Pathology and valvular heart disease

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Over the past 25 to 30 years advances in therapeutics and pathology have considerably modified traditional concepts of valve disease, and much of the earlier literature of cardiac pathology has become mainly of historic interest. The introduction of antibiotics changed the pathology and course of infective endocarditis and is reducing the incidence of chronic rheumatic and syphilitic valve disease; new pathological observations have brought the realization that not all chronic valve disease is rheumatic, congenital, or syphilitic, and increasing longevity is reflected in the increasing importance of degenerative heart disease.

Infective endocarditis

After the studies of several groups of American workers (Robinson and Ruedy, 1962; Vogler, Dorney, and Bridges, 1962; Wilson, 1963; Uwaydah and Weinberg, 1965; Lerner and Weinstein, 1966), and Hughes and Gauld (1966) in Britain, and Capoferro (1970) in Norway, it is now generally recognized that infective endocarditis is no longer predominantly a disease of young adults with chronic rheumatic heart disease. For most pathologists the typical case is now an elderly patient with infection of a valve showing either degenerative changes or no apparent pre-existing abnormality. In 31 cases examined personally during the past 10 years 58 per cent were aged over 60, infection was superimposed on degenerative valve disease in 13 per cent, and on rheumatic type deformities in only 10 per cent; 62 per cent showed no apparent pre-existing abnormality. The importance of the α -haemolytic streptococcus has also declined and the infecting organism is now more likely to have been a staphylococcus or enterococcus. The pathologist's view is naturally biased by the better prognosis

in haemolytic streptococcal infections and by the higher mortality and number of clinically undiagnosed cases in elderly patients in whom atypical clinical features frequently obscure the diagnosis. Nevertheless, the changes in age, infecting organism, and type of underlying heart disease have been striking, even in clinical studies.

With the development of effective chemotherapy, cardiac failure replaced uncontrolled infection as the leading cause of death in infective endocarditis (Cates and Christie, 1951; Morgan and Bland, 1959; Robinson and Ruedy, 1962), and in many cases this was due to damage to the valve cusps, particularly those of the aortic valve. More recently, advances in cardiac surgery have made valve replacement a practicable treatment, and the pathologist now rarely sees the torn or perforated cusps that were a prominent feature of deaths due to infective endocarditis in the 1950's and '60's, except as surgical specimens. In my own experience only 1 of 10 fatal cases seen in the past 10 years died as a result of valve damage compared with 9 in the 23 necropsied cases of bacterial endocarditis in the previous 6 years.

Although therapeutic advances have greatly improved prognosis, they have also created new situations that favour the development of infective endocarditis. The surgical and diagnostic procedures now carried out on elderly patients undoubtedly contribute to the increased incidence of bacterial endocarditis in this age group. Intracardiac foreign bodies predispose to infection and these now include pacemaker wires and Spitz-Holtzer valves, as well as suture material and replacement heart valves. Prolonged treatment with antibiotics or steroids and modern therapy of malignant disease are the main factors that have transformed fungal endocarditis from a curiosity of cardiac pathology to a comparatively unremarkable form of valvular disease.

The past decade has also probably seen the solution of the problem of pathogenesis of

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infective endocarditis. From x-ray and microangiographic studies (Clarke, 1965; M. H. Tarbit and G. Farrer-Brown, personal communication), it is now clear that embolic implantation of bacteria is possible only in valves vascularized by previous inflammation, and these are now found only in a small proportion of cases. Angrist and Oka (1963), Nakao, Angrist, and Mao (1967), and Oka *et al.* (1968) have shown that exposure of valve collagen attracts platelets, and that transformation of the resulting thrombus to an infective vegetation follows bacteraemia. The essential endothelial damage may occur over valves thickened by previous inflammation or over nonspecific changes provoked by a variety of stimuli, including stress, or may be caused by inadequate lateral perfusion pressures (Rodbard, 1963). Transition from thrombotic to infective vegetations has been observed in man as well as experimentally (Angrist and Oka, 1963), and the increased incidence of nonbacterial thrombotic endocarditis since the advent of antibiotics (Angrist and Marquiss, 1954; Eliakim and Pinchas, 1966) also supports the view that infective endocarditis results from bacteraemia in a patient with nonbacterial endocarditis.

Nonsyphilitic aortic incompetence

After the introduction of penicillin, syphilitic aortic valve disease has now literally become a museum piece in most hospitals. Previously responsible for about a third of aortic valve disease (Wood, 1968), it is now found in less than 1 per cent of necropsies (Heggtveit, 1964). Most of the decline is of course the result of effective therapy in the earlier stages of syphilis, but a small part is due to the realization that appearances indistinguishable from syphilitic aortic incompetence can occur in other diseases. The pathological basis of these appearances is stretching of the valve ring due to degeneration of the aortic media. The characteristic thick rolled edges of the cusps themselves are stretch lesions, the result of mechanical factors and not inflammation (Martland, 1930; Edwards, 1958). The free edges are subject both to tension as the ring dilates and to friction from the regurgitant flow, and the result is a band of laminar fibrosis localized to the traumatized zone. In syphilis the medial destruction is secondary to obliterative vasculitis of the aortic vasa vasorum, but clearly any disease in which loss of medial integrity occurs may result in identical macroscopical pathology which has doubtless been misinterpreted as syphilitic in the past. We now recognize that aortic incompetence of this type may develop

in ankylosing spondylitis, Reiter's disease, cystic medionecrosis of aorta, nonspecific aortitis, and senile or hypertensive dilatation of the aortic root.

The aortic incompetence of rheumatoid disease does not resemble that seen with aortic ring dilatation. It is due to valvulitis which affects particularly the cusp fibrosa (Roberts *et al.*, 1968) and results in thickened contracted cusps without commissural adhesions. Lack of endocardial changes, and the frequent occurrence of typical rheumatoid granulomas in the cusp, distinguish the microscopical pathology from that of chronic rheumatic valve disease. Failure to recognize the true nature of the valvular changes usually results in a pathological diagnosis of rheumatic aortic disease, a misapprehension which doubtless contributed to the erroneous conclusions of earlier studies as to the high frequency of chronic rheumatic heart disease in rheumatoid arthritis.

Degenerative heart disease

One result of increasing longevity and the decline of rheumatic fever and untreated syphilis is that cardiac pathology now consists largely of degenerative conditions, this term being used for the non-reversible abnormalities whose development appears related to advancing age. This fact will perhaps be more apparent to pathologists than to cardiologists, since the proportion of patients with these abnormalities who require, or respond to specialist treatment is probably small. Apart from rarities, such as valvular amyloidosis, degenerative valve disease affects primarily the collagen forming the cusp fibrosa or valve ring, and takes two forms – calcification and mucoid (myxomatous) degeneration. Calcification is confined to the left heart valves; mucoid degeneration also occurs in the tricuspid valve.

Mitral ring calcification

In the mitral valve, degenerative calcification develops in the ring, in contrast to cusp calcification which is associated with previous inflammation or haemorrhage. Though the condition was described at the beginning of this century, appreciation of its practical importance is comparatively recent (Rytand and Lipsitch, 1946; Simon and Liu, 1954; Korn, DeSanctis, and Sell, 1962; Pomerance, 1970). Like aortic valve calcification this is a disease of the elderly, found in over 8 per cent of patients over 50 years and increasing sharply with age. The reasons for its development are not known though mechanical factors are probably concerned (Lev, 1964). Unlike aortic

calcification or other forms of degenerative heart disease (Pomerance, 1968), it is much commoner in women. As in calcific aortic disease the commonest manifestation is a systolic murmur, which is generally associated with distortion of the posterior mitral cusp by spurs of calcification projecting towards the atrium. Surprisingly, in view of their size and the degree of distortion often produced by the calcific masses, ulceration of the overlying endocardium occurs in only about 5 per cent of cases, but when present this complication predisposes to thrombotic and infective endocarditis. Conduction abnormalities are common since one of the early sites of calcification is the junction of mitral valve cusps and interventricular septum, which is where the bundle of His and its main branches are found.

Mucoid degeneration of valves

This finding is a well-known feature of the Marfan syndrome (Goyette and Palmer, 1953; McKusick, 1966) but its recognition as a comparatively common isolated abnormality is recent. The condition is characterized by stretching of the affected leaflets which prolapse or overshoot on closing, with consequent mitral or aortic incompetence. The pathological change is replacement of the normally dense, collagenous, fibrosa by loose myxomatoid metachromatically staining connective tissue, with a high acid mucopolysaccharide content, which stretches under normal intracardiac pressures. The published reports have been somewhat confused by the number of names used, which are based on surgical, radiological, or pathological appearances: floppy valve syndrome (Read, Thal, and Wendt, 1965), ballooning (Behar, Whalen, and McIntosh, 1967), and billowing (Oka and Angrist, 1961; Bittar and Sosa, 1968) deformity, aneurysmal protrusion (Barlow and Bosman, 1966), and prolapse (Criley *et al.*, 1966) of the posterior mitral cusp, and mucinous (Frale, 1969) or myxomatous (Read *et al.*, 1965) degeneration. The pathology, when recorded, appears identical with that in the 2 cases described as mucoid degeneration by Fernex and Fernex in 1958. Pathologists unfamiliar with the condition tend to attribute the appearances to previous rheumatism, though the increase in cusp area, parachute-like appearance, lack of commissural adhesions, or fibrous contraction of the chordae contrast with the usual findings in chronic rheumatic disease and the histological features are also distinct. Its comparatively high incidence in general hospital necropsy material

has therefore not been appreciated until comparatively recently. In the Central Middlesex Hospital conspicuous mucoid degeneration of one or both mitral cusps has been seen in almost 1 per cent of necropsies on adult patients over the past 10 years. Patients with murmurs and cineangiographic evidence of the deformity are also common in cardiac clinics (Linhart and Taylor, 1966; Behar *et al.*, 1967); the incidence in Behar *et al.*'s series was 6 per cent. Though these patients almost invariably have clinical or pathological evidence of mitral incompetence, this is well tolerated in most cases (Linhart and Taylor, 1966). Only 58 per cent of the 50 cases studied personally had been in cardiac failure. Apart from the minority of cases whose mitral incompetence becomes severe, the main practical importance of mucoid degeneration is the liability to infective endocarditis and 'spontaneous' rupture of chordae tendineae (Read *et al.*, 1965; Linhart and Taylor, 1966; Pomerance, 1969). Infective endocarditis probably develops on the areas of endocardial thrombosis and ulceration, which are found in about one-third of cases, and which are not unexpected in view of the endocardial damage likely to occur as the cusp is stretched. Mucoid degeneration is now probably the commonest cause of rupture of the chordae tendineae, particularly when those of the posterior cusp are involved (Selzer *et al.*, 1967). Rupture occurs either because the chordae are also affected by the degenerative process, or because of the excessive strain to which the chordae are subjected by the overshooting cusps (Edwards, 1971). Surgical correction of valve abnormalities also presents difficulties because of the abnormal consistency of the tissues (Read and Thal, 1966; Frable, 1969). The tricuspid valve fibrosa is also affected microscopically in about a quarter of cases, but distortion is minor because of the lower pressures and so of no clinical significance.

The pathogenesis of mucoid degeneration is unknown, and as with many other examples of 'end-stage pathology' (such as endocardial fibrosis) various aetiological factors are probably concerned. A similar condition occurs in dogs and is related to ageing and breed (Oka and Angrist, 1961; Pomerance and Whitney, 1970). In man too it is seen most often in the elderly, but this fact is more an expression of the long natural history than an indication that ageing itself is the aetiological factor. Murmurs have not infrequently been present for over 20 years before operation or death, and in my own series, though the average age was 73 years, the age distribution was much the same as that of our necropsy material

during the same 10-year period. An association with chronic pulmonary disease has been noted (Salazar and Edwards, 1970) and was common in my material, but the importance of this association is difficult to assess in an urban hospital where chronic pulmonary pathology is a frequent finding. Genetic factors are undoubtedly concerned in some cases. The relation to hereditary connective tissue abnormalities of Marfan type is now well recognized (and has replaced older findings of an increased incidence of 'rheumatic' heart disease in these patients), and many familial cases have been reported without the stigmata of the Marfan syndrome (Shell *et al.*, 1969; Hunt and Sloman, 1969). However, in most cases there is no evidence of either generalized connective tissue disease or of familial incidence, and the pathogenesis is, at present, obscure.

Aortic valve calcification and pathogenesis of isolated aortic stenosis

Degenerative calcification of the aortic valve develops in the cusp fibrosa, initially in the cusp bases, a site that suggests that damage from repeated flexing may be the initiating factor. In most cases it is of no clinical significance other than as a source of aortic systolic murmurs, though it may provide a basis for the development of endocarditis. However, degenerative calcification increases with age (Sell and Scully, 1965; Pomerance, 1967) and may eventually involve the whole cusp from base to linea alba and form large masses projecting into the aortic sinuses. The consequent loss of cusp mobility results in aortic stenosis. Not surprisingly, this type of stenosis occurs almost exclusively in the elderly, but over 75 years it has been found in 61 per cent of cases (Pomerance, 1972). Its occasional occurrence in young patients has been associated with familial hyperlipoproteinaemias. This 'wear and tear' calcification is of particular importance in congenitally bicuspid aortic valves. Their abnormal anatomy results in excessive flexion, folding, and tension in the cusps which therefore calcify at an earlier age than the normal three-cusped valve (Edwards, 1962; Campbell, 1968).

The 'dogmatic view that all cases of valvular disease except syphilitic aortic incompetence were rheumatic' (Campbell, 1968) seems to have been responsible for the mistaken belief that isolated aortic stenosis in adults was almost invariably of rheumatic aetiology. This was generally held throughout the first half of this century (Hall and Ichioka, 1940; Karsner and Koletsky, 1947), but the

evidence on which it was based is unacceptable by modern pathological standards. Papers of this period often include undoubted congenitally bicuspid valves as illustrations of rheumatic aortic stenosis, and the microscopical lesions that were considered evidence of past rheumatic carditis can be found in 90 per cent of normal hearts (Hall and Anderson, 1943). The evidence against the rheumatic aetiology is well summarized in a paper by Roberts (1970a). Recognition that isolated aortic stenosis could be based on congenitally bicuspid valves followed Bacon and Matthews' study, in 1959, and it is now generally accepted that this abnormality underlies the majority of cases (Roberts, 1970b; Hudson, 1970). It seems that the popularity of the rheumatic theory was largely due to the uncritical acceptance of preconceived ideas, an outlook that tends to impede progress.

In most cases there should be no difficulty in differentiating acquired cusp fusion from a congenitally bicuspid valve. Osler (1886) and Lewis and Grant (1923) set out distinguishing features which, in effect, pointed out that anatomical evidence of two complete sets of cusp structures is demonstrable in an acquired commissural fusion but is absent in the congenitally fused cusp. The nature of an individual specimen of aortic stenosis can almost always be correctly deduced if simple inspection of the unopened valve from above is included in the examination, since the gross appearances are a logical consequence of the original valve anatomy and subsequent pathological reaction. A transverse, slit-like or slightly crescentic orifice can only be produced between two approximately equal length free edges, and therefore by a congenitally bicuspid valve. Three originally equal-sized cusps, fused and contracted by previous valvulitis, will produce a central fixed triangular or circular orifice, or immobilized by degenerative calcification without previous inflammation will form the triradiate orifice of a normal, almost closed valve.

Applying these simple pathological observations, the congenitally bicuspid valve emerges as the commonest finding in isolated calcific aortic stenosis (Roberts, 1970b; Pomerance, 1972). Previous valvulitis is undoubtedly a cause of stenosis in a substantial minority of cases, the proportion depending on the age group of the patients under consideration. The inflammation may have been due to brucella (Peery, 1958), rickettsia (Kristinsson and Bentall, 1967), or Coxsackie virus infections (*Lancet*, 1971), and there seems no reason why other organisms, which are known to cause occasional myocarditis,

should not also affect the valves. However, at present, most cases of post-inflammatory aortic stenosis are still rheumatic. Sixty per cent of a consecutive series of National Heart Hospital specimens were from patients with histories of rheumatic fever or chorea. Since rheumatic fever is mainly a disease of the young, it is not surprising that post-inflammatory aortic stenosis tends to be found in a younger age group than the degenerative type, even when degenerative changes have been accelerated, as in the congenitally bicuspid valve.

Rheumatic heart disease and rheumatic type valve pathology

Though treatment of rheumatic type mitral and aortic disease still forms the bulk of the work of cardiac units, the importance of rheumatic heart disease appears to be declining. Following the decrease in acute rheumatic carditis, the incidence of chronic rheumatic valvulitis has naturally fallen, the age group in which it is mainly found has risen, and an increasing proportion of cases are middle-aged or elderly. The valvular abnormalities of rheumatoid disease, isolated aortic stenosis, mucopolysaccharidosis, and the Marfan syndrome were once included as rheumatic but their true pathogenesis is now recognized. Finally, there is growing evidence that a substantial minority of cases with pathology regarded as typical of chronic rheumatic valve disease are due to causes other than past rheumatic carditis. This is apparent in the growing use, by pathologists, of the term 'rheumatic-type' deformity (Baggenstoss and Titus, 1968) where there is no rheumatic history. There is no doubt that, at the present time, most cases of severe mitral stenosis are still of rheumatic aetiology. Seventy-nine per cent of patients undergoing mitral valve operations at the National Heart Hospital in 1970 had histories of rheumatic fever or chorea as did 75 per cent of Dr. Aubrey Leatham's patients from St. George's Hospital (M. J. Davies, 1971, personal communication). Nevertheless, even in this highly selected material over 20 per cent had no rheumatic background, and in older patients and those with less serious valve deformities the proportion is even greater (Bedford and Caird, 1960). Vendsborg, Hansen, and Olesen (1968) noted that the number of cases without rheumatic histories had not fallen in recent years, as had those with a known rheumatic background, a finding that supports a nonrheumatic origin for the former, rather than subclinical rheumatic carditis. The pathology of the chronic rheu-

matic valve is not specific. Much of the thickening and deformity is due to organization of thrombus, a process that is the usual consequence of valve damage from almost any cause, and the fibrotic disorganization of architecture and vascularization seen histologically could follow any valvulitis affecting the deeper layers of the cusp. Nonrheumatic valvulitis is now an accepted cause of aortic valve deformities, and there seems no reason why the mitral valve should be exempt from such reactions. Indeed, de Vecchi (1931) observed that focal valvulitis was common in fatal acute infections, and suggested that such lesions might be related to chronic valve deformities. A variety of infective agents is known to affect the heart and Coxsackie B and infantile encephalomyocarditis in particular have been suggested as likely factors in the pathogenesis of chronic valve disease (*Lancet*, 1971). Burch and Colcolough (1969) reviewed the problem of virus-induced valvulitis in animals and it was apparent that many viruses were associated with acute lesions. Chronic mitral fibrosis and commissural adhesions have also been produced experimentally with Coxsackie B virus (DePasquale *et al.*, 1966; Burch and Tsui, 1971), and this virus has also been demonstrated in human mitral valves (Burch *et al.*, 1967). The possibility that psittacosis may be concerned in chronic valve disease has been suggested by a significantly higher incidence of bird contact in patients with no rheumatic history, when compared with those with histories of rheumatic fever (Ward, 1971). It has also been suggested that viruses may be implicated even where there is a rheumatic history, the streptococcus activating a latent virus or acting as a conditioning factor with subsequent viral infection (Burch, Giles, and Colcolough, 1970; Burch and Tsui, 1971). This last hypothesis is somewhat speculative, but there is now sufficient evidence to indicate that rheumatic carditis is not the only cause of chronic rheumatic type valve pathology. With the decline in rheumatic fever, true rheumatic heart disease should eventually follow syphilitic heart disease into the category of uncommon cardiac pathology, but it seems likely that similar changes from other causes will remain a frequent finding in both surgical and necropsy pathology.

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