British Heart Journal, 1972, 34, 569–574.

Pathogenesis of aortic stenosis and its relation to age

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In 108 of 111 hearts from adults with isolated aortic stenosis the pathogenesis could be determined macroscopically if inspection of the unopened valve from above was included in the examination. Calcified congenitally bicuspid valves were the commonest finding (43%) and were characterized by a transverse slit-like or crescentic orifice. The majority of patients were men. Senile degenerative calcification alone was responsible for stenosis in 31 per cent. This was characterized by a triradiate orifice without commissural adhesions. Women predominated in this group. Post-inflammatory (rheumatic type) commissural adhesions producing a fixed central circular or triangular orifice were found in 24 per cent of cases, and inflammatory fusion of one commissure of a congenitally bicuspid valve in a further 7 per cent.

The relative frequency of these three pathogeneses varied in different age groups. Stenosis due to previous inflammatory valve disease predominated in patients under 60 years, calcification in congenitally bicuspid valves between 60 and 75 years, and degenerative calcification was not seen under 75 years, but predominated over this age and was responsible for almost all cases of isolated aortic stenosis over 85 years.

The large number of papers on aortic stenosis is impressive evidence of the efforts that have been made to decide its pathogenesis. Mönckeberg (1904) is usually credited with the first attempt, concluding that isolated aortic stenosis was due either to previous inflammation or to arteriosclerotic calcification. The following half century produced numerous studies supporting one or other of these aetiologies which were summarized in Karsner and Koletsky's monograph (1947). Most favoured a rheumatic aetiology, in spite of the low incidence of previous rheumatic fever in cases without coexisting mitral disease, and the pathological evidence on which these views were based is now also unacceptable. By present-day standards the changes described by Hall and Ichioka (1940) and Karsner and Koletsky (1947) would be considered non-specific, and not evidence of previous rheumatism. They are common in hearts from patients without histories or gross evidence of rheumatic heart disease. To quote Campbell (1968) 'these writers were unduly influenced by the dogmatic view that all cases of valvular disease except syphilitic aortic regurgitation were rheumatic'. The possible role of congenital bicuspid valves was unaccountably ignored until the study by Bacon and Matthews (1959), though Peacock had pointed out in 1866 that these were prone to calcify and become stenotic. Current opinion (Storstein, 1969; Hudson, 1970; Roberts, 1970a) regards the congenital bicuspid valve as the most important cause of isolated aortic stenosis in adults. Rheumatic carditis has been relegated to an unlikely cause (*Lancet*, 1968; Roberts, 1970b), though Hudson (1970) still sees it frequently at the National Heart Hospital. Jokipii (1963) and Austen *et al.* (1970) considered degenerative (Mönckeberg) calcification to be the most important cause of aortic stenosis in their material, while Hudson (1965) was of the opinion that this process rarely caused real obstruction. It seems probable that these differing conclusions reflect differing ages of patients in the centres concerned. The present study shows that while isolated aortic stenosis may be due to any of the three pathological processes suggested, the most likely pathogenesis in individual cases is related to age.

[1] In receipt of a grant from the British Heart Foundation.

Received 27 July 1971.

Subjects and methods

The material consisted of 111 adult cases of isolated aortic stenosis, i.e. excluding hearts with rheumatic type mitral deformities. All were necropsy specimens from general hospitals without cardiac surgery units, in the London and Home Counties area, and were otherwise unselected. Aortic valves were regarded as stenotic if they did not admit one finger (1·5 cm diam.) without palpable resistance. Sex and age of the cases are shown in the Table.

The aortic valves were first examined from above with the ring closed, and then the ventricular surface was examined with the valve opened. The number and configuration of commissures and commissural adhesions, number, shape, and relative size of cusps, presence of raphes, and shape of the orifice as seen from above were noted, together with site and severity of calcification, extent of distortion, and thickening of the uncalcified parts of the cusps. The mitral valve was also inspected for minor scarring or vascularization which would suggest previous valvulitis. Blocks for histology were taken from any commissural adhesions or raphes, anterior mitral and contiguous aortic cusp, middle part of posterior mitral cusp with adjacent atria and ventricular wall and valve ring, and any scarred areas of valves. Sections were all stained with haematoxylin, and Weigert's elastic van Gieson methods.

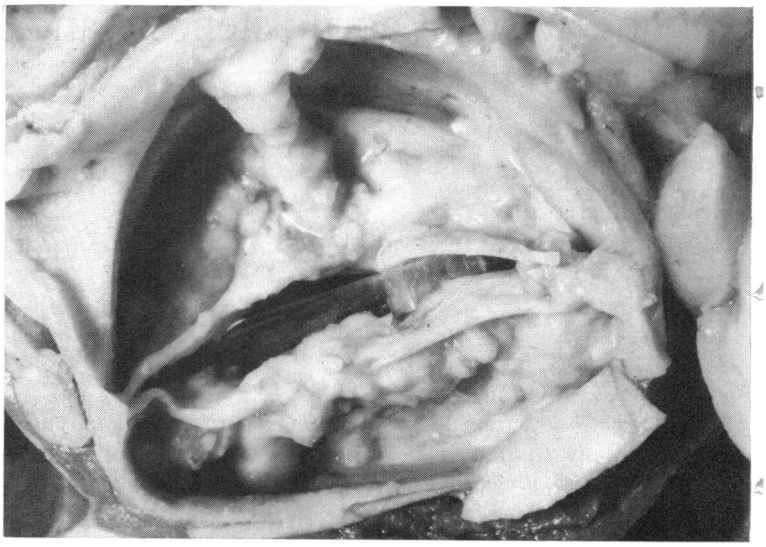


FIG. 1 *Calcified congenitally bicuspid aortic valve viewed from aortic aspect. One cusp is divided by a calcified raphe. The free margins are of approximately equal length, resulting in a slit-like orifice (held open by glass rod) traversing the aortic lumen.*

Results

Apart from three cases with extreme distortion and disorganization of anatomy, the aortic valves fell into three distinct groups.

1) The largest (43%) had only 2 cusps, with free edges of almost equal length. The larger cusp had a slightly lobulated ventricular aspect and was partly divided by a central raphe or fibrous ridge extending across the floor of the aortic sinus from aorta to free edge (Fig. 1). In most examples both coronary ostia arose behind the slightly larger conjoined cusp. Calcification was found in the cusp fibrosa and fibrous ridge. It was most obvious in the base of the cusps, frequently projecting into the aortic sinus, but rarely through the ventricular aspect of the cusps. Macroscopically these were clearly congenitally bicuspid valves, fulfilling the criteria of Osler (1886) and Lewis and Grant (1923). Viewed from above, the orifice was characteristically slit-like, extending the whole diameter of the aortic ring, except in the 8 cases described below. The microscopical relations of the aortic root structures observed by Lewis and Grant (1923) were not assessable in this material because of heavy calcification, but on examination of the van Gieson stained sections no normal valve structure was present in the fibrous raphes, thus confirming the congenital nature of the 'fusion' (Lewis and Grant, 1923). Small acquired adhesions between the cusp were often observed in continuity with the raphe, but the congenital and acquired elements were easily distinguishable in the elastic van Gieson preparations. In 8

TABLE

Age group (yr)	*< 40*	*40–4*	*45–9*	*50–4*	*55–9*	*60–4*	*65–9*	*70–4*	*75–9*	*80–4*	*> 85*
Men	0	1	2	5	7	2	11	8	7	12	7
Women	0	0	0	0	1	9	5	3	7	13	11
Total	0	1	2	5	8	11	16	11	14	25	18

cases adhesions were also present at one of the commissures (Fig. 2) restricting the width of the orifice. Sections in these cases showed vascularization and chronic inflammatory cell infiltration, but the presence of calcium made the significance of these changes difficult to assess. Three cases, all over 75 years old, had past histories of rheumatic fever, but none showed any pathological evidence of previous valvulitis. Men predominated in this group, in a ratio of 2·5:1.

2) The next most frequent finding (31%) was a valve consisting of three equal-sized cusps, with no fibrosis, contraction, or commissural adhesions, other than endocardial agglutination of senile type (Fig. 3). Stenosis was due to large deposits of calcium which immobilized the individual cusps. As in the calcified congenitally bicuspid valves the calcification was mainly basal, with large masses frequently projecting into the aortic sinuses, and occasionally almost filling them. Seen from above, the orifice was characteristically Y shaped. Histology showed nodular masses of calcium mainly involving the fibrosa, with no thick vessels or disorganization of architecture indicating previous inflammation. None of these cases had past histories of rheumatic fever. They appeared to be due to degenerative changes of Mönckeberg type. There was a slight preponderance of women in this group (19 women, 15 men).

3) The smallest group (24%) consisted of valves that were also originally tricuspid, with approximately equal sized cusps, but rendered stenotic by extensive fusion of commissures (Fig. 4). Diffuse fibrous thickening and distortion of cusps affecting particularly the free edge was a conspicuous feature in this group. Calcification varied in location and severity, often found in the fused commissures and ulcerating through the ventricular surfaces of the cusps. In many cases it appeared of relatively minor importance in the genesis of the stenosis. Seen from above, the orifice was characteristically central, fixed, and circular or triangular. This group appeared to be due to previous valvulitis, and histology confirmed this. Abnormal vascular channels and chronic inflammatory cell aggregates were present in the valve rings and cusps. The acquired nature of the commissural adhesions was also confirmed by identification of two separate cusp structures. Nine of these 26 cases had past histories of rheumatic or scarlet fever, and showed microscopical evidence of old valvulitis in the mitral valve sections. Both sexes were almost equally represented in this group, with 13 men and 14 women.

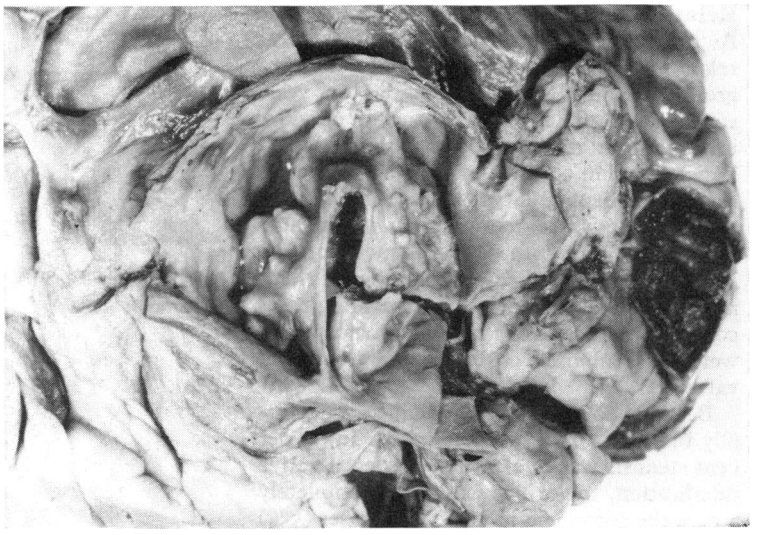
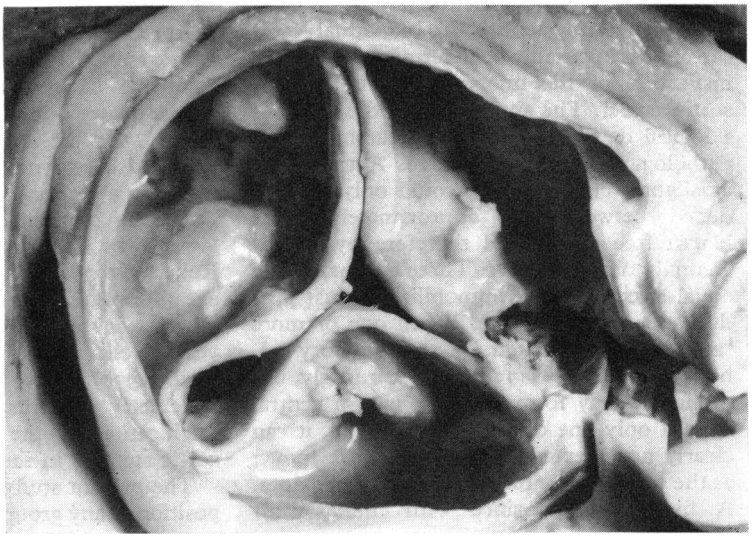


FIG. 2 *Calcified congenitally bicuspid stenotic aortic valve viewed from the aortic aspect. One commissure is adherent and calcified, and the slit-like orifice does not extend completely across the aortic lumen.*

FIG. 3. *Calcified tricuspid aortic valve viewed from aortic aspect. The cusps are not thickened or distorted other than by calcium deposits and the commissures are not fused. Stenosis has resulted from immobilization of the cusps by heavy calcification alone.*



Relation of aortic valve pathology to age

As can be seen from Fig. 5, there is a clear relation between type of pathology and age group. In all the patients under 60 years stenosis was at least partly due to previous inflammation resulting in commissural adhesions, and in 9 (60%) of the 15 cases in this age group rheumatic type changes alone were present, the valve retaining an identifiably tricuspid origin, with central stenotic orifice. Four of the 9 cases had past histories of rheumatic or scarlet fever. In the remaining cases commissural adhesions of inflammatory type were superimposed on congenitally bicuspid valves.

Between 60 and 75 years calcified congenitally bicuspid valves predominated. In 59 per cent stenosis was due entirely to degenerative calcification, the orifice extending completely across the aorta, and in a further 2 cases (5%) partial fusion of one commissure was also present. The remaining 13 cases (36%) had rheumatic type aortic valve deformities, and 4 had past histories of rheumatic or scarlet fever.

In the oldest patients, from 75 to over 90, the predominant pathology was degenerative (Mönckeberg) calcification in otherwise normal tricuspid valves. This was responsible for 61 per cent of the cases of aortic stenosis and was almost universal over 85 years. Four patients (7%) had rheumatic type valvular pathology, one with a history of rheumatic fever 68 years before her last admission. Eighteen patients (32%) had calcified congenitally bicuspid valves. None of these lived beyond 83 years.

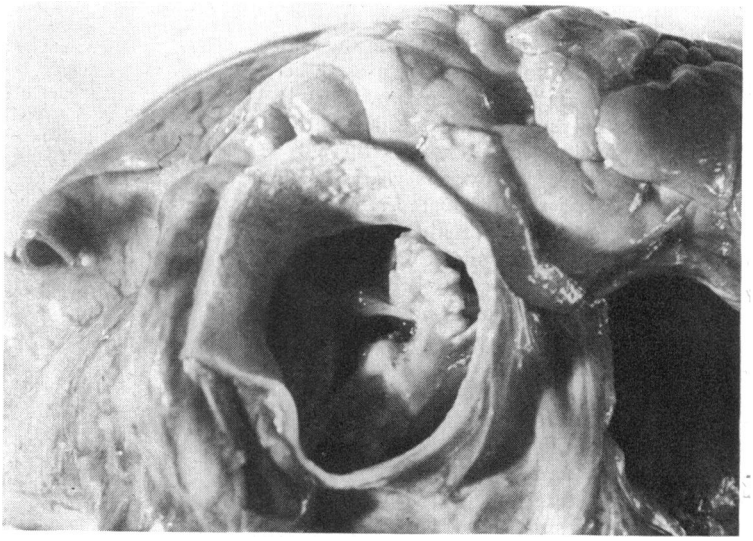


FIG. 4 *Stenotic tricuspid valve due to previous valvulitis viewed from aortic aspect. Two commissures are extensively fused, one heavily calcified, and the orifice forms a central triangle.*

Discussion

This study shows that the pathogenesis of acquired aortic stenosis in individual cases can almost invariably be determined by simple inspection of the unopened valve from its aortic aspect. The appearance of the orifice is a logical development of the anatomical and pathological factors concerned. A transverse or slightly crescentic slit could only be produced between two approximately equal length free edges, and therefore by a congenitally bicuspid valve. Three approximately equal-sized cusps, if immobilized, must produce a triradiate orifice. When one or more 'arms' are obliterated by inflammatory adhesions the orifice is reduced accordingly, but though it may form an angle with a central apex if only one commissure is fused, it can clearly never extend across the aortic lumen as the congenitally bicuspid valve orifice does. A fixed central orifice with fused, well-developed commissures must be the result of inflammation. For the experienced eye histology serves merely as confirmation of the conclusions arrived at by inspection, and in the few cases where distortion was too extreme for macroscopical diagnosis, histology also proved unhelpful. Calcification had obscured the original valve anatomy and provoked inflammatory changes which could not be distinguished from those of previous valvulitis.

In the present series of 111 adult cases the pathogenesis of the isolated aortic stenosis could be determined in 108, and chronic inflammatory adhesions, congenital bicuspid valves, and degenerative calcification each occurred. As in most recent surveys, the congenitally abnormal valves formed the largest group, 43 per cent, but the proportion was lower than in other series (Storstein, 1969; Roberts, 1970a). The explanation lies in the age groups represented; more than half the patients in the present study were over 75 years. Geill (1959), Jokipii (1963), and Austen *et al.* (1970), whose material consisted mainly of elderly patients, regarded degenerative calcification as the main cause of isolated aortic stenosis in their material.

The present study shows that the age composition of any group of cases of isolated aortic

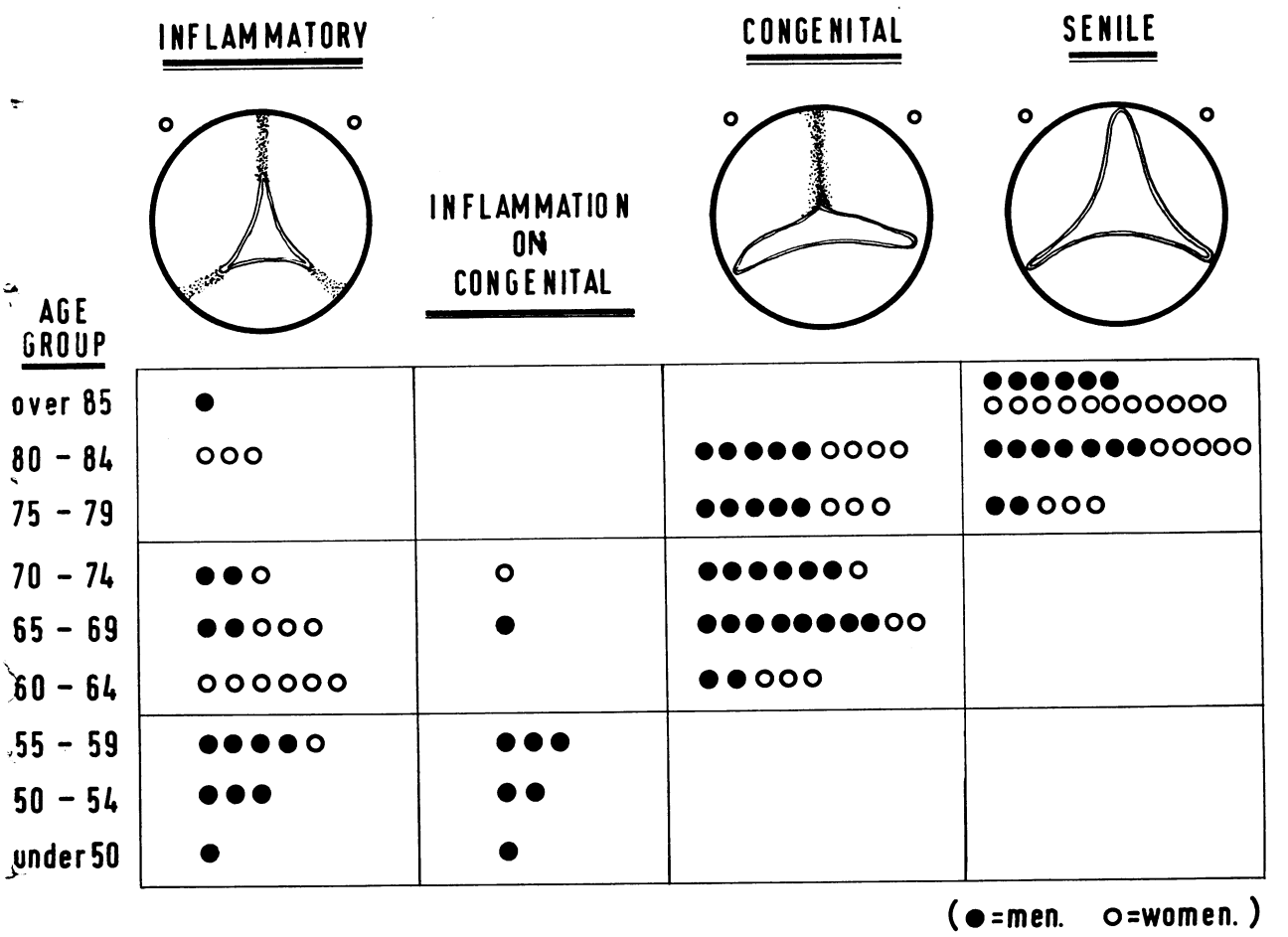


FIG. 5 *Age and sex distribution of the different pathological types of isolated aortic stenosis.*

stenosis is likely to influence the relative importance of the three common pathological findings. Degenerative calcification is commonest in those over 75, who are not usually represented in surgical series, while chronic inflammatory changes predominate in patients under 60, and calcified congenitally bicuspid valves without previous inflammation are commonest only in the group 60–75 years. These findings would be anticipated if one accepts that calcification is a consequence of damage to the valve (Edwards, 1962). Damage resulting from rheumatic inflammation is likely to have occurred comparatively young since rheumatic carditis was mainly a disease of children and young adults, and calcification in these cases will develop earlier than in cases where damage is due to cusp movements alone. The normal cusp seems able to tolerate repeated flexion and impact for an average lifetime without visible deterioration, but with longer survival the likelihood of damage and subsequent calcification increases. This is substantiated by the rarity of calcific stenosis in otherwise healthy tricuspid valves before 75 years and its rapid increase after this age. When the valve is subject to abnormal stresses in opening and closing, as in the bicuspid form, 'wear and tear' collagen changes would be expected at a younger age (Edwards, 1962), as in the present series.

Edwards (1965) pointed out that the type of valve deformity in aortic stenosis was related to the age at which symptoms developed: children and adolescents had fibrous intrinsically stenotic valves, usually unicommissural, while adults showed either rheumatic type stenosis in a tricuspid valve or calcification in one which was almost always bicuspid. The present study shows that this concept of relation between age and pathology in isolated aortic stenosis can be extended

further. Inflammatory changes predominate in young middle age, calcification in congenital bicuspid valves in the seventh and eighth decades, with degenerative calcification alone being responsible for stenosis in the really elderly.

I should like to thank Drs J. W. Lacey and K. A. D. Turk of the Chelmsford Group Hospitals and Dr. C. R. Tribe of Wycombe General Hospital who contributed many of the specimens included in this study.

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