA).

RESULTS

Frequency of Unicuspid and Bicuspid Aortic Valves

Of the 218 patients, 28 (13%) had unicuspid aortic valves and 190 (87%) had bicuspid aortic valves (Table 2). The men (80% of the total) at death ranged in age from 21 to 89 years (mean, 54 ± 15 yr) and the women (20% of the total), from 21 to 87 years (mean, 59 ± 15 yr). Of the 28 unicuspid valves, 26 (93%) were in men and 2 (7%) were in women; of the 190 bicuspid aortic valves, 78% were in men and 22% were in women. Thus, of the congenitally malformed aortic valves in men, 85% were bicuspid and 15% were unicuspid; in the women, 95% were bicuspid and 5% were unicuspid.

Age and Race

The ages of patients with unicuspid and bicuspid aortic valves differed significantly ($p < 0.02$): 48 ± 15 years in the unicuspid group and 56 ± 15 years in the bicuspid group (Table 2). The mean age of patients with stenotic valves was greater than that of patients with normally functioning valves before IE occurred (age 59 ± 14 yr vs. 48 ± 16 yr, respectively; $p < 0.0001$) (Table 3). Of the total patients, 89% were white, 8% were black, and 3%, other.

Aortic Valve Function

Of the 28 patients with unicuspid valves, 27 (96%) were stenotic and 1 (4%) was purely regurgitant (no apparent evidence of stenosis) (Figure 3, Table 3). Of the 190 bicuspid valves, 74 (39%) appeared to have functioned normally (until IE appeared and caused AR in 15 [20%] of the 74 patients) (Figure 4); 115 (61%) were clearly stenotic as judged morphologically (Figures 5–8); and 1 (<1%) was purely regurgitant without evidence at any time of IE. Thus, none of the 28 unicuspid valves appeared to have functioned normally, whereas 74 (39%) of the bicuspid valves (at least before IE altered that status) appeared to have functioned normally; only 2 valves (1 unicuspid, 1 bicuspid) were purely regurgitant (neither having

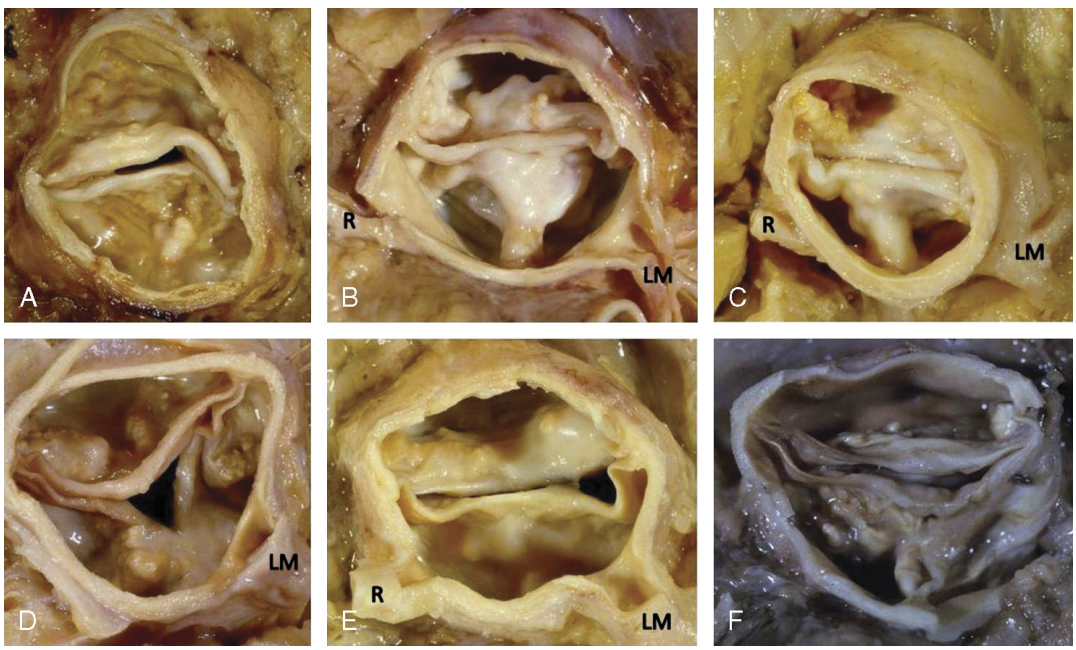

FIGURE 6. Stenotic bicuspid aortic valves in 6 patients, none of whom had undergone cardiac catheterization. At autopsy, the left ventricular walls in each were free of foci of necrosis and fibrosis. The cusps in each of these 6 patients are located anterior and posterior. A, Valve in a 69-year-old woman who died suddenly while driving. Necropsy disclosed a tear in the ascending aorta and an aortic dissection limited to the ascending and arch portions. The heart weighed 400 g. Both right and left circumflex coronary arteries were narrowed by atherosclerotic plaque. B, Valve in a 57-year-old woman in whom aortic valve stenosis was never diagnosed clinically. She presented to the hospital in severe pulmonary edema, and precordial examination did not disclose a murmur because of the chest noise. The coronary arteries were insignificantly narrowed. LM = left main coronary artery; R = right coronary artery. C, Valve in a 56-year-old woman who died suddenly after running up a flight of stairs. Previously she had fainted on 2 occasions during exertion, the first time was 10 months before she died. She never went to a physician and was not known to have medical problems. At autopsy, the heart weighed 380 g. D, Valve in a 62-year-old man who had nonfatal cardiac arrest 5 months before death and severe acute heart failure beginning 14 days before death, which progressively worsened. The patient weighed >135 kg and had considerable pulmonary hypertension (pulmonary artery pressure was 70/30 mm Hg). He also developed ventricular tachycardia. His heart weighed 900 g. E, Valve in a 48-year-old man who died suddenly while eating. At autopsy, there was no evidence of aspiration. The heart weighed 540 g. F, Valve in a 56-year-old man who had evidence of heart failure during his last 3 years of life. He died suddenly. The heart weighed 670 g and the coronary arteries were devoid of atherosclerotic plaques.

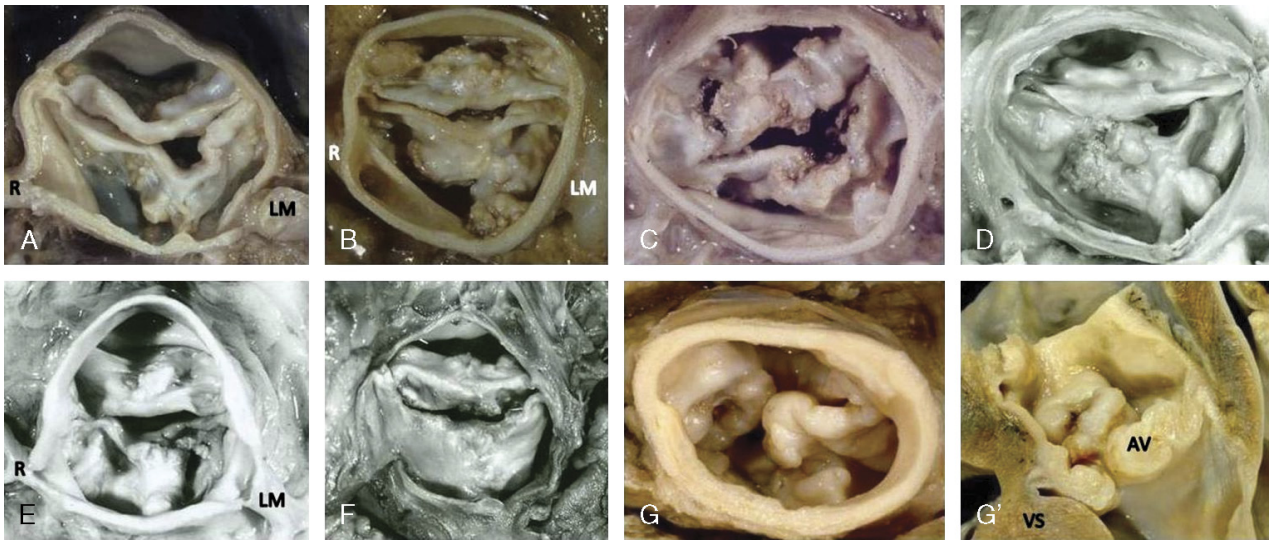

FIGURE 7. Stenotic aortic valves in 7 patients, none of whom had cardiac catheterization but all of whom had morphologic evidence of severe aortic valve stenosis. A, Valve in a 66-year-old man who died suddenly but also had severe coronary disease. A healed myocardial infarct was present in the left ventricular wall. LM = left main coronary artery; R = right coronary artery. B, Valve in an 81-year-old man who also had considerable coronary disease, a healed left ventricular myocardial infarct, and severe angina pectoris. The heart weighed 750 g. C, Valve in a 60-year-old man who died of heart failure. Heavy calcific deposits were found in the aortic valve cusps, the mitral valve annulus, and the major epicardial coronary arteries. At necropsy, he had both a healed and an acute myocardial infarct. His coronary arteries were severely narrowed. His heart weighed 1050 g. D, Valve in a 64-year-old woman who developed exertional dyspnea 4 months before death and the heart failure progressed. At necropsy the coronary arteries were essentially devoid of atherosclerotic plaques and there were no foci of necrosis or fibrosis in the ventricular walls. The heart weighed approximately 500 g. Additionally, the patient had evidence of pulmonary fibrosis. E, Heart in a 51-year-old man who died suddenly while taking a shower. At necropsy, the heart weighed 800 g, the coronary arteries were devoid of plaques, and the ventricular walls were free of foci of necrosis or fibrosis. F, Valve in a 69-year-old woman who had evidence of heart failure intermittently for 2 years but never chest pain or syncope. She was hospitalized for evaluation and found to have AS but she refused to have cardiac catheterization or operation and died of worsening heart failure. At necropsy, the aortic valve, mitral annulus, and epicardial coronary arteries were heavily calcified. The coronary arteries were severely narrowed but the left ventricular wall was devoid of foci of necrosis or fibrosis. G and G′, Aortic valve from above and from the side in a 23-year-old man who died suddenly while walking home after playing tennis for 2 hours. The heart weighed 590 g and a small scar was present near the apex of the left ventricle. The coronary arteries were devoid of plaques. AV = aortic valve; VS = ventricular septum.

IE). Thirty-four percent of the men and 37% of the women had normally functioning aortic valves; 65% of the men and 63% of the women had stenotic valves, and 2 men and no women had intrinsically purely regurgitant valves.

Frequency of IE

Of the 25 patients with active IE, 16 (64%) involved a previously normally functioning aortic valve (Figures 9–13) and 9 (36%), a previously stenotic valve (Figures 14–18, Table 4).

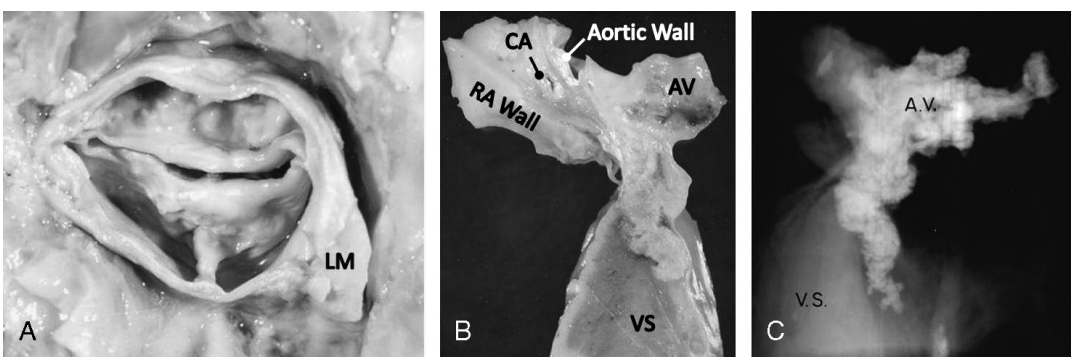

FIGURE 8. Stenotic bicuspid aortic valve. A, Aortic valve from above in a 59-year-old man who died of heart failure. The left ventricular peak systolic pressure gradient across the aortic valve was 45 mm Hg by catheterization. A raphe is present in the anterior cusp. LM = left main coronary artery. B, Longitudinal section through the right atrial (RA) wall, coronary artery (CA), aortic valve (AV), and ventricular septum (VS) showing heavy calcific deposits in the aortic valve and in the apex of the muscular ventricular septum obliterating the AV bundle and also the left bundle branch. C, Radiograph of the same longitudinal section showing heavy calcific deposits again in the aortic valve, membranous ventricular septum, and in the area of the AV bundle and left bundle branch. An electrocardiogram showed complete heart block.

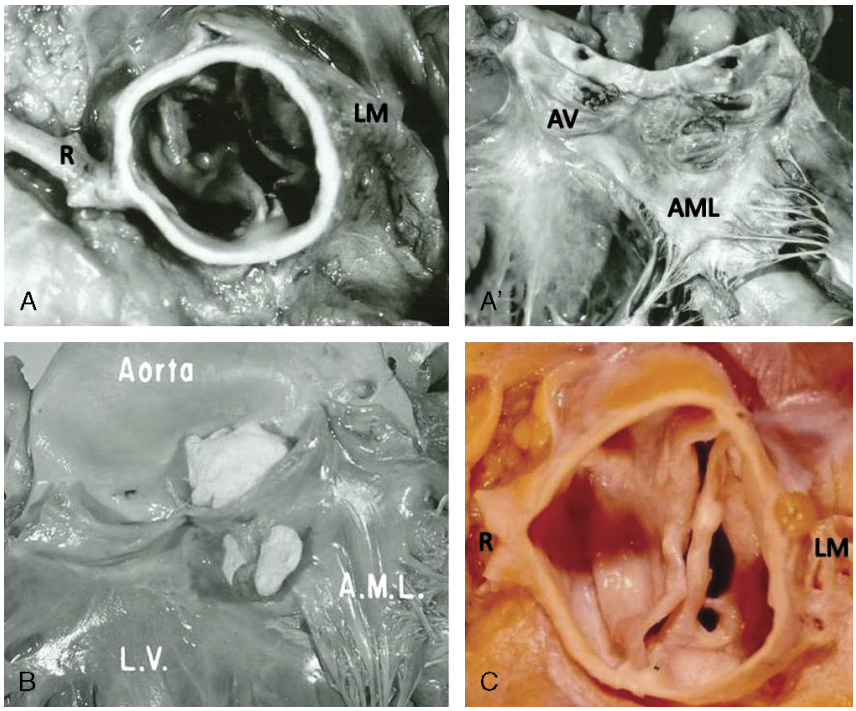

FIGURE 9. Infective endocarditis involving a bicuspid valve. A and A′, Aortic valve from above and after opening showing perforations in each of the 2 cusps and vegetative material on the ventricular surface of each cusp and bordering the perforations. The patient was a 39-year-old man who died suddenly on the golf course. His heart weighed 1010 g and he had evidence of severe AR. In addition to evidence of both active and healed infection on the aortic valve, several chordae tendineae from the mitral valve had ruptured due to dislodgment of vegetative material from the aortic valve. The ventricle, despite its severe dilatation, was devoid of foci of necrosis and fibrosis in its wall. Three months before his sudden death he underwent cardiac catheterization. The left ventricular pressure was 140/20 and simultaneous aortic pressure, 140/38 mm Hg. AML = anterior mitral leaflet; AV = aortic valve; LM = left main coronary artery; R = right coronary artery. B, Valve opened in a 33-year-old man who had had IE that healed and left severe AR thereafter. Cotton has been placed in the posterior (noncoronary) cusp. One of the 2 cusps was perforated by the infection, and heart failure was the consequence. He died of severe heart failure, becoming emaciated. The heart weighed 430 g. No foci of ventricular wall necrosis or fibrosis were present at autopsy. LV = left ventricle. C, Valve in a 47-year-old man who had active IE in the past that had healed. He died suddenly from a skull fracture when a horse kicked him in the head. In addition to the bicuspid aortic valve he had a congenitally bicuspid pulmonic valve that had functioned normally. His heart weighed 590 g. The regurgitation was due mainly to the perforations in 1 of the 2 cusps.

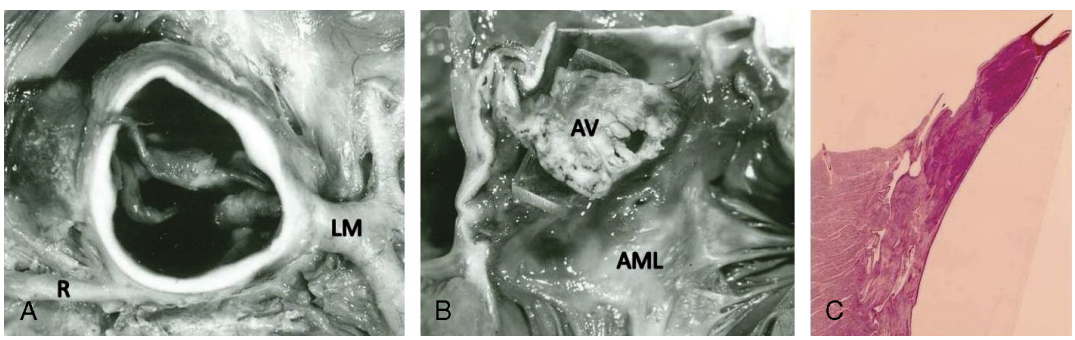

FIGURE 10. Active IE superimposed on a congenitally bicuspid valve. A, Valve from above in a 22-year-old man, an opiate addict who developed *Staphylococcus epidermidis* endocarditis several weeks before death. The cusps are located anterior and posterior. The infection involves mainly the anterior cusp which is perforated by the vegetative material. LM = left main coronary artery; R = right coronary artery. B, Longitudinal view of the vegetation that has spread to the aortic wall causing a ring abscess in it. AML = anterior mitral leaflet; AV = aortic valve. C, Photomicrograph of a histology section of a left ventricular papillary muscle that is completely necrotic. The epicardial coronary arteries were entirely normal. The patient developed severe AR with resulting severe heart failure. At necropsy, the heart weighed 670 g. A mycotic aneurysm also developed in the membranaceous portion of the ventricular septum protruding into the right side of the heart. (Hematoxylin and eosin stain, 5× magnification.)

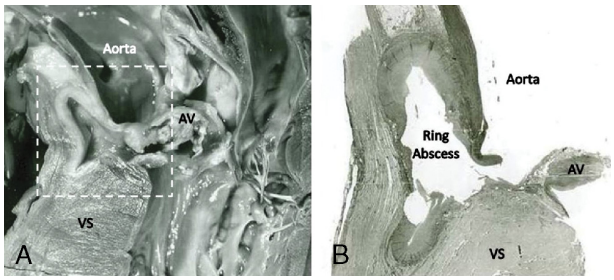

FIGURE 11. Active IE superimposed on a previously normally functioning bicuspid aortic valve. A, Longitudinal view of an aortic valve showing massive destruction of the cusps with a ring abscess adjacent to the aorta within the ventricular septum in a 41-year-old man. The valve was made severely incompetent by the infection. AV = aortic valve; VS = ventricular septum. B, Photomicrograph showing an incompetent aortic valve cusp, wall of aorta and ring abscess that separates the aorta from the left ventricle. VS = ventricular septum. The valve cusps were oriented right and left. This patient developed alpha streptococcus IE following a dental procedure approximately 2 months before the onset of symptoms or approximately 4 months before death. During the infection he developed evidence of severe AR. When hospitalized 20 days before death his blood pressure was 100/0 mm Hg and he was in pulmonary edema. He died the night before scheduled aortic valve replacement, which almost certainly would have been fruitless. His heart weighed 500 g. The residual aortic valve cusps contained minimal calcific deposits. (Movat stain, 5 × magnification.)

Additionally, 6 patients had both histories of and morphologic residual damage from active IE that had healed. Of the 31 total cases of IE, 3 (10%) involved a unicuspid valve (3 [11%] of the 28 unicuspid valves) and 28 (90%) involved a bicuspid valve (28 [15%] of the 190 bicuspid valves). Of the 31 cases, 26 (84%) were men (15% of total men), and 5 (16%) were women (12% of total women). Various clinical and morphologic findings in the 31 patients with active and healed IE are summarized in Table 4.

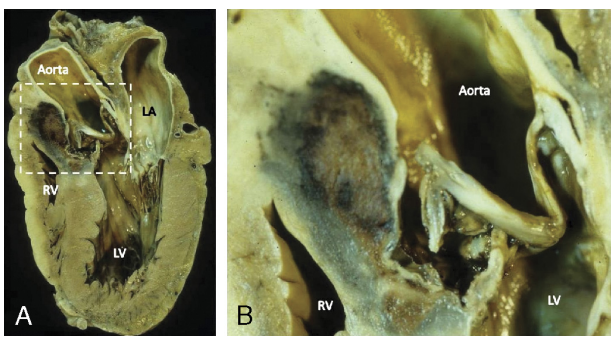

FIGURE 12. Active IE involving a bicuspid aortic valve that had probably functioned normally before the infection. A, Longitudinal view of a heart showing a huge ring abscess anteriorly in a 36-year-old woman who had multiple myeloma and Turner syndrome. LA = left atrium; LV = left ventricle; RV = right ventricle. B, Close-up of the ring abscess. The cusps are slightly thickened by fibrous tissue and were oriented right and left. The patient was in her usual state of health until approximately 6 weeks before death, when she developed abdominal pain and was found to have a large spleen. A bone marrow biopsy was done and it was consistent with multiple myeloma. Several days before death she lost consciousness and was hospitalized. Blood cultures grew alpha streptococcus. She died shortly thereafter. At autopsy, the cardiac infection was limited to the aortic valve and adjacent para-aortic areas. The spleen weighed 1850 g and the liver, 2600 g. The heart weighed 460 g and was devoid of myocardial lesions except in the area adjacent to the aortic valve.

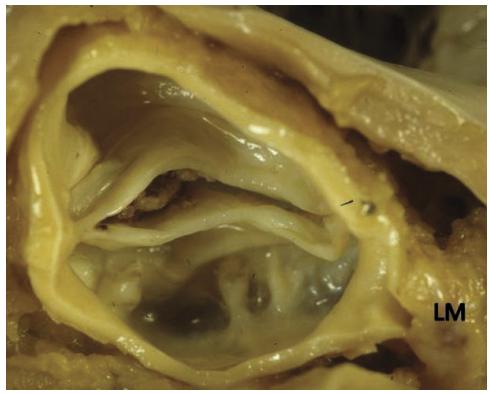

FIGURE 13. Active IE involving a normally functioning bicuspid aortic valve. View of the aortic valve from above showing vegetation between the 2 cusps but no vegetative material on the aortic aspect of either cusp. The patient was a 52-year-old man who had undergone bone marrow transplantation 1 month before death because of myelodysplastic syndrome. After the bone marrow transplant he never left the hospital. Infective endocarditis was never diagnosed clinically. Necropsy disclosed vegetation on each of the 2 cusps of the bicuspid valve, and the cusps were located anterior and posterior. The heart weighed 610 g. LM = left main coronary artery.

Hemodynamic Data

Of the 218 patients, hemodynamic data were available in 36 patients (17%): 34 had AS, with peak transvalvular gradients ranging from 11 to 148 mm Hg (mean, 69; median, 69 mm Hg).

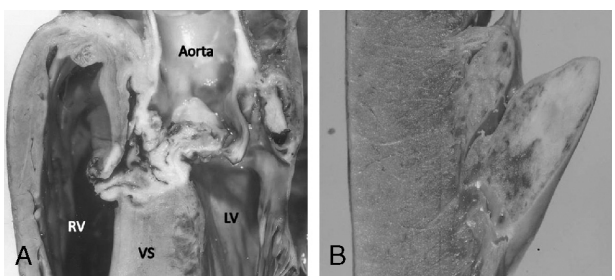

FIGURE 14. Active IE. A, Longitudinal cut of the aortic valve and adjacent structures showing severe destruction of the aortic valve cusps and large ring abscesses both anteriorly burrowing into the right ventricle (RV) and posteriorly pushing toward the left atrium in a 30-year-old man who was a habitual fingernail biter to the extent that his fingernail area would bleed. X-ray of the heart at necropsy showed calcific deposits in the aortic valve. LV = left ventricle. VS = ventricular septum. B, A left ventricular papillary muscle that is necrotic due to extremely diminished profusion of the left ventricle. The epicardial coronary arteries were normal. The patient was hospitalized 16 days before death because of fever, chills, malaise, and myalgia. Several blood cultures grew *Staphylococcus aureus*. He developed several signs typical of active IE. An electrocardiogram showed right bundle branch block, and an echocardiogram suggested a bicuspid aortic valve. The heart at autopsy weighed 560 g.

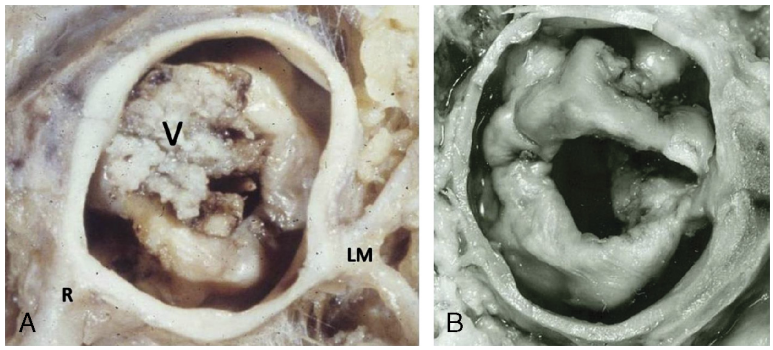

FIGURE 15. Active IE superimposed on a stenotic unicuspid unicommissural aortic valve. A, View of the valve from above showing vegetation (V) further narrowing the orifice. LM = left main coronary artery; R = right coronary artery. B, View of the valve after excising the vegetation showing the underlying stenotic valve with heavy calcific deposits. The patient was a 35-year-old man, an opiate addict who became ill 6 weeks before death, including the last 4 weeks in a hospital. Despite septic emboli in the kidneys and spleen, blood cultures throughout his hospitalization were negative. At necropsy, the heart weighed 550 g.

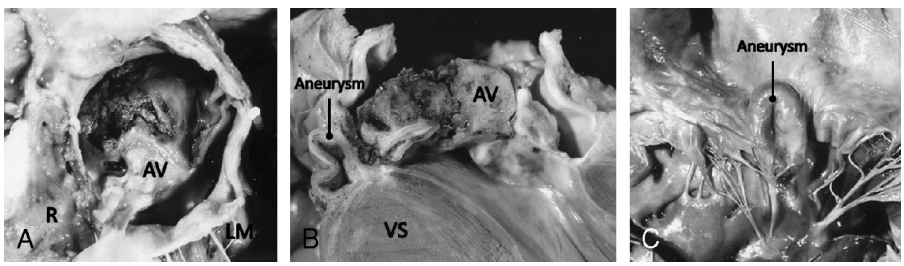

FIGURE 16. Active IE superimposed on a stenotic bicuspid aortic valve. A, Aortic valve from above showing vegetation superimposed on the right cusp of a congenitally bicuspid aortic valve in a 67-year-old man who was known to have AS and had some evidence of heart failure for at least a year before his final illness, which was rapidly progressing heart failure. Calcific deposits are present in both right and left cusps but the vegetative material involves the right cusp much more than the left. AV = aortic valve; LM = left main coronary artery; R = right coronary artery. B, Longitudinal section across the aortic valve showing the large vegetation involving mainly the right cusp with rather heavy calcific deposits in the left cusp. A ring abscess is also present in the base of the aorta. VS = ventricular septum. C, View of the tricuspid valve, right atrium, and right ventricle showing an aneurysm of the membranaceous ventricular septum bulging into the right side of the heart. Blood cultures were all positive for alpha hemolytic streptococcus, and the patient was treated with penicillin. During the infection his electrocardiogram changed from prolonged P-R interval to complete heart block. Not only did he have evidence of AS, but mitral regurgitation also developed during the infection. This is an example of IE superimposed on a heavily calcified stenotic aortic valve. The infection rapidly spread to the soft tissue both above and below the valve creating a ring abscess of the aorta and an aneurysm of the membranaceous ventricular septum.

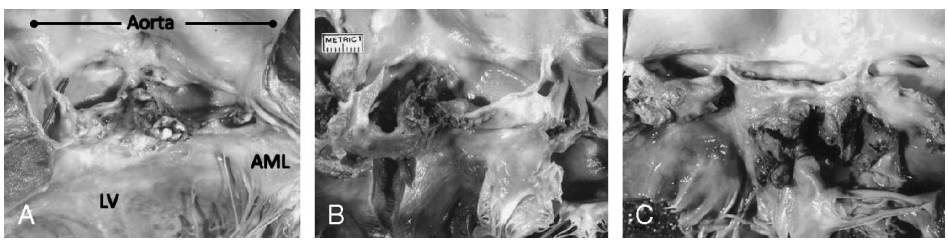

FIGURE 17. Active IE: opened aortic valves exposing vegetations that have destroyed the 2 aortic valve cusps to varying degrees. A, Valve in a 35-year-old man who had alpha streptococcus IE with a ring abscess and severe AR. This patient was an opiate addict who probably had infection in the past that healed because the heart at necropsy weighed 760 g. The cusps are located anterior and posterior, and a raphe is present in the anterior cusp. The infection caused severe AR. AML = anterior mitral leaflet; LV = left ventricle. B, Valve in a 60-year-old man. The cusps are located anterior and posterior, and vegetative material is particularly heavy in the area of the raphe. This patient had the triad of active IE, meningitis, and pneumonitis. The vegetative material had burrowed into the aortic wall causing a large ring abscess and complete heart block. The patient was a habitual alcoholic. The last episode of IE produced acute symptoms beginning 7 days before death. Blood cultures grew *Streptococcus pneumoniae*. Complete heart block developed 2 days before death. Six months before death he had undergone cardiac catheterization because of severe AR: an 11 mm Hg peak transvalvular pressure gradient and severe AR were found. C, Bicuspid valve in a 45-year-old man with pre-existing aortic valve stenosis who was hospitalized 12 days before death because of confusion, fever, and leukocytosis. Echocardiogram showed vegetation on the aortic valve, and blood cultures grew *Streptococcus milleri*. Computed tomogram (CT) disclosed multiple cerebral infarcts. The patient weighed >135 kg. At autopsy, the heart weighed 920 g. The 2 aortic valve cusps were calcified. The vegetative material had burrowed into the right ventricular cavity. Emboli were present in the brain. Additionally, there was diffuse fibrinous pericarditis. Both left ventricular papillary muscles were necrotic in the absence of significant coronary disease. Both aortic valve cusps were perforated by the vegetation.

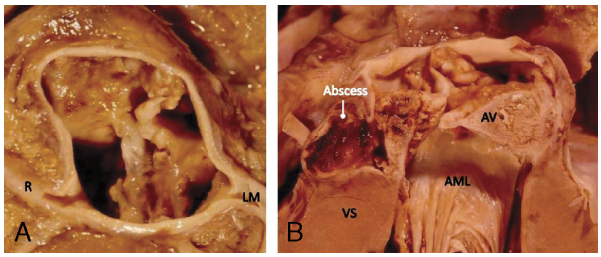

FIGURE 18. Active IE superimposed on a heavily calcified stenotic bicuspid aortic valve. A, Valve from above with vegetative material involving the cuspal margins with underlying heavy calcific deposits. The cusps are located right and left. LM = left main coronary artery; R = right coronary artery. B, Longitudinal cut of the aortic valve area showing destruction by vegetative material of 1 cusp with extension into the ventricular septum (VS) producing a large ring abscess. The aortic valve (AV) is heavily calcified and was quite stenotic. At autopsy, the heart weighed 850 g. The patient was a 54-year-old man who was known to have a precordial murmur for at least 10 years. He developed exertional dyspnea 2 years before death. Cardiac catheterization 2 months before death disclosed severe AS. The aortic valve could not be crossed by the catheter, and he was discharged to have his carious teeth extracted before planned aortic valve replacement. He developed alpha streptococcus endocarditis with onset of symptoms 23 days before death. While being treated on the ward he had sudden fatal cardiac arrest. Both left ventricular papillary muscles were necrotic. AML = anterior mitral leaflet.

TABLE 4. Patients Having Infective Endocarditis (IE) on a Unicuspid or Bicuspid Aortic Valve (n = 31)

	Infective Endocarditis	
Variable	**Active n = 25 (81%)**	**Healed n = 6 (19%)**
Unicuspid aortic valve	2	1
Bicuspid aortic valve	23	5
Aortic valve function before IE		
Normal	16	4
Stenosis ± regurgitation	9	2
Pure regurgitation	0	0
Aortic valve function after IE		
Normal	5	0
Stenosis ± regurgitation	9	2
Pure regurgitation*	11	4
Predisposing factors		
Intravenous opiate use	5	0
Alcoholism	4	1
Dental procedure	4	1
Stepped on a nail	1†	0
Habitual fingernail biter	1	0
Heart block		
First degree	1	0
Right bundle branch	1	0
Complete	2	0
Infected aneurysm		
Cerebral	3	0
Aorta	4	2

*The 15 patients with pure aortic regurgitation as a result of infective endocarditis had normally functioning aortic valves prior to infection.

†Patient is also an alcoholic.

TABLE 5. Men With Bicuspid Aortic Valves and Coronary Artery Bypass Grafting (n = 12)

Patient	Aortic Valve Function*	Age (Years)	Total Number of CABG Procedures	Total Number of Distal Anastamoses	Interval From Last (First) CABG to Death (Months)	Heart Weight (g)	Cause of Cardiac Death
1	Normal	43	1	3	0	530	CABG
2	Normal	62	1	4	<1	470	CABG
3	Normal	63	1	4	110	690	CAD-IC
4	Normal	63	2	—	<1 (—)	590	CABG
5	Normal	69	1	2	108	700	CAD-IC
6	Normal	71	2	7	<1 (84)	650	CABG
7	Stenotic	49	1	2	96	525	CAD-IC
8	Stenotic	53	2	3	0 (132)	460	CABG
9	Stenotic	56	1	2	17	475	AS-SD
10	Stenotic	58	1	—	2	—	CABG
11	Stenotic	68	1	4	17	550	CAD-IC
12	Stenotic	69	2	4	48 (132)	760	CAD-SD

Abbreviations: AS = aortic stenosis, CABG = coronary artery bypass grafting, CAD = coronary artery disease, IC = ischemic cardiomyopathy, SD = sudden death, — = no information available.
*Prior to infective endocarditis.

TABLE 6. Causes or Modes of Death in Patients Studied at Necropsy Having a Unicuspid or Bicuspid Aotic Valve (n = 218)

Variable	Aortic Valve Function Prior to Infective Endocarditis: Normal n = 74 (34%)	Stenosis n = 142 (65%)	Pure Regurgitation n = 2 (1%)	Total n = 218 (100%)	
Cardiac					
Aortic valve disease					
Heart failure	0	62		62	
Infective endocarditis					
Active	16*	9		25	
Healed	4†	2‡		6	124
Sudden	0	21	1§	22	(57%)
Cardiac catheterization	0	7		7	
Anesthesia induction for aortic valve replacement	0	1		1	
Ruptured sinus of Valsalva aneurysm	1	0		1	
Coronary artery disease					
Acute myocardial infarction	2	5		7	
Ischemic cardiomyopathy	3	2		5	25
Sudden	3	4		7	(11%)
Early post coronary bypass¶	4	2		6	
Other					
Hypertrophic cardiomyopathy (sudden)	1	0		1	
SUBTOTAL	34	115	1	150 (69%)	
Non-cardiac vascular					
Ascending aortic tear (±dissection)	12**	4	1	17	
Cerebrovascular accident	0	1		1	
Pulmonary embolism	1	0		1	
Early postop after vascular surgery	0	3‖		3	
SUBTOTAL	13	8	1	22 (10%)	
Non-cardiac non-vascular					
Cancer	14	3		17	
Suicide	2	0		2	
Trauma	3#	0		3	
Renal failure	1	3		4	
Pancreatitis (alcoholism)	1	0		1	
Gastrointestinal hemorrhage	0	1		1	
Food aspiration	0	1		1	
Hypothermia	0	1		1	
Cirrhosis	1	0		1	
Parenchymal lung disease	1	1		2	
Parkinson's disease	1	0		1	
Early postop after bowel surgery	0	2		2	
SUBTOTAL	24	12	0	36 (17%)	
Cause unclear					
Sudden death outside hospital, cause unclear	2	0		2	
Unknown	1	7		8	
SUBTOTAL	3	7	0	10 (5%)	

*The aortic valve appeared to have been normal before the active infective endocarditis (IE) appeared. Of the 16 patients, all but 1 died of the active infection; the remaining patient developed IE after a bone marrow transplant for myelodysplastic syndrome, and the aortic valve appeared funtionally normal despite the infection.

†The IE caused perforation in 1 or both aortic valve cusps in 3 of these 4 patients leading to severe aortic regurgitation (AR) in each. The remaining patient had no cuspal perforations, but had a prolapsed aortic valve, several ruptured chords of anterior mitral leaflet, and a saccular aneurysm of ascending aorta causing residual AR from IE; he died suddenly; he also had coarctation of the aorta.

‡The degree of stenosis probably was worsened by the superimposed IE which healed in each.

§Patient had massive cardiomegaly: heart weight 920 g. Of the 218 patients, 5 (2%) had hearts weighing >900 g. One had AR secondary to healed cuspal perforation from IE; 3 others had severely stenotic aortic valves, and of these 3, 1 had superimposed IE.

‖One patient died 1 day after resection of abdominal aortic aneurysm; 1 patient died 3 days after femoral-popliteal bypass grafting; 1 patient died 6 hours after axillo-femoral bypass grafting.

¶A total of 12 patients (6%) had coronary artery bypass grafting (CABG): 6 died within 2 months of the last CABG operation and are included here; of the other 6 patients having had CABG, all died late: 2 with ischemic cardiomyopathy (IC) and a normally functioning aortic valve; 2 with IC and a stenotic aortic valve; 1 died suddenly secondary to aortic stenosis, and 1 with a stenotic aortic valve died suddenly secondary to coronary artery disease.

#One patient, a habitual alcoholic, died from injuries in a single-car accident; the other 2 from broken necks from falls. None had significant coronary disease.

**One patient died during operative repair of ascending aortic dissection, and another, 3 weeks after operative repair for dissection.

The peak transvalvular gradient was ≤50 mm Hg in 12 patients (35%) and >50 mm Hg in 22 patients (65%). Neither of the 2 patients with normally functioning aortic valves had a gradient across the valve. The heart weights in the patients with hemodynamically confirmed AS ranged from 410 to 880 g (mean, 629; median, 655 g).

Coronary Artery Bypass Grafting

Twelve (6%) (all men) of the 218 patients had coronary artery bypass grafting (CABG), in 4 patients on 2 occasions (Table 5). In none of the 16 CABG operations on those 12 patients was a procedure performed on the aortic valve. At necropsy, the bicuspid aortic valve appeared to have functioned normally in 6, and to be stenotic in the other 6. Two of the latter 6 had CABG twice. The presence of AS in these latter 6 patients was either not diagnosed at the time of CABG or the degree of AS was not considered severe enough to warrant aortic valve replacement at the time of CABG.

Causes of Death

Causes of death are divided into 4 major groups: cardiac, noncardiac vascular, noncardiac and nonvascular, and cause unclear (Table 6). Of the 218 patients, death was attributed to aortic valve disease in 124 patients (57%), to the consequences of coronary arterial atherosclerosis in 25 (11%), and to hypertrophic cardiomyopathy in 1. Thus, death was attributed to cardiac disease in 150 (69%) of the 218 patients. Death in 22 patients (10%) was attributed to noncardiac vascular causes, and in 36 patients (17%) to neither cardiac nor vascular causes. Among the 22 patients with noncardiac vascular causes of death, 17 (8% of the total) died of tears in the ascending aorta with resulting fatal hemopericardium; 14 had tears with dissection and 3 had tears without dissection[86] (Table 7; Figure 19).

Reasons Aortic Valve Operation Was Not Performed

We considered the reasons an aortic valve operation was not performed in these patients (Table 8). Of the 131 patients with AS without superimposed IE, 25 patients (19%) died suddenly outside the hospital, and most of them previously were asymptomatic. Another 32 patients (24%) died before 1970, a period when aortic valve replacement essentially was limited to only those with severe symptoms and severe AS. Most patients with acute IE were not operated on because their physicians believed aortic valve replacement to be fruitless in the circumstances.

Heart Weight and Its Relation to Aortic Valve Structure, Valve Function, and Sex

Heart weight data were available in 178 (82%) of the 218 patients (Tables 2, 3, and 9). The mean heart weights were greater in patients with unicuspid aortic valves than in those with bicuspid aortic valves (603 ± 143 g vs. 551 ± 164 g, respectively; $p = 0.14$); in patients with stenotic compared to those with normally functioning valves (598 ± 152 g vs. 477 ± 148 g, respectively; $p < 0.0001$); and in men compared to women (586 ± 156 g [270–1050 g] vs. 433 ± 136 g [170–730], respectively; $p < 0.0001$).

Orientation of the 2 Cusps and Presence of a Raphe Among Patients With Bicuspid Valves and Relation to Valve Complication

In 69% of the valves, 1 cusp was located anterior, and the other posterior, such that both coronary arteries arose from the anterior cusp; in 31% of cases, 1 cusp was right and the other, left, such that 1 coronary artery arose from 1 cusp and the other

TABLE 7. Patients Studied at Necropsy Having a Unicuspid or Bicuspid Aortic Valve and Tear in Ascending Aorta (n = 17)

Patient	Aortic Valve Function*	Age (Years)	Gender	Heart Weight (g)	Number of Aortic Valve Cusps	Aortic Valve Orientation	Raphe Present	SH
Aortic Tear With Dissection								
1	Normal	21	M	450	2	A/P	+	+
2	Normal	30	M	410	2	A/P	+	—
3†	Normal	48	M	—	2	A/P	+	+
4	Normal	52	M	530	2	A/P	+	+
5†	Normal	57	M	—	2	A/P	+	+
6	Normal	62	M	690	2	A/P	0	—
7	Normal	67	M	—	2	R/L	+	+
8	Normal	69	F	—	2	A/P	+	0
9	Normal	71	F	430	2	A/P	+	—
10	Regurgitant	32	M	470	1	—	—	—
11	Stenotic	25	M	610	1	—	—	—
12	Stenotic	69	F	400	2	A/P	0	—
13	Stenotic	70	M	390	2	R/L	+	+
14	Stenotic	82	M	590	2	A/P	+	+
Aortic Tear Without Dissection								
15	Normal	21	M	450	2	A/P	+	—
16	Normal	32	F	310	2	A/P	+	—
17	Normal	32	M	510	2	A/P	0	—

Abbreviations: — = no information available or not applicable, 0 = absent, + = present, A/P = anterior/posterior, R/L = right/left, SH = systemic hypertension by history.

*Prior to infective endocarditis.

†Patient had operative intervention for acute aortic dissection.

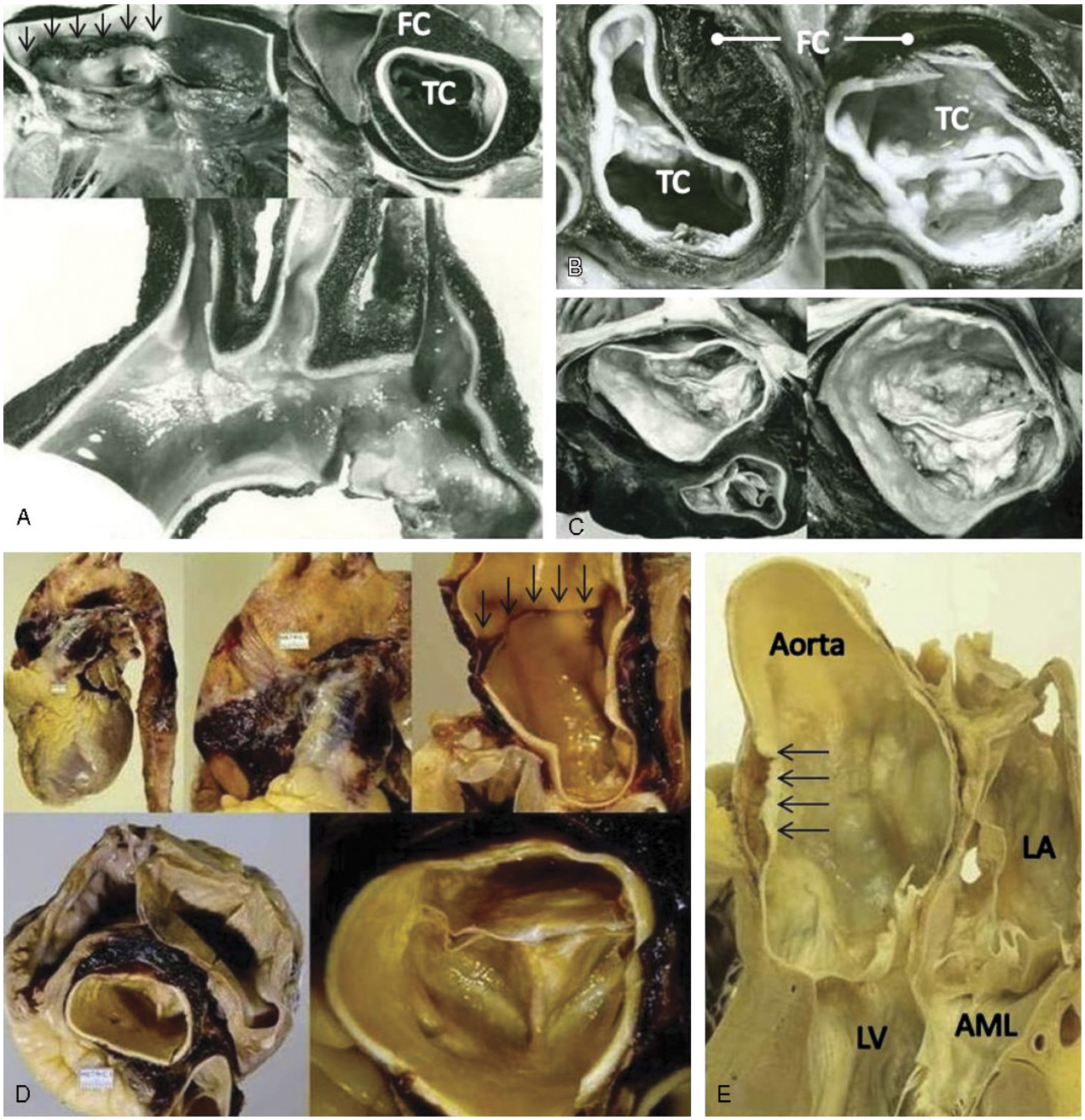

FIGURE 19. Acute aortic dissection with tear (arrows) in ascending aorta in 5 patients with congenitally bicuspid aortic valves. All patients died from rupture of the false channel (FC) into the pericardial sac. A, Views of the opened bicuspid aortic valve and a transverse tear just above that with hematoma in the false channel of ascending aorta and in the false channel of each of the arch arteries and in a portion of descending thoracic aorta. This woman had Turner syndrome. The aortic valve had functioned normally. The heart weighed 310 g. The medial dissection of aorta extended into its adventitia and then into the adventitia of the pulmonary trunk, which shares a common adventitia with the aorta. TC = true channel. B, Two views of hematoma in the false channel just above the aortic valve (left) and at the level of the aortic valve (right). The true channel is indented by the hematoma in the false channel. The bicuspid valve is calcified and stenotic. The heart weighed 385 g. C, Stenotic bicuspid valve with a hematoma in the false channel and fatal rupture into the pericardial sac. The valve is stenotic. Symptoms of the acute dissection began 36 hours before death. The dissection was limited to ascending aorta. A large tear was present in the distal ascending aorta. The heart weighed 585 g. D, Bicuspid valve that functioned normally in a 69-year-old woman who developed chest and neck pain a few hours before dying suddenly in the hospital. The dissection was limited to ascending aorta. The dissection extended into the adventitia of aorta and then into the adventitia of pulmonary trunk. E, Longitudinal view of ascending aorta, left atrium (LA), and left ventricle (LV) showing a false channel in the anterior of the aorta just above the 1 aortic valve commissure. The patient had an aortic isthmus coarctation that had been resected earlier in life. The proximal ascending aorta had a diameter of 8.5 cm. The heart weighed 690 g. The bicuspid aortic valve was devoid of calcium and appeared to have functioned normally. AML = anterior mitral leaflet.

TABLE 8. Reasons Patients With Aortic Stenosis or Pure Aortic Regurgitation Did Not Undergo Aortic Valve Replacement (Excludes 74 Patients With Normally Functioning Aortic Valves With or Without Superimposed Infective Endocarditis)

Variable	AS (n = 142)	AR Without IE (n = 2)
Not diagnosed during life	43	1
Active infective endocarditis	9	0
Diagnosed clinically but		
Died before 1962 (before AVR established)	5	0
Severe heart failure/too sick to have AVR	23	0
Another condition preventing AVR	8	0
AVR planned but died before operation	10	1
Refused AVR	7	0
Refused cardiac catheterization	1	0
Death in the cardiac catheterization lab	7	0
AS not severe enough to warrant AVR or severity of AS not appreciated clinically	12	0
Reason unclear/died suddenly	5	0
Unknown	12	0

Abbreviations: AR = aortic regurgitation, AS = aortic stenosis, AVR = aortic valve replacement, IE = infective endocarditis.

TABLE 9. Comparison of Heart Weights According to Gender, and Structure and Function of the Congenitally Malformed Aortic Valve (n = 178*)

Variable	Heart Weight (g) Mean ± SD [Median] (Range), Number (%) of Enlarged Hearts†
Total	
Men (n = 146)	586 ± 156 [570] (270–1050), n = 127 (87%)
Women (n = 32)	433 ± 136 [413] (170–730), n = 21 (66%)
Valve structure	
Unicuspid	
Men (n = 23)	607 ± 144 [610] (320–880), n = 21 (91%)
Women (n = 1)	510, n = 1 (100%)
Bicuspid	
Men (n = 123)	582 ± 159 [550] (270–1050), n = 106 (86%)
Women (n = 31)	431 ± 138 [410] (170–730), n = 20 (65%)
Aortic valve function	
Aortic stenosis	
Men (n = 95)	622 ± 149 [610] (320–1050), n = 88 (93%)
Women (n = 20)	491 ± 130 [478] (300–730), n = 17 (85%)
Pure aortic regurgitation secondary to IE	
Men (n = 12)	583 ± 175 [545] (405–1010), n = 12 (100%)
Women (n = 3)	350, 400, 460, n = 2 (67%)
Unassociated with IE	
Men (n = 2)	920, 470, n = 2 (100%)
Women (n = 0)	—
Functionally normal	
Men (n = 37)	487 ± 120 [470] (270–700), n = 25 (68%)
Women (n = 9)	314 ± 81 [310] (170–430), n = 2 (22%)
Infective endocarditis	
Active	
Men (n = 21)	571 ± 147 [540] (375–920), n = 20 (95%)
Women (n = 4)	363 ± 93 [375] (240–460), n = 2 (50%)
Healed	
Men (n = 4)	670 ± 245 [620] (430–1010), n = 4 (100%)
Women (n = 1)	510, n = 1 (100%)

— = not applicable.

*Heart weights were only available in 178 (82%) of the 218 patients included in this study.

†Hearts weighing >350 g in women and >400 g in men.

coronary artery from the other cusp (Tables 3 and 10). A raphe (false commissure) was present in at least 83%: if the configuration of the cusps was anterior and posterior, the raphe, if present, was always in the anterior cusp; if the cusps were configured right and left, the raphe, if present, was always in the right cusp.

Associated Congenital Cardiovascular Anomalies

Six patients had aortic isthmic coarctation, with operative excision in 2 early in life; 5 patients had a congenitally bicuspid pulmonic valve, and 1 had a quadricuspid pulmonic valve, all of which functioned normally and otherwise were structurally normal; 1 patient had a parachute mitral valve or single papillary muscle syndrome (Shone syndrome); 2 patients had Turner syndrome; and 4 had a congenital coronary anomaly (Table 11). None of the coronary anomalies was clinically important.

DISCUSSION

We describe here the findings in 218 patients studied at necropsy with congenitally unicuspid (n = 28) or bicuspid (n = 190) aortic valves. Of the 4 major complications of this congenital anomaly—valve stenosis, pure valve regurgitation, valve infection, and aortic dilatation—most (142 [65%]) had AS including 27 (96%) of the 28 patients with unicuspid valves and 115 (61%) of the 190 patients with bicuspid valves. Of the 17 with pure AR, 15 developed it as a consequence of IE and 2 as a consequence of the aortic valve malformation without superimposed IE; of these 17 patients, 1 had a unicuspid valve and 16 (94%) had a bicuspid valve. Possibly the most intriguing observation in this study was the finding of 59 patients (27%) (aged 21–82 yr; mean, 51 ± 16 yr) with congenitally bicuspid valves that appeared to have functioned normally during their entire lifetimes. Although 31 (14%) of the 218 patients developed IE at some time, the infection was superimposed on an already stenotic valve in 11, and on a previously normally functioning valve in 20. Of the latter 20 patients, 15 developed AR as a consequence of IE; of the other 5, all of whom died during the active infection, none apparently had AR during life as a consequence of IE.

Although several studies have discussed the natural history of AS, particularly of congenital origin,[11,16,21,22,32,45,46,55,58,59,84,89] to our knowledge only 4 reports have described the natural history of patients with bicuspid aortic valve. Roberts[58] in 1970 described at necropsy 85 patients in whom he found a congenitally bicuspid aortic valve, but only 42 (19% of 218) of them are included in the present study because the other 43 patients underwent operative therapy for AS (n = 40) or pure AR (n = 3). Nevertheless, as far as we know it was the first study to separate the patients into those with AS, pure AR, and IE. Nearly all of the AS patients had severe AS (peak transvalvular gradient ranging from 12 to 165 mm Hg [mean, 92 mm Hg]).

Fenoglio and colleagues[22] in 1977 described 152 patients with congenitally bicuspid aortic valves studied at autopsy. Of their 43 patients with AS, 23 (53%) had "died with congestive heart failure or during attempted surgical repair of the stenotic aortic valve." Therefore, their "natural history" was also interrupted by this iatrogenic event, namely aortic valve surgery. Nevertheless, their study is the closest to the present study, and some similarities and differences are shown in Table 12. The percentage of patients with AS and pure AR, for reasons unclear, is quite different between the 2 studies. It appears that their study was based on examination of observations recorded in autopsy reports prepared by a number of different prosectors.

TABLE 10. Comparison of Various Variables Among Patients With Bicuspid Aortic Valves Oriented Right to Left vs Anterior to Posterior (n = 153)

	Aortic Valve Orientation	
Variable	**Right/Left, n = 47 (31%)**	**Anterior/Posterior, n = 106 (59%)**
Age at death (years)		
Mean ± SD [median]	53 ± 16 [57]*	56 ± 15 [59]*
(Range)	(23–82)	(21–89)
Gender†		
Men	38 (84%)	79 (75%)
Women	7 (16%)	26 (25%)
Aortic valve function (before infective endocarditis)		
Normal	20 (43%)	43 (41%)
Stenosis	27 (57%)	62 (58%)
Pure regurgitation	0	1 (1%)
Infective endocarditis		
Active	11 (23%)	7 (7%)
Healed	2 (4%)	3 (3%)
Infective endocarditis superimposed on a:		
Previously normally functioning valve	10 (21%)	7 (7%)
Previously stenotic valve	3 (6%)	3 (3%)
Previously purely regurgitant valve	0	0
Heart weight (g)		
Mean ± SD [median]	545 ± 163 [505]‡	535 ± 165 [510]‡
(Range)	(320–1010)	(170–1050)

*-*p - value = 0.27

† Data missing on 3 patients.

‡-‡p - value = 0.76.

TABLE 11. Patients Studied at Necropsy Having a Unicuspid or Bicuspid Aortic Valve and Other Congenital Cardiovascular Malformations (n = 19)

Congenital Abnormality	Aortic Valve Function*	Age (Years)	Gender	Number of AV Cusps	Aortic Valve Orientation	Raphe Present	Infective Endocarditis		Heart Weight (g)
							Active	Healed	
Coarctation of aorta									
1†,‡	Normal	21	M	2	A/P	+	0	0	450
2	Normal	30	M	2	A/P	+	0	0	410
3	Normal	36	M	2	A/P	+	+	0	500
4	Stenotic	39	M	2	—	—	0	0	1000
5†	Normal	46	M	2	A/P	0	0	+	650
6	Normal	62	M	2	A/P	0	0	0	690
Coronary anomalies									
Hypoplasia									
RCA and LMCA									
7	Stenotic	26	M	1	—	—	0	0	760
High takeoff									
LMCA									
8	Normal	29	M	2	A/P	+	+	0	500
LMCA and RCA									
9	Normal	40	M	2	A/P	+	0	0	320
RCA									
10	Normal	52	M	2	—	—	+	0	610
Pulmonic valve									
Bicuspid									
11	Stenotic	34	M	1	—	—	0	0	570
12	Stenotic	37	M	2	R/L	+	0	0	860
13	Stenotic	47	F	2	R/L	+	0	0	340
14	Normal	47	M	2	R/L	+	0	+	590
15	Stenotic	66	M	2	R/L	+	0	0	—
Quadricuspid									
16	Normal	57	F	2	A/P	0	0	0	—
Shone syndrome									
17	Normal	30	M	2	R/L	+	0	0	395
Turner syndrome									
18	Normal	32	F	2	A/P	+	0	0	310
19	Normal	36	F	2	R/L	+	+	0	460

Abbreviations: — = not applicable or no information available, 0 = absent, + = present, A/P = anterior/posterior, AV = aortic valve, LMCA = left main coronary artery, RCA = right coronary artery, R/L = right/left.

*Prior to infective endocarditis.

†Early operative intervention for isthmic coarctation.

‡Patient also has a separate left main and circumflex coronary ostia.

TABLE 12. Comparison of the Present Necropsy Study to the Earlier Study (1977) by Fenoglio et al

Aortic Valve Function (After Infective Endocarditis)	Fenoglio Series (n = 152)	Roberts Series (n = 218)
Aortic stenosis	43 (28%)	142 (65%)
Age (year) (mean)	28–89 (55)	23–89 (59)
Men	40 (93%)	110 (77%)
Infective endocarditis		
Acute	5 (12%)	9 (6%)
Healed	4 (9%)	2 (1%)
Coarctation of aorta	5 (12%)	1 (1%)
Heart weight (g) (mean)	320–900 (603)	300–1050 (598)
Unicuspid aortic valves	0	27 (19%)
Aortic valve calcium	43 (100%)	142 (100%)
Pure aortic regurgitation	61 (40%)	17 (8%)
Age (year) (mean)	21–69 (35)	22–52 (37)
Men	61 (100%)	14 (82%)
Infective endocarditis		
Acute	28 (46%)	11 (65%)
Healed	19 (31%)	4 (24%)
Coarctation of aorta	6 (10%)	1 (6%)
Heart weight (g) (mean)	310–1300 (611)	350–1010 (569)
Unicuspid aortic valves	0	1 (6%)
Aortic valve calcium	25 (41%)	4 (24%)
Functionally normal	48 (32%)	59 (27%)
Age (year) (mean)	20–81 (48)	21–82 (51)
Men	41 (85%)	45 (76%)
Infective endocarditis*		
Acute	5 (10%)	5 (8%)
Healed	0	0
Coarctation of aorta	7 (15%)	4 (7%)
Heart weight (g) (mean)	200–675 (386)	170–700 (453)
Unicuspid aortic valves	0	0
Aortic valve calcium	7 (15%)	15 (25%)

*Infective endocarditis on a previously normally functioning aortic valve resulting in no valvular dysfunction.

Mills and associates[46] in 1978 described 41 patients with "non-invasive" evidence of a bicuspid aortic valve and followed them for 5–25 years (mean, 11 yr). Two patients underwent an aortic valve operation for severe AS; 2 developed pure AR; 3 developed IE resulting in AR in 2 and death in 1; 5 developed mild AS; 3 died (none as a consequence of aortic valve disease); and the clinical status did not change in the remaining 26.

The study by Michelena and colleagues[45] in 2008 from the Mayo Clinic was an analysis of 212 asymptomatic patients (mean age, 32 ± 20 yr) in whom a bicuspid aortic valve was found by echocardiogram. Survival 20 years after diagnosis was 90% ± 3%. The natural history centered on the status (operated, unoperated, dead, symptomatic, asymptomatic) 20 years after diagnosis.

We found only 1 study that included any natural history information on patients with unicuspid aortic valves, the study by Falcone and colleagues[21] in 1971 who described at necropsy 21 patients with stenotic unicuspid aortic valves, 3 of whom had undergone an aortic valve operation. Their ages (17 males) ranged from 16 to 62 years (mean, 44 yr). The transvalvular peak gradients (13 patients) ranged from 15 to 158 mm Hg (mean, 87 mm Hg). The heart weights ranged from 400 to 800 g (mean, 590 g).

Today, most congenitally malformed aortic valves are encountered by echocardiogram, computed tomography, or magnetic resonance imaging and not at operation or autopsy.[62] Although prophylactic use of antibiotics to prevent infectious endocarditis has not been recommended,[102] the identification of a congenitally malformed aortic valve allows patients and physicians to have a heightened awareness for symptoms that may suggest valve infection. Further, noninvasive imaging can help determine the need for, and proper timing of, valve surgery, and can identify aortic dilatation, which often occurs without causing symptoms. Because aortic valve malformations may occur in families, the finding in 1 family member should probably suggest a search in other family members.[27]

It is also well to keep in mind that another malformation of the aortic valve, namely aortic valve atresia, is the worst known cardiac condition because it allows the shortest lifespan. Indeed, aortic valve atresia is the most common cause of death in the first week of life.[85]

Some positive features of the present study include the following: 1) a large number of unoperated cases were collected during the 50 years in which aortic valve commissurotomy and replacement operations were available; 2) all cases were studied by a single investigator (WCR) and data were not simply retrieved from autopsy protocols prepared by a variety of physicians with varying expertise in cardiovascular disease; 3) most of the patients appeared to have had severe AS or AR; and 4) natural history data were presented on patients with unicuspid aortic valves.

Deficiencies or limitations of the present study include the following: 1) hemodynamic and echocardiographic data were available in a minority of patients; 2) 12 (6%) of the 218 patients studied had had CABG but no aortic valve surgery (possibly considered a "contaminant"); and 3) despite an extensive examination of a large number of patients, all studied at necropsy, the reason that some patients with bicuspid valves developed AS, some developed IE, a few developed AR without superimposed IE, and some (59 [31%] of the 190 with bicuspid valves) never developed an aortic valve complication, was not forthcoming.

Conclusion

In conclusion, the current study highlights several important findings in patients with congenitally malformed aortic valves. A patient with a unicuspid or bicuspid aortic valve 1) may go through life without ever developing dysfunction of the valve (27% of the total); 2) will most likely develop AS as a result of the congenital malformation (65% of the total); 3) is most likely male (80% of the total); 4) appears to be highly susceptible to IE (14% of the total); 5) is at a relatively high risk of developing aortic dissection or tears in the ascending aorta (8% of the total); and 6) is at an increased risk of dying from complications related to the aortic valve (57% of the total).

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