
Pathological Considerations in Replacement Cardiac Valves

Frederick J. Schoen, MD, PhD,* Robert J. Lévy, MD[†], and Henry R. Piehler, ScD[‡]

**Department of Pathology, Brigham and Women's Hospital and Harvard Medical School,
Boston, Massachusetts,*

[†]Department of Pediatrics, University of Michigan, Ann Arbor, Michigan, and

*[‡]Department of Metallurgical Engineering and Materials Science, Carnegie Mellon University,
Pittsburgh, Pennsylvania*



The long-term outcome following cardiac valve replacement is primarily determined by three factors: irreversible cardiac and pulmonary pathology secondary to the valvular disease (especially left ventricular myocardial hypertrophy and degeneration, and pulmonary vascular disease), pre-existing cardiac disease, including congenital lesions and coronary arterial atherosclerotic occlusions, and prosthesis–host interactions. For most of the approximately 40,000 patients who undergo valve replacement each year in the United States, prosthesis-associated pathology is a major determinant of prognosis. In this article, the significance, morphology, and pathogenesis of the major complications and other alterations during function of mechanical, bioprosthetic, and allograft valves are reviewed. Other reviews of pathologic considerations in cardiac valve replacement are available (1–7).

Structure and Function of Heart Valve Substitutes

Heart valve prostheses respond passively to pressure and flow changes within the heart, and are generally classified into two types: mechanical and tissue. Mechanical valves are composed of synthetic, nonphysiological materials. In

contrast, tissue valves are composed, at least in part, of animal or human tissue. Bioprosthetic valves are usually fabricated from chemically-preserved (usually cross-linked) animal tissue, mounted on a prosthetic frame (stent). The other important tissue valve type is the human aortic valve allograft, processed but not cross-linked, that is implanted directly into the aortic root without a stent. Thus, although unmounted allografts can only be used as aortic valve replacements, stent-mounted allografts can be used to replace the mitral valve, and mechanical or bioprosthetic valves can be used in either site. Detailed descriptions of specific models of valve substitutes are available (8).

The Starr–Edwards caged-ball valve, Bjork–Shiley and Hall–Medtronic tilting-disk valves, and St. Jude Medical bileaflet tilting-disk valve have been the most widely used mechanical prostheses. The latter comprises approximately one-half of valve replacements done today. Three basic components constitute a mechanical valve prosthesis: the rigid, mobile, occluder (poppet) around which blood must flow, the cage-like superstructure that guides and restricts poppet motion, and the valve body or base. Most caged-ball valve occluders are composed of silicone rubber, but contemporary tilting-disk valve occluders are coated with pyrolytic carbon, a material with high strength, low propensity toward wear and fatigue, and high thromboresistance. Mechanical valve cages are constructed of nearly pure titanium (e.g., Hall–Medtronic) or cobalt–chromium alloy (e.g., Starr–Edwards, Bjork–Shiley). Some designs have carbon

Manuscript received April 30, 1991; revised May 28, 1991.

Address for reprints: Frederick J. Schoen, MD, PhD, Department of Pathology, Brigham and Women's Hospital, 75 Francis Street, Boston, MA 02115.

disks and supports (St. Jude). Blood flow through a mechanical valve prosthesis must course around the poppet; thus, these valves are somewhat obstructive to forward flow and frequently have areas of stasis distal to the orifice. The combination of stasis and nonphysiological surfaces yields a tendency toward thrombus formation; chronic anticoagulation therapy is thereby mandatory in patients with mechanical valves (9,10).

Bioprosthetic heart valves generally have better hemodynamic efficiency and thromboresistance than mechanical valves. Flexible, trileaflet, biological tissue valves have a central orifice analogous to natural valves. Tissue valves are heterografts/xenografts (e.g., porcine aortic valve or bovine pericardial bioprostheses), homografts/allografts (e.g., aortic valves from either human cadavers or hearts removed at transplantation, with or without an aortic sleeve as a conduit), or autografts (e.g., composed of fascia lata or pericardium, or the patient's own pulmonary valve transplanted to the aortic root). The preferred terminology is xenograft-allograft-autograft. Detailed terminology germane to tissue heart valves is summarized in reference 5. Stent-mounted porcine aortic valve bioprostheses, fabricated from a pig aortic valve preserved in glutaraldehyde (0.2% for the Hancock and 0.6% for the Carpentier-Edwards), are widely used (presently approximately one-third of all valve replacements). In porcine bioprosthetic valves, the natural cuspal attachments to the aortic wall are maintained intact. Since the right coronary cusp of a pig (but not human) aortic valve is partially supported by septal myocardium, a porcine valve has a muscular shelf which extends into the right coronary cusp. This muscle can prevent full-opening of the cusp, be a site at which inflammation or tearing can occur, and/or aid in orienting the valve for analysis. Valve obstruction related to impaired opening of the right coronary cusp can be of importance in a porcine bioprosthesis of relatively small size. A modified orifice Hancock prosthesis for small sizes has a cusp without a muscular ridge substituted from another valve, as a means of widening the valve inlet area (11).

Pericardial valves were used in the last decade but are not presently implanted in the United States. Each cusp of a pericardial valve is an individual piece of glutaraldehyde-treated parietal pericardium (usually of bovine origin) that is attached to the frame. Various designs of pericardial bioprostheses differ widely in their method of mounting the tissue on the frame.

Cuspal structure and hence physical properties of porcine aortic valve and bovine pericardium are different (4,5,12-14). The structure of natural aortic valve cusps is highly specialized for function. Material properties in the plane of the tissue are anisotropic (not the same in all directions), reflecting the nonrandom orientation of architectural elements that effectively transmits stress to the aorta. Moreover, aortic valve cusps (porcine or other species) have three layers: the predominantly collagenous ventricularis, near the inflow surface; the central spongiosa, with loosely arranged

collagen and abundant amorphous extracellular matrix, and the fibrosa, with densely packed collagen, facing the outflow surface. In contrast, pericardial tissue is a relatively homogeneous sheet of laminated collagen without clear layers; properties are similar in all directions (isotropic). Generally, the smooth side of the pericardium (formerly the serosa) forms the cuspal outflow aspect and the rough surface is the inflow.

A fabric sewing cuff (usually Dacron) that surrounds the base of both mechanical and tissue prostheses facilitates suturing the device into the surgically prepared annulus. In most cases, organized thrombus or fibrous tissue derived from the adjacent myocardium or aortic wall ultimately covers the rough cloth surface. The tissue-valve interface is sealed by adherent tissue in most cases, but the strength of the valve-tissue bond is primarily provided by the sutures. Although sewing cuff configurations differ slightly for semilunar and atrioventricular sites, prosthetic valves used in either site are otherwise virtually identical.

Prosthesis-Related Complications

Within 10 years postoperatively, valve-related complications occur in approximately 50% or more of patients having previously and currently used substitute valves (15). Reoperations, almost always necessitated by valve-related complications, presently account for approximately 20% of all valve surgery. Furthermore, many patients die from prosthesis complications; prosthesis-related events cause approximately half of late deaths (16). Valve prosthesis pathology revealed by autopsy is often clinically unappreciated. Nevertheless, although most large studies show little difference in overall valve-related complication rates between mechanical prostheses and bioprostheses at 10 years, the frequency and, in some cases, the nature of specific valve-related complications varies widely with the type, model and site of the replacement device (as well as with patient characteristics) (4).

The most frequent valve-related complications in patients with mechanical or bioprosthetic valves are thromboembolic problems (including anticoagulant-related hemorrhage), infective endocarditis, paravalvular leak, intrinsic degradative dysfunction, and extrinsic interference with function, usually by tissue overgrowth (Table 1) (17). The causes of failure of 112 consecutive porcine bioprostheses and 45 mechanical valve prostheses surgically removed at our hospital during 1980-1985 included thrombosis (9%), tissue overgrowth (5%), endocarditis (16%), paravalvular leak (11%), and degenerative dysfunction (53%) (18). Thrombosis, a major cause of mechanical valve dysfunction (18% of their failures), was infrequent with bioprostheses. In contrast, 74% of removed bioprostheses had primary tissue degeneration. Thus, in selecting a substitute valve for a specific patient, a surgeon generally weighs the risks of thromboembolic complications of mechanical prostheses versus the limited long-term durability of bioprostheses. Moreover, thromboembolic complications are frequently

Table 1. Mortality and Morbidity Following Cardiac Valve Replacement

Thrombosis/thromboembolism
Anticoagulant-related hemorrhage
Prosthetic valve endocarditis
Structural deterioration (intrinsic failure)
Wear
Fracture
Poppet escape
Cuspal tear
Calcification
Nonstructural dysfunction
Pannus
Suture/tissue entrapment
Paravalvular leak
Disproportion
Hemolytic anemia
Noise

Modified from Edmunds LE et al.; *J. Thorac Cardiovasc Surg* 96:351, 1988.

catastrophic and fatal. In contrast, bioprosthetic valve dysfunction infrequently causes precipitous clinical deterioration (only 5 to 10% of patients require reoperation emergently) (19). Patients with intrinsic bioprosthetic valve failure that is recognized promptly can usually be reoperated with an operative mortality not substantially higher than that of primary valve replacement surgery (20).

Thromboembolic complications. Thromboembolic complications include thrombosis, thromboembolism, and anticoagulation-related hemorrhage. Thrombotic occlusion and thromboemboli can occur with all currently available types of prostheses, at rates of 1 to 4% per patient-year; actuarial freedom from thrombosis or thromboembolism at 10 years for patients with either porcine bioprostheses (usually without anticoagulation) or tilting disk prosthetic valves (with anticoagulation) is typically 70 to 80% (9,15). The risk of thromboembolism depends on the specific prosthesis used and adequacy of anticoagulation (particularly high in poorly anticoagulated patients with mechanical valves), cardiac rhythm (increases with atrial fibrillation), and anatomic site of valve replaced (mitral > aortic). Thromboembolic complications occur most frequently in the first postoperative year, in part due to thrombogenicity of the valve sewing ring prior to tissue incorporation. Nevertheless, traditional chronic oral anticoagulation carries a risk of hemorrhage, particularly retroperitoneal, gastrointestinal or cerebral, with a frequency approximately 4% per patient year, of which 15 to 25% of events are fatal (21). Consequently, there is considerable interest in developing less intense anticoagulation regimens. Although customary practice aims for maintaining the prothrombin time at 1.5 to 2.5 times normal, recent studies suggest that a target of 1.3 to 1.5 times normal maintains low rates of thromboembolism without excessive hemorrhagic risk (22).

Prosthetic heart valve thrombi, either red (fibrin) or white (platelet), can impair occluder opening or closing or gen-

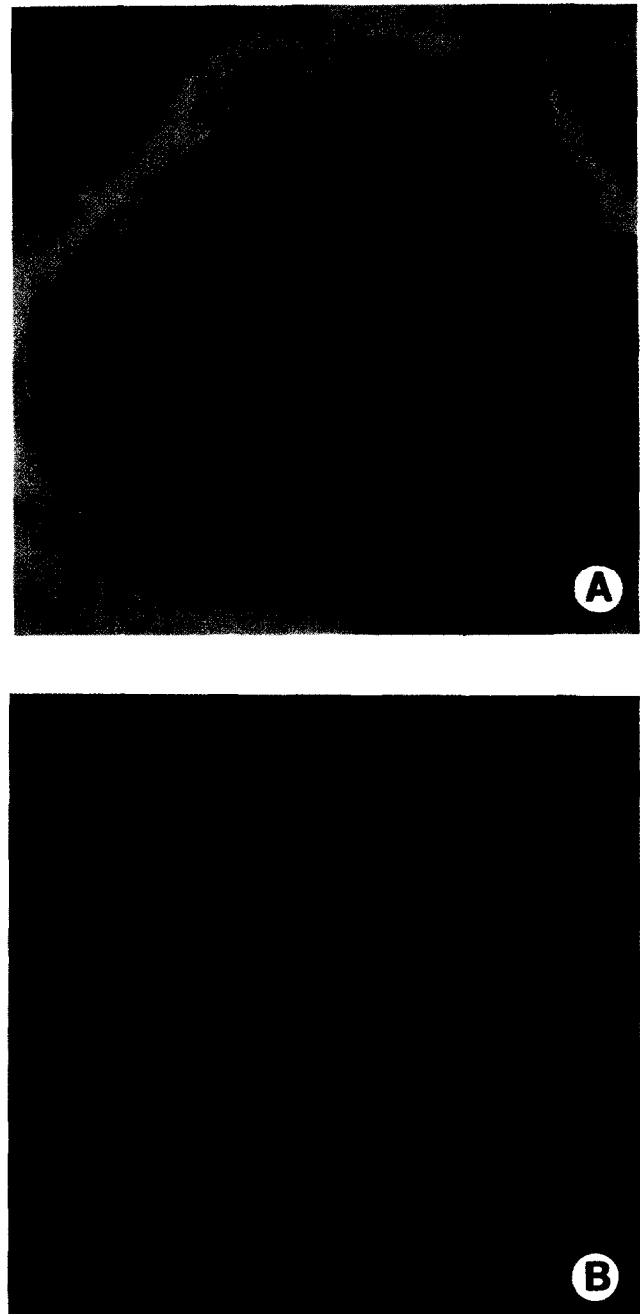


Figure 1. Prosthetic valve thrombosis. A. Aortic Bjork-Shiley tilting disk valve prosthesis, viewed from distal (outflow) aspect, demonstrating localization of thrombus to outflow strut near minor orifice, the site of flow stasis (arrow). **B.** Porcine aortic valve prosthesis, from distal (outflow) aspect, demonstrating thrombotic deposits in two of three sinuses of Valsalva.

erate thromboemboli to distal arterial beds. Clinically-detectable thromboemboli most frequently (over 80%) involve the central nervous system. Since the lack of adjacent vascular tissue retards typical histologic organization, bioprosthetic or mechanical valve-associated thrombi are fri-

able for extended periods. Similarly, determination of duration of a thrombus on a prosthesis is nearly impossible.

The relative propensity for and sites of thrombus on specific valve prostheses are determined by surface thrombogenicity, hypercoagulability, and locally static blood flow (Virchow's triad) (23). Valve sites where thrombi occur are associated with local hemodynamic disturbances, and designs having increased turbulence or well-defined regions of stasis yield higher rates of thromboembolism. For example, thrombi/thromboemboli arise at the cage apex of a caged-ball prosthesis, a region of considerable flow abnormality (24), in contrast, a tilting disk prosthesis is particularly susceptible to thrombus formation in a stagnation zone in the minor orifice of the outflow region (Fig. 1A) (25). Thrombotic deposits on the cusps of bioprostheses involve one or more of the prosthetic sinuses of Valsalva (Fig. 1B); in most cases, no causal cuspal pathology can be demonstrated (26). Since platelet deposition dominates initial blood-surface interaction when valves and other cardiovascular devices are exposed to blood at high fluid shear stresses (27–30), antiplatelet agents are often administered in conjunction with anticoagulants (10,31,32).

Prosthetic valve endocarditis. Infective endocarditis is infrequent (1 to 6% of patients with valve replacements), but serious (over 50% mortality) (33–35). Patients requiring valve replacement for native valve endocarditis frequently develop prosthetic valve endocarditis with the original organism. Infection rates of mechanical valves and bioprostheses are approximately the same. Complications of prosthetic valve endocarditis include embolization of vegetations, congestive heart failure secondary to valvular obstruction or regurgitation caused by bulky vegetations, or the consequences of local tissue destruction.

Similar to other infections involving biomaterials, prosthetic valve endocarditis is resistant to host defense mechanisms and antibiotics, and thereby difficult to cure medically (4,33). Infections of mechanical prostheses are almost always localized to the prosthesis-tissue interface at the sewing ring, causing a ring abscess, since synthetic biomaterials (polymers, metals, carbons) generally cannot support bacterial or fungal growth (Fig. 2A) (36,37). The resultant tissue destruction may induce separation (dehiscence) of the prosthesis from the annulus, with regurgitation of blood around the prosthesis (paravalvular or paraprosthetic leak), or cause septic pericarditis, pseudoaneurysm, or complete or partial interference with atrioventricular conduction. Rarely, mechanical valve infection is confined to tissue associated with the valve superstructure or poppet (38).

Bioprosthetic valve endocarditis can be either localized to the prosthesis sewing ring and complicated by ring abscess, or confined to the cuspal tissue (Fig. 2B), often with tearing, perforation, or destruction leading to valve incompetence (39,40). Cusps of bioprosthetic valves with endocarditis often have deep clusters of organisms with few inflammatory cells. Degenerating bacteria and inflammatory cells within

cuspal vegetations of bioprosthetic valve endocarditis can undergo mineralization (extrinsic calcification) (Fig. 2C), often in a characteristic pattern that can rapidly suggest the diagnosis (Fig. 2D) (5).

Prosthetic valve endocarditis is generally classified as early (within 60 days following valve replacement) or late (after 60 days), with etiology, risk factors, and causative microorganisms different in each of these time periods. Organisms comprising normal skin flora predominate in early infections, emphasizing the importance of both valve contamination during implantation and early postoperative infection. Late infections are more likely to be precipitated by bacteremia associated with poor dental hygiene, dental or surgical procedures, or extracardiac pyogenic infections. The high frequency of staphylococcal infection on prosthetic valves (*Staphylococcus epidermidis*, *Staphylococcus aureus*), particularly in early cases, contrasts with the relatively low frequency of these organisms in natural valve endocarditis; streptococci, gram-negative bacilli and fungi also are prevalent. In about 15% of cases, a causative organism cannot be cultured. Although some of these infections could be caused by anaerobes, culture-negative prosthetic valve endocarditis has been recently related to legionella (41) and Q fever (42).

Paravalvular leak (dehiscence, paraprosthetic leak) (Fig. 3). Early dehiscence is usually the result of technical error or separation of sutures from a pathologic annulus when valve replacement was done for endocarditis with ring abscess, myxomatous degeneration or calcified aortic valve or mitral annulus (43). In contrast, late, small paravalvular leaks are usually caused by tissue retraction from the sewing ring between sutures during healing. Small periprosthetic defects are often clinically inconsequential; large tears can aggravate or cause hemolysis or heart failure. A valve removed for paravalvular leak appears unremarkable to the surgical pathologist; detection at autopsy may require careful probing.

Durability Considerations

Prosthetic valve failure is frequently precipitated by the limited durability of biomaterials. Specific failure modes vary widely for mechanical valves and bioprostheses, and frequently, for specific types of each, for prostheses utilizing different materials or design features, or for the same model placed in the aortic rather than the mitral site (4).

Mechanical prostheses. Silicone elastomeric ball occluders of early caged-ball prostheses absorbed blood lipids, causing swelling, distortion, cracking, and embolization of poppet material or abnormal poppet movement (ball variance), particularly in the aortic position (Fig. 4A) (44). Lipid-related ball variance was subsequently eliminated by changes in elastomer fabrication in 1964. With cloth covered, caged-ball valves used to provide a substrate for tissue overgrowth, abrasion by the occluder often induced frag-

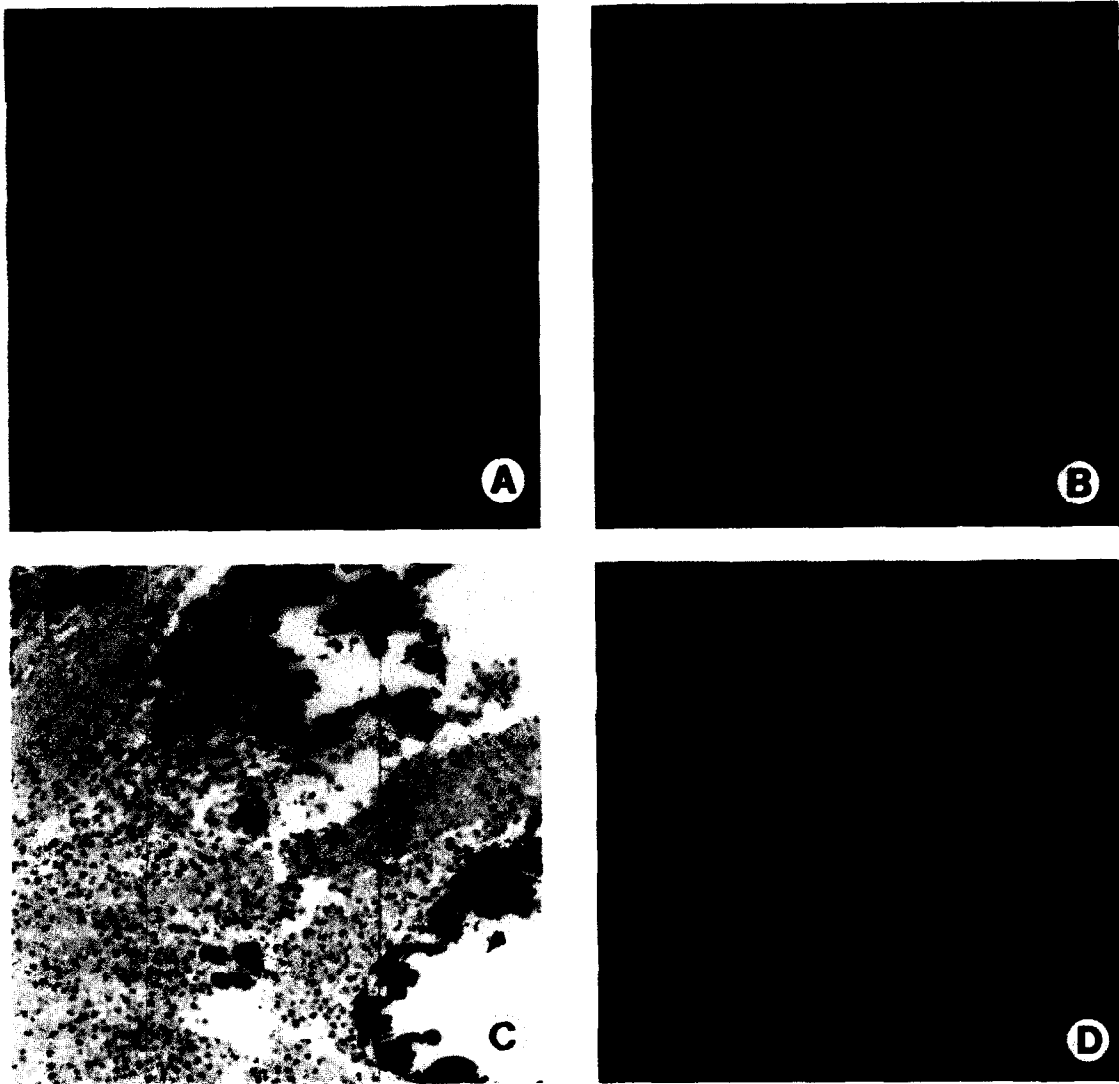


Figure 2. Prosthetic valve infective endocarditis. **A.** Ventricular view of mitral tilting disk prosthesis in patient dying of infective endocarditis. Large bulky vegetations consisting of bacterial organisms and platelet/inflammatory cell/fibrin thrombus cover part of the sewing ring and form an abscess within tissue of the annulus (arrow) (Reproduced by permission from Schoen FJ. Cardiac valve prostheses: pathological and bioengineering considerations. *J. Cardiac Surg* 1987; 2:65-108. © 1987, Futura Publishing Company.) **B.** Bioprosthetic bacterial endocarditis involving cusps, viewed from inflow aspect; large vegetations are apparent. (Reproduced by permission from Schoen FJ and Hobson CE Anatomic analysis of removed prosthetic heart valves: causes of failure of 33 mechanical valves and 58 bioprostheses, 1980-1983. *Hum Pathol* 1985; 16:549-559. © 1985, W.B. Saunders.) **C.** Photomicrograph of calcified endocarditic vegetation on porcine bioprosthetic valve (H/E \times 175). **D.** Radiograph of infected porcine bioprosthetic valve with calcified vegetations, demonstrating diffuse distribution of calcific deposits characteristic of endocarditis.

Figure 3. Paravalvular leak, mitral prosthesis, viewed from left atrium (probe in defect). (Reproduced by permission from Schoen FJ. Pathology of cardiac valve replacement. In: Morse, D, Steiner RM, Fernandez J, eds. *Guide to Prosthetic Cardiac Valves*. New York: Springer Verlag, 1985:209-238.)



mentation of cloth, thrombosis, fibrous overgrowth and resultant ball entrapment (models with metal poppets), or poppet escape (in aortic, but not mitral, models with silicone occluders, due to mutual cloth-poppet abrasive wear) (Fig. 4B) (45,46). Nevertheless, structural failure of presently used caged-ball prostheses is rare. Caged-disk valves with plastic disks suffered disk wear and resultant valve incompetence, and are no longer used (47,48); plastic-coated stents can also wear down (Fig. 4C). Since microfragments of worn nonphysiologic material may embolize systemically, demonstration of foreign body granulomas on biopsy of the liver or other organs may aid the recognition of ball or disk variance (49).

Contemporary tilting disk designs with pyrolytic carbon occluders, with or without carbon cage components, have generally favorable durability. Fractures of metallic or carbon valve components and escape of parts from such valves rarely occur. (50-52). However, in a specific cohort of Bjork-Shiley 60 and 70° convexo-concave (C-C) heart valves, the welded outlet strut has fractured and separated from the valve, leading to disk escape that is frequently fatal (Fig. 4D). Over 300 such cases are known; in each fractured valve, the previously completely machined housing (integral) was replaced by a housing in which the outflow strut was welded to the housing. Fatigue failure of the welded metallic joint likely precipitates the fracture of this valve (53,54). This problem is discussed in detail below.

In contrast to the free disk rotation of contemporary tilting disk valves, bileaflet disk valves have a fixed pivot point at the periphery of each disk; the configuration varies with specific manufacturer and design. Fractures of components of the St. Jude valve are rare; however, at least 17 cases of leaflet escape from the Edwards-Duramedics bileaflet valve have been reported (Fig. 4E) (55). Detailed pathologic studies of removed valves not suffering overt structural dysfunction may be useful in predicting long-term durability (56,57).

Bioprostheses. The major cause of bioprosthetic valve dysfunction is primary tissue failure, especially when it is related to cuspal mineralization (58-61). Noninfective tissue degeneration (primary tissue failure) of glutaraldehyde-pretreated porcine bioprostheses is strongly time dependent. In adults, less than 1% of valves implanted for 5 years have failed, 20 to 30% fail within 10 years, and more than half are no longer functional by 15 years postoperatively. Regurgitation through tears forming adjacent to calcific nodules is the most frequent failure mode (Fig. 5A); pure calcific stenosis (Fig. 5B) and noncalcific cuspal defects are less frequent (1,4,61); rarely, important emboli arise from calcific valves (Fig. 5C) (62). Noncalcific tissue tears, revealed by scanning electron microscopy as fraying and disruption of collagen fibers, usually reflect direct mechanical damage to collagen (63).

The amount of calcification of removed valves after long-term implantation is highly variable (64). Although calcifi-

cation is noted in almost all porcine aortic valve bioprostheses implanted for at least 4 years, valves with minimal or no calcific deposits are occasionally encountered after 10 years or more. Calcification is markedly accelerated in bioprostheses implanted in children, adolescents, and young adults (1,65).

Degenerative cuspal calcific deposits form within the cusps (intrinsic mineralization), and are composed of calcium phosphates, closely related to physiologic bone mineral (hydroxyapatite). Calcific deposits generally predominate at the cuspal commissures and basal attachments, are grossly visible as nodular gray/white masses that often ulcerate through the cuspal tissue, and are most extensive in the porcine valve spongiosa layer. Ultrastructurally, calcific deposits are associated with connective tissue cells and collagen (66,67).

Pericardial bioprostheses also suffer calcific degenerative failure in both adults and children (68,69). However, noncalcific cuspal perforations and tears more frequently cause failure of clinical pericardial bioprostheses (70-72). Defects occur near the cuspal attachments and are usually related to either continuous trauma of the tissue against the Dacron cloth strut covering, causing abrasion (Fig. 6A), or fatigue of the tissue near the free edge of the leaflet, adjacent to the stent post (Fig. 6B).

Other tissue valves. Noncommercial, hospital-made autologous and homologous tissue valves constructed from pericardium, fascia lata, or dura mater mounted on cloth-covered metal stents have also been used. Clinical studies reveal extremely high failure rates, with removed valves having thick connective tissue overgrowth, cuspal stiffening and shrinkage, calcification, and tearing (4,5,73,74). In contrast, unstented, cadaver-derived aortic homografts, used for selected patients with isolated aortic valve disease or congenital malformations, have excellent short- and medium-term function (75-78). Pathologic issues related to valve allografts are discussed below.

Miscellaneous Valve-Related Pathology

Prosthetic valves are not only partially obstructive to forward flow but also have some variable regurgitant flow, often intentionally designed into the mechanism to enhance closing. The increased hemodynamic burden of the resultant chronic pressure and/or volume overload probably contributes to progressive myocardial deterioration in some patients. Contemporary tilting and bileaflet tilting disk valves and bioprostheses have favorable hemodynamic performance (79,80). However, bioprostheses can be significantly obstructive, particularly in small sizes, where the bulk of the struts is not proportionally reduced. Moreover, inward deflection of the stent posts (stent creep) during function of some porcine bioprostheses may contribute to progressively increasing stenosis (Fig. 7) (81). Prostheses inappropriately large for the anatomic site of implantation can have re-

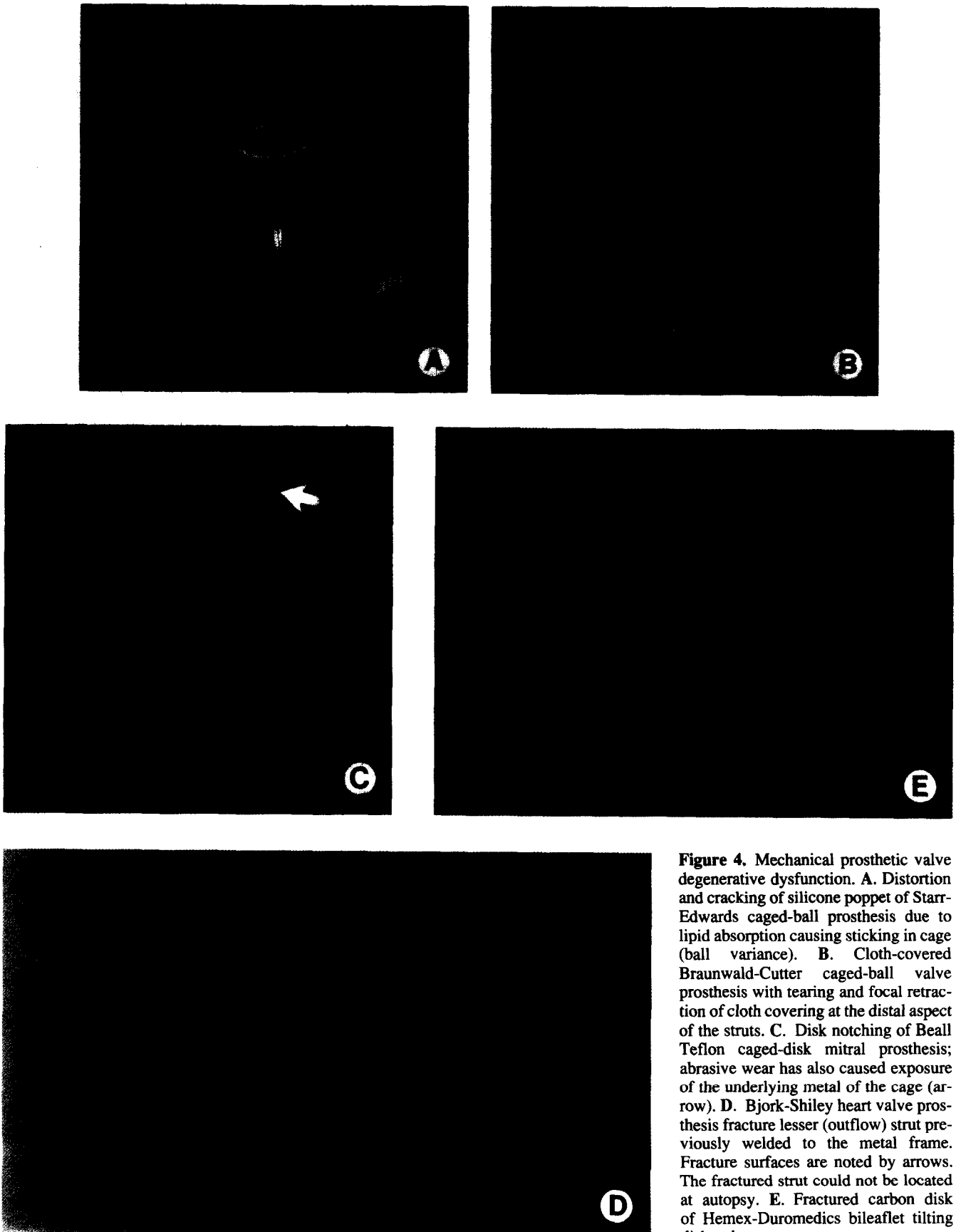


Figure 4. Mechanical prosthetic valve degenerative dysfunction. **A.** Distortion and cracking of silicone poppet of Starr-Edwards caged-ball prosthesis due to lipid absorption causing sticking in cage (ball variance). **B.** Cloth-covered Braunwald-Cutter caged-ball valve prosthesis with tearing and focal retraction of cloth covering at the distal aspect of the struts. **C.** Disk notching of Beall Teflon caged-disk mitral prosthesis; abrasive wear has also caused exposure of the underlying metal of the cage (arrow). **D.** Bjork-Shiley heart valve prosthesis fracture lesser (outflow) strut previously welded to the metal frame. Fracture surfaces are noted by arrows. The fractured strut could not be located at autopsy. **E.** Fractured carbon disk of Hemex-Duromedics bileaflet tilting disk valve.

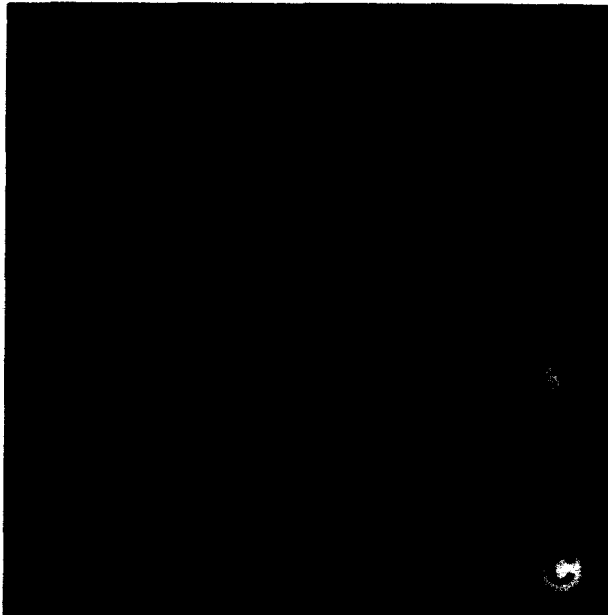
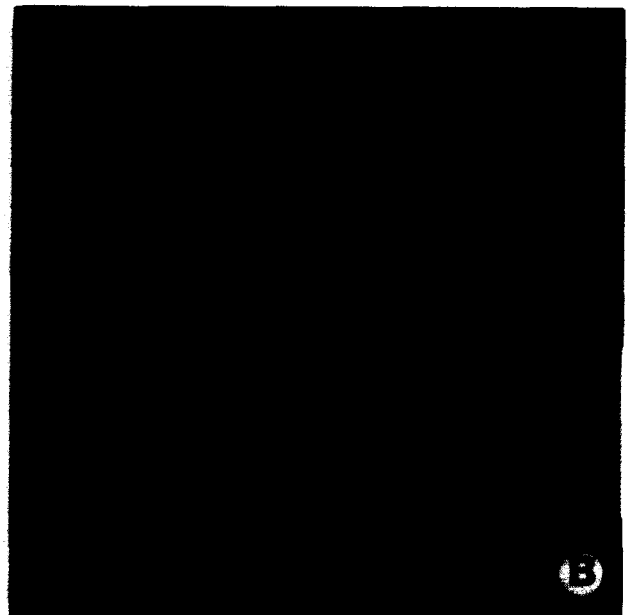
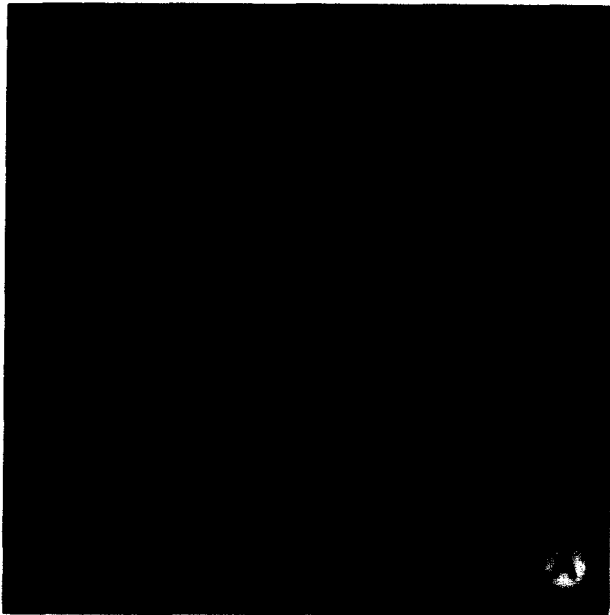


Figure 5. Porcine bioprosthetic valve calcific failure. **A.** Calcific stenosis, **B.** Calcification with secondary tear. (A and B are reproduced by permission from Schoen FJ and Hobson CE. Anatomic analysis of removed prosthetic heart valves: causes of failure of 33 mechanical valves and 58 bioprostheses, 1980–1983. *Hum Pathol* 1985; 16:549–559. Copyright 1985, W.B. Saunders.) **C.** Calcification, tearing and calcific embolus (arrow) removed from left anterior descending coronary artery.

stricted poppet motion, impinge on surrounding structures, or be obstructive, since flow around the poppet may be impeded (prosthetic disproportion) (82). Mitral prostheses too large for the ventricle into which they are placed can interfere with left ventricular filling or emptying.

Factors extrinsic to a prosthesis can promote stenosis or regurgitation (82–95). A trend in mitral valve replacement surgery is the retention of as much of the mitral apparatus as possible, in the belief that this enhances postoperative left ventricular function (83). However, either retained valve remnants or unraveled or excessively long ends of sutures can interfere with valve occluder motion (Fig. 8). A large

mitral annular calcific nodule or septal hypertrophy can prevent full excursion of a mitral tilting disk valve occluder. Exuberant overgrowth of fibrous tissue can obstruct the inflow orifice of any valve (Fig. 9), prevent full mechanical valve occluder excursion, or cause stenosis or regurgitation of bioprostheses. Intermittent sticking of tilting disk prostheses has been recognized; sometimes, such valves appear to function normally when removed, and the cause of malfunction remains obscure, despite careful pathologic examination. Sutures may be looped around bioprosthetic valve stents, particularly with pericardial bioprostheses, restricting cuspal motion, and suture ends cut too long may perforate a bioprosthetic valve cusp (1).

Some red blood cell destruction by the turbulent flow in prosthetic heart valves is common, but hemolysis is generally slight and well compensated; severe hemolytic anemia is unusual without paravalvular leaks or valvular dysfunction (96–98). Renal tubular hemosiderosis or cholelithiasis noted at autopsy suggests chronic hemolysis (99,100).

The spectrum of morphologic changes that occurs prior to and following bioprostheses implantation and the specific differences between porcine aortic valve and bovine pericardium are summarized elsewhere (5,7,101–105). Systemic diseases can also involve bioprosthetic valves (106, 107).

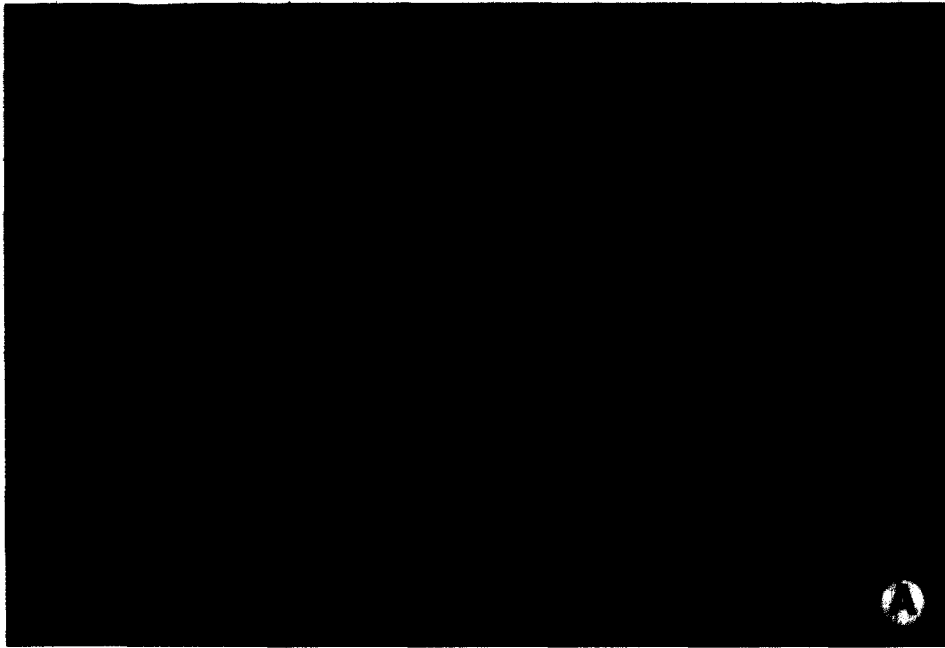


Figure 6. Noncalcific failure of bovine pericardial valves. **A.** Tear (open arrow) and incipient tear (arrow), due to abrasion at stent post. (Reproduced by permission from Schoen FJ. Pathology of bioprostheses and other tissue heart valve replacements. In: Silver MD, ed. Cardiovascular Pathology, 2nd ed. New York: Churchill Livingstone, 1991:1547-1605.) **B.** Commissural tear. (Reproduced by permission from Schoen FJ. Cardiac valve prostheses: pathological and bioengineering considerations. *J. Cardiac Surg* 1987; 2:65-108. Copyright 1991, Futura Publishing Company).

Aortic Valve Allografts

Homograft/allograft aortic valves are advantageous for selected patients with aortic valve disease or those requiring pulmonic valve and/or pulmonary artery replacement for congenital heart disease (3,75-78). Allograft aortic valve/root replacement is considered a useful method for management of active endocarditis complicated by annular destruction and for surgical treatment of many kinds of congenital

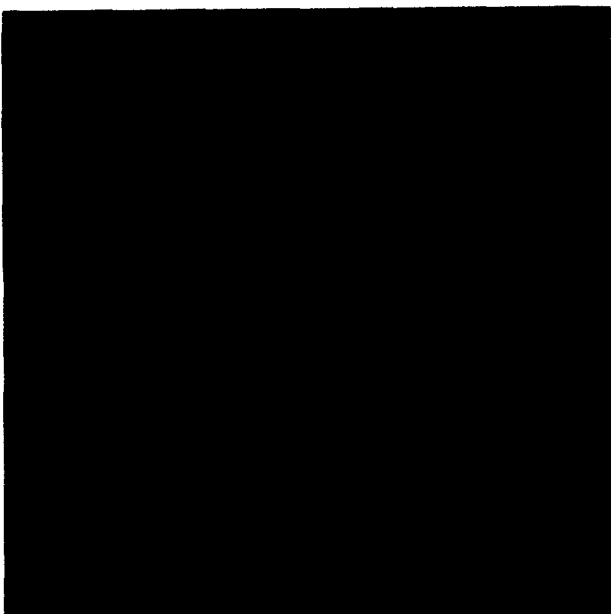
heart disease where the creation of a pathway from a ventricle to the pulmonary arteries is necessary (108). Representative failure rates are 19 to 50% at 10 to 12 years and 54 to 89% at 15 to 20 years for variously prepared valves, including chemically-treated and antibiotic-sterilized allografts (75-78). In general, however, results for contemporary allograft heart valves appear to be somewhat better than those using obsolete tissue treatments, and it is well accepted that the time course of failure of allografts is slower than that for other tissue valves, especially in a young population. Thus,



Figure 7. Stent creep of porcine bioprosthesis. **Left,** a 25-mm aortic prosthesis implanted for 36 months; compromise of the outflow orifice is apparent. **Right,** an unimplanted 25-mm prosthesis for comparison. (Reproduced by permission from Schoen FJ, Schulman LJ, Cohn LH. Quantitative anatomic analysis of "stent creep" of explanted Hancock standard porcine bioprostheses used for cardiac valve replacement. *Am J Cardiol* 1985; 56:110–114. Copyright 1985, Yorke Medical Publishers).

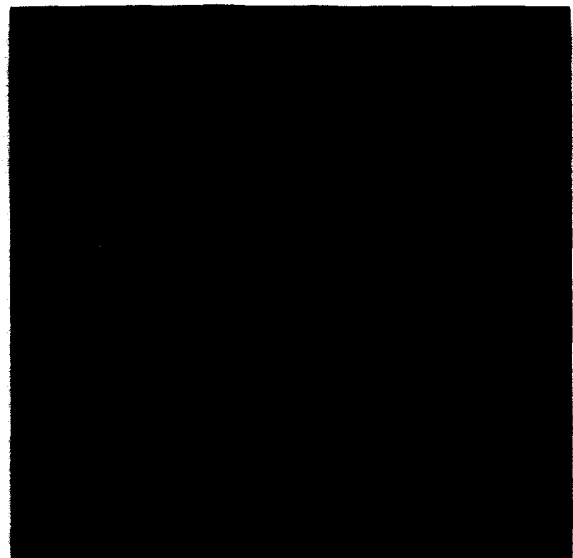
the allograft, when available, is the replacement of choice in many centers. Current interest is directed toward allografts cryopreserved in liquid nitrogen at -196°C using dimethyl

Figure 8. Interference with tilting disk valve occluder motion by suture with long cut end (arrows). (Reproduced by permission from Schoen FJ. *Surgical Pathology of removed natural and prosthetic heart valves.* *Hum Pathol*, 1987; 18:558–567. Copyright 1987, W.B. Saunders.)



sulfoxide (DMSO) as a protective agent; some studies suggest that these valves perform significantly better than antibiotic-treated grafts (75,78). The major advantages of allografts are excellent hemodynamic performance, nearly equivalent to that of the natural aortic valve, and an exceedingly low rate of thromboembolism (less than 4% total up to

Figure 9. Tissue overgrowth compromising inflow orifice of porcine bioprosthesis.



15 years, compared to 1 to 4% per year for mechanical and bioprosthetic valves). Nevertheless, failure resulting from progressive degeneration occurs frequently, with incompetence the major limitation generally caused by cuspal rupture, distortion with retraction, or perforations (76,77). The relative advantages and disadvantages of mechanical, bioprosthetic and allograft valves are summarized in Table 2.

Allograft valves are historically obtained from cadavers, but many are now harvested from diseased hearts removed from cardiac transplant recipients. Early cadaver-derived allograft valves were procured aseptically and implanted within 1 to 3 weeks. However, due to logistical difficulties, valves were subsequently sterilized either chemically or by radiation, following nonsterile procurement. Such valves suffered a high rate of leaflet calcification and rupture (109-113). Antibiotic-sterilized but not cross-linked valves, used more recently, are often considered "fresh," but they are essentially nonviable. Although studies suggest that some metabolic activity and viable cells may remain in the grafts at the time of implantation of valves cryopreserved using current technology (114), it is unknown whether allograft cell viability at implantation time is an important determinant of long-term durability. Impetus to achieve cell viability may be a search for a more "gentle" treatment of the valve that may preserve other important elements, such as extracellular matrix, irrespective of the state of the cells. Moreover, the presence of viable cells could be deleterious, for example, by potentiating immunological reactivity (115) or calcification.

Pathologic features noted in removed failed or nonfailed aortic valve allografts are illustrated in Figure 10 and summarized in Table 3. Nearly all valves removed following various periods of implantation are devoid of surface endothelium and deep connective tissue cells of both valve cusps and contiguous aortic wall. Inflammatory cellularity is variable. Late explants frequently have some degree of proximal intimal fibrous sheath, aortic wall calcification and, occasionally, cuspal calcific deposits (116, 117). Stent-mounted aortic allografts used for mitral valve replacement

Table 2. Allograft Valve Morphology

Nearly All Valves
Loss of cuspal connective tissue cells
Loss of endothelium
Minimal inflammatory cellularity
Aortic wall calcification
None to minimal cuspal calcification
Intimal fibrous sheath
Occasional Valves
Cuspal distortion
Cuspal tears
Suture line dehiscence
Commissural fusion
Mural thrombus
Fraying of cuspal free edge
Cuspal hematomas

Table 3. Major Merits and Problems of Contemporary Valve Substitutes

	Advantages	Disadvantages
Mechanical valves	More durable*	More obstructive Thrombogenic
Bioprosthetic valves	Less obstructive† More thromboresistant	Less durable
Homograft valves	Near-normal hemodynamics Thromboresistant Slightly more durable	Limited availability

*Except for some models.

†Except for small sizes.

often show detachment of the allograft tissue from the supporting stent posts with cuspal tears (118). Calcification of unstented aortic valve allografts occurs predominantly in the contiguous aortic wall, prominently involving elastic elements (4,116).

Histocompatibility issues in the transplantation of heart valve allografts are not well established. Most allografts are not matched to the recipient's ABO blood group. Nevertheless, immunosuppression is generally not used. Significant lymphocytic infiltrate is unusual; the extent to which classical rejection contributes to failure is unknown.

Several tissue banks and one commercial organization are now procuring, processing, and distributing allograft valves in the United States. The Cardiovascular Devices Panel of the Food and Drug Administration recently developed a set of guidelines for heart valve allografts. Because of the paucity of retrieved devices and because most are removed at reoperations where the surgeon has difficulty removing the valve intact, allograft pathology has been relatively difficult to characterize. Previous detailed reports described pathologic features of valves using treatments no longer employed (108-113). Consequently, pathologists receiving explanted clinical allografts should make every effort not only to address pressing patient management questions but also to put the underlying changes of these valves in the context of larger pathologic concerns. Plans are underway to set up an evaluation protocol and establish a central registry for allograft pathology. In this respect, consideration should be given to the use of contemporary techniques of molecular forensics and DNA fingerprinting to assess cell lineage issues (i.e., donor vs. recipient).

Pathologic Analysis of Contemporary Valve Substitutes

The etiology of valve failure is documented by careful and informed examination of artificial valves, either removed or in situ, by surgical and autopsy pathologists. Cumulative data compiled by several case studies provides the basis for improved valve selection criteria, patient/prosthe-

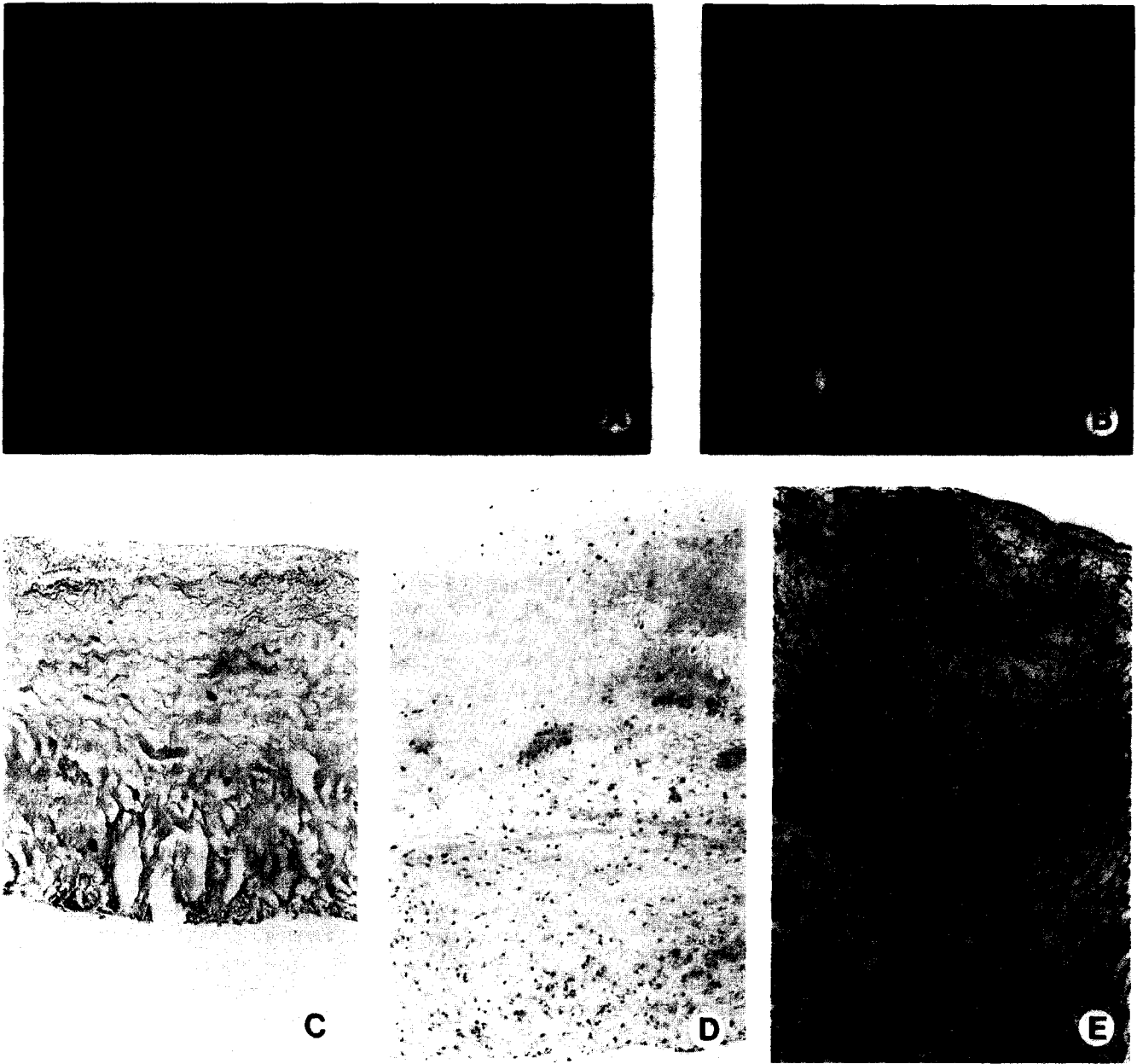


Figure 10. Allograft heart valve pathology. **A.** Aortic valve removed as a result of cuspal laxity causing insufficiency (courtesy William D. Edwards, M.D., Mayo Clinic). **B.** Aortic homograft used as right ventricle to pulmonary artery shunt in infant with congenital heart disease. The aortic wall is heavily calcified and the valve cusps are variably shortened and retracted (arrow). **C.** Typical cuspal morphology with loss of original cellularity and few recipient inflammatory cells (hematoxylin & eosin $\times 175$). **D.** Aortic valve homograft with loss of cuspal cells, but moderate mononuclear inflammatory cellularity (hematoxylin & eosin $\times 100$). **E.** Immunoperoxidase staining demonstrating T-lymphocytic, origin of majority of cuspal cells in specimens shown in D, suggesting immunological process. (E) Immunoperoxidase using UCHL-1 antibody for T-lymphocytes (hematoxylin & eosin $\times 150$). (C) 175X; (D) 100X; (E) 150X.

sis matching, patient management strategies, and recognition of complications. Informed analysis of removed clinical and experimental prostheses often provides data not obtainable by either in vitro hemodynamic and durability tests or preclinical animal investigations, and elucidates mechanisms of patient-prosthesis and tissue-biomaterials interactions, thereby guiding potential improvements in valve design and materials. Pathologists have an important role in recognizing prosthesis-associated complications, a key element of the Safe Medical Devices Act of 1990 (PL101-629). This legislation requires hospitals to report to manufacturers and/or the FDA incidents in which a medical device has

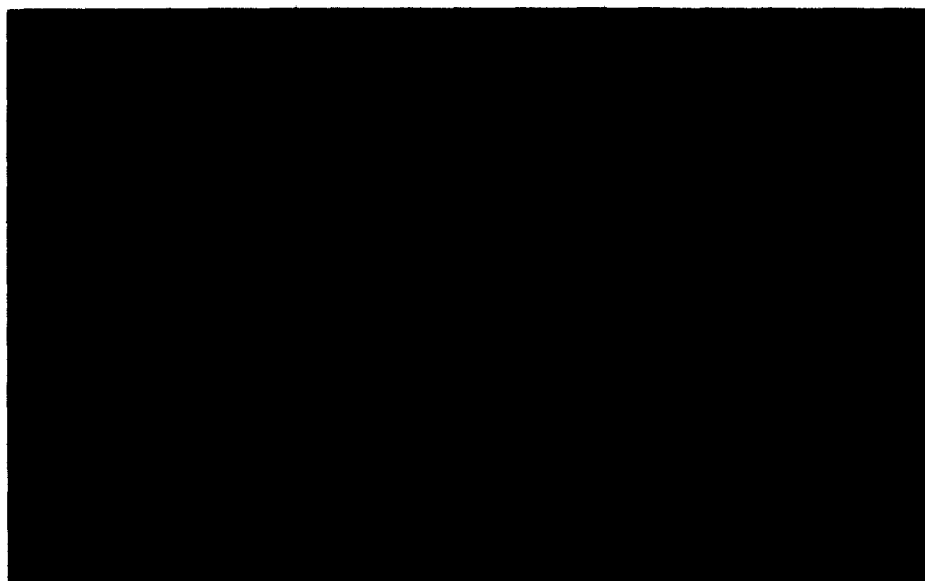


Figure 11. Opened porcine valve bioprosthesis, demonstrating superior visualization of cuspal tear. In this case, a catheter-induced tear was suggested.

caused or contributed to death of or serious injury to a patient.

Complete explant analysis includes gross examination and photography, radiography (for bioprostheses), dissection, histologic examination, and microbiologic cultures. Key morphologic features are summarized in Table 4. Special procedures, such as functional testing, dimensional analyses, surface topographic measurements, biochemical procedures, polarized light examination, or scanning or transmission electron microscopy can be used judiciously in experimental investigations of new valve materials or configurations and in clinical studies where specific clinico-pathologic correlations are sought. While the anticipated pathology and thus the detailed protocol for analysis depends in large part on the type of prosthesis under consideration, generalized approaches to dissection of heart valve

prostheses and documentation of their most important pathologic findings have been described (4,5,18). The specific type and model of the prosthesis may be identified using radiographic and morphologic keys (4,8,120). A serial number placed by the manufacturer that uniquely identifies each valve is usually hidden under the sewing ring on the valve base.

In brief, a prosthesis at either autopsy or surgical removal is photographed from all pertinent angles and examined for thrombi, vegetations, exuberant tissue overgrowth, and structural defects. Autopsy specimens are carefully probed for paravalvular leaks. Mechanical heart valve prostheses are checked for adequacy of poppet excursion and seating, defects and fractures of components, asymmetries, sites of abrasive wear, and poppet swelling or distortion. Bioprostheses are gently examined to assess cuspal excursion and the presence of fenestrations, tears, cuspal hematomas, calcific nodules, and central migration of struts. Removing the valve from the stent, then opening and pinning it on cork aids characterization of gross cuspal pathology (Fig. 11). Routine morphologic analysis of bioprostheses includes radiography (we have used the Faxitron, Hewlett Packard, McMinnville, OR, 0.8 min x 40 KV), that aids identification of the prosthesis type and assessment of calcific deposits. Calcification is semiquantitatively graded (usually, 0 = not present, 1+ = mild, 2+ = moderate, 3+ = more severe, and 4+ = most severe), and the location of calcific deposits noted (with respect to cuspal bodies, commissures, basal attachment sites, and at the free cuspal edges) (Fig. 12) (64). Specimens of cuspal and adherent tissue are specifically labeled and mounted in cross section for histologic analysis. Histologic analysis is directed toward determination of the morphology of tissue/prosthesis interactions, cuspal degen-

Table 4. Pathological Analysis of Mechanical and Bioprosthetic Valves

Gross Examination	Radiography	Histology
Tissue overgrowth	Valve identification	Vegetations/ Organisms
Thrombi	Calcification	Thrombi
Vegetations	Degree	Host cell interactions
Cuspal stiffness	Localization	Degeneration
Cuspal hematomas		Calcification
Calcification		Degree
Fenestrations/tears		Morphology
Cuspal abrasion		Location
Cuspal stretching		Endothelialization
Strut relationships		
Mechanical dysfunction		
Extrinsic interference/ damage		



Figure 12. Composite radiograph of calcified porcine aortic valve bioprostheses, demonstrating the various levels of mineralization, 1+ through 4+, and providing radiographic standards for examination. Uncalcified (0), 1+, and 2+ (**top**); 3+, 3+ and 4+ (**bottom**). (Reproduced from Schoen FJ, Kujovich JL, Webb CL, Levy RJ. Chemically determined mineral content of explanted porcine aortic valve bioprostheses: correlation with radiographic assessment of calcification and clinical data. *Circulation* 1987; 76:1061-1066. Copyright 1987, American Heart Association.)

Table 5. Implant Failure Analysis

Related to Design Feature
High stress
Abrasion
Tolerances too high or too low
Blood stasis
Related to Stock Material/Processing
Inclusions/bubbles/porosity
Heterogeneity
Weld defects/phase changes
Related to Device Assembly
Scratches
Cracks
Crush
Contamination
Related to Shipping/Storage
Freezing
Contamination
Degradation
Related to Surgical Implantation
Scratches
Cracks
Crush
Suture entrapment
Related to Changes During Function
Fatigue
Abrasive wear
Cavitation
Biological degradation
Calcification

eration, and the degree and specific morphology of calcific deposits. Embedding in glycolmethacrylate allows sectioning of undecalcified specimens with good morphological preservation.

Role of the Pathologist in Prosthetic Heart Valve Failure Analysis

While not appropriate in the routine hospital setting, investigations using highly detailed implant retrieval and analysis elucidate mechanisms of prosthesis failure and thereby stimulate directed development of improved prostheses. Moreover, pathologists frequently participate as expert witnesses in product liability litigation involving cases of prosthetic valve failure. The essential objective in either situation is the assignment of a failure mechanism that distinguishes the relative roles of design, materials, fabrication, shipping, storage, implantation, and changes during function (Table 5). Determination of the etiology of an outlet strut fracture in a Bjork-Shiley 60° convexo-concave tilting disk valve exemplifies general retrieval and analysis procedures that maximize obtainable data, without compromising further examination by other parties. This case illustrates the major factors in outlet strut failure, determined from evaluation of more than 20 explanted fractured Bjork-Shiley heart valves for which all three components (annulus with integral inlet strut, fractured outlet strut, and disk) were retrieved (121).

Outlet strut fatigue fractures in Bjork-Shiley convexo-concave valves have been attributed to abnormal loads and/

or welding flaws (54,121). The source of these abnormal loads is illustrated in Figure 13A, a cross section of the valve through the midpoints of both the welded outlet strut (left, above) and integral inlet strut (right, below). Under normal conditions, the disc of the closed valve would be in a horizontal position and come to rest on the larger integral inlet strut. In the valve illustrated, abnormally high clearance between the inlet and outlet struts permits the disk to rotate in a clockwise direction beyond the horizontal plane, causing a hard contact with the tip of the outlet strut (indicated by arrow). This results in excessive bending stresses at and near the welds joining the outlet strut to the annulus; a marker for this abnormal loading is a pronounced wear flat on the tip of the outlet strut (Fig. 13B). In some cases, contact between the disk and the tip of the outlet strut is manifest by localized pyrolytic carbon wear deposits on the inlet strut near its junction with the annulus. Such deposits result from contact between the inlet strut and the periphery of the disk at the same time that the center of the disk is contacting the tip of the outlet strut. In other instances, abnormal motion leads to two distinct overlapping wear flats on the tip of the outlet strut.

The first outlet strut leg to fail invariably shows signs of extensive abrasion and wear resulting from the relative motion of the halves of this fractured strut as fatigue fracture of the second strut leg is occurring. Low magnification scanning electron micrographs of the fracture surfaces of the first and second strut leg to fail are shown in Figures 13C and 13D, respectively; slip bands from bending during manufacture are also evident on both strut legs. Both fractures initiated on the inlet side of the outlet strut, as in other valves that fractured. The first strut leg fracture typically initiates at or near the point of maximum bending stress in the center of the inlet strut leg/annulus junction. The initiation site in the second strut leg to fracture is often rotated slightly toward the first, since the remaining intact strut leg is subjected to both bending and torsion after the first fracture occurs.

Observations on the sides of an annulus and strut leg that have fractured are often useful in evaluating the mechanism of fatigue fracture and its relationship to microstructure and material flaws, especially in situations where there has been extensive abrasion and wear of the mating fracture surfaces of the initially fractured strut leg. Secondary cracks below the heavily abraded fracture surface of the first strut leg to fracture are associated with weld shrinkage porosity and/or inclusions (Fig. 13E).

Standards for use by experts in the product liability system developed by ASTM Committee E-40 on Technical Aspects of Product Liability Litigation are recommended for such analyses, including ASTM E-620-85(90) and E-678-84 (American Society for Testing and Materials, Philadelphia, PA). The detail shown in the above micrographs can only be observed if the devices are carefully preserved after explanation, particularly avoiding contact between fracture sur-

faces, since wear patterns clearly provide valuable insights into the mechanism of failure. Destructive testing, such as sectioning, polishing, and etching the housing metal alloy, is useful in characterizing the valve microstructure and its relationship to fracture. However, such destructive testing should proceed only after all interested parties have had an opportunity to complete nondestructive tests, since potential observations may be precluded.

Pathobiology of Bioprosthetic Valve Calcification

In both circulatory and subcutaneous experimental models, bioprosthetic tissue calcifies progressively, with morphologic features similar to those observed in clinical specimens, but with markedly accelerated kinetics (122-124). Valves implanted into sheep or calves calcify extensively in 3 to 6 months, and subcutaneous implants of bioprosthetic tissue in young rats achieve calcium levels comparable to those of failed clinical explants in 8 weeks or less. We have utilized the subcutaneous implantation model extensively as a technically convenient, economically advantageous, and quantifiable model for investigating host and implant determinants and pathobiology of mineralization, as well as for screening and understanding the mechanisms of potential strategies for mineralization inhibition (122-131).

Clinical and experimental studies indicate that calcification of bioprosthetic valves depends on host, implant, and biomechanical factors (1,4,122,132). Although calcification is most pronounced in areas of leaflet flexion, where deformations are maximal (i.e., cuspal commissures and bases), dynamic mechanical stress and strain are not prerequisites for calcification. Young age and renal failure potentiate mineralization, but the specific basis for age-dependent kinetics is uncertain (122,132). In rat subcutaneous implants, calcification requires pretreatment of tissue with an aldehyde cross-linking agent; nonpreserved cusps do not mineralize in this model (122,126). Glutaraldehyde-treated porcine aortic valve and bovine pericardium calcify comparably with respect to kinetics, extent, and morphology (123,124). This suggests that the fundamental mechanisms of bioprosthetic tissue mineralization depend on specific biochemical modifications of implant microstructural components induced by aldehyde pretreatment.

Neither nonspecific inflammation nor specific immunologic responses appear to mediate bioprosthetic tissue calcification (122,125). The tissue reaction associated with circulatory and subcutaneous porcine or pericardial valve implants is a classical foreign body reaction, primarily composed of nonlymphocytic mononuclear cells (i.e., macrophages) (4,122). Although several experimental studies have suggested that bioprosthetic tissue can be immunogenic, despite both high collagen content and cross-linking (133,134),

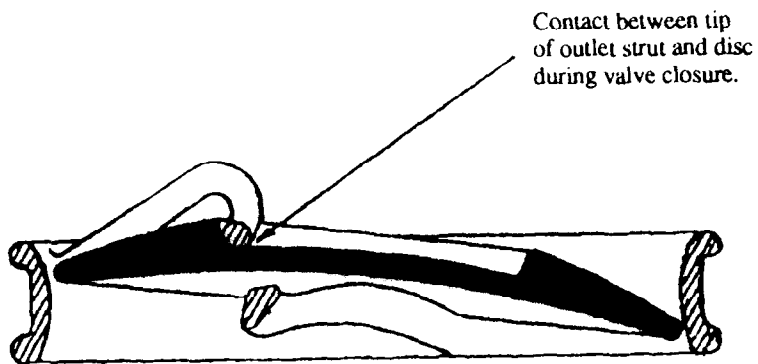


Figure 13. Bjork-Shiley convexo-concave valve fracture analysis (B-E are scanning electron micrographs). A. Cross section through center of valve showing contact between tip of outlet strut (cross-hatched circle) and disk (black) during valve closure. Contact area is indicated by arrow.

(A)

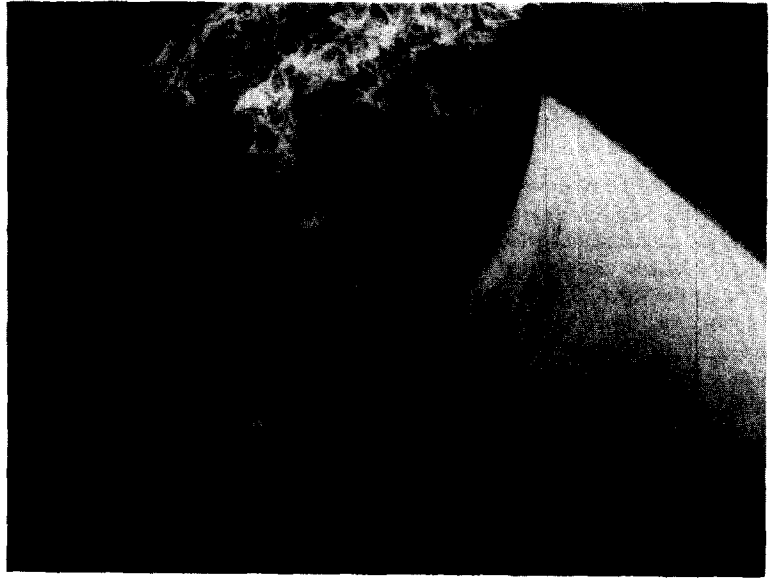


(B)



(C)

D. Fracture surface of second strut leg to fracture. Absence of pronounced wear and slip bands is apparent.



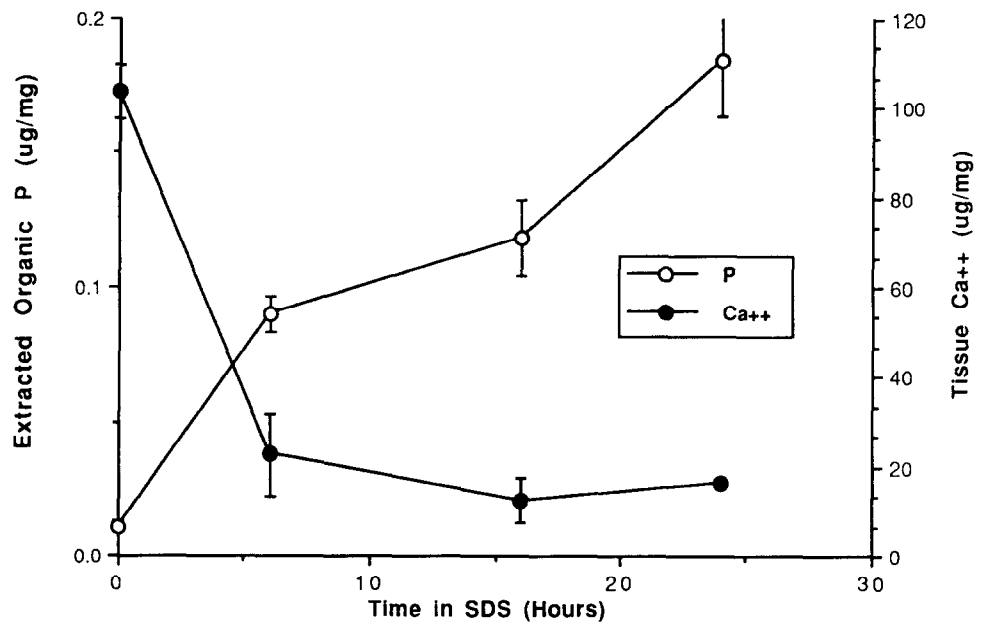
(D)

E. Slide of annulus near origin of fracture (**top**). Welding porosity and secondary cracking are present on the side of the annulus.



(E)

Figure 14. Effects of preincubation in 1% SDS on calcification in a rat subcutaneous model of glutaraldehyde cross-linked porcine aortic valve. These results support the concept that phospholipid extraction is an important but perhaps not the only mechanism of SDS efficacy.



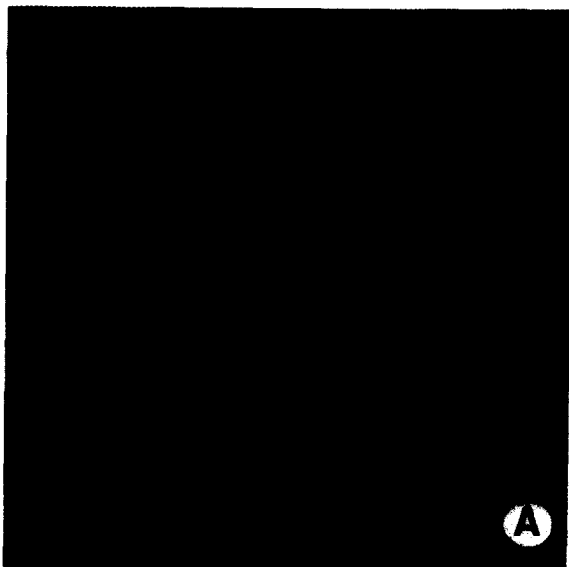
there is no evidence that immunological reactivity is causal to mineralization.

The earliest mineral deposits in both clinical and experimental bioprosthetic tissue are localized to transplanted connective tissue cells; collagen involvement occurs later (122–124). As the implant period increases, cell-associated deposits increase in size and number, obliterating cells and dissecting among collagen bundles. Analogous to clinical valve failures, gross nodules focally obliterate implant architecture and ulcerate through the cuspal surface (123,124).

Mineralization of the connective tissue cells of bioprosthetic tissue is hypothesized to result from glutaraldehyde-induced cellular devitalization and the resulting disruption of cellular calcium regulation (124). Intact living animal

cells have low intracellular free calcium concentration (approximately $10^{-7}M$), while extracellular free calcium is much higher (approximately $10^{-3}M$), resulting in a 10,000 fold gradient across the plasma membrane. In healthy cells, cellular calcium is maintained low by energy-requiring metabolic processes, including the plasma membrane-bound Ca^{2+} -ATPase, and intracellular binding by soluble cytosolic

Figure 15. Heavily calcified experimental polyurethane mitral trileaflet heart valve removed from sheep following 5 months implantation. **A.** Gross photo from distal aspect. **B.** Photomicrograph of extrinsic calcific deposits on cusp. (von Kossa stain [calcium phosphates black] $\times 175$.)



or membrane-bound proteins. Moreover, the observed sites of nucleation of bioprosthetic tissue mineralization (i.e., organellar and plasma membranes), contain considerable phosphorus, largely in the form of phospholipids. We hypothesized that passive calcium entry occurs unimpeded in cells modified by aldehyde cross-linking, but the mechanisms for calcium removal are dysfunctional. In this model, calcium influx contributes to apatite formation by reacting with compartmentalized, bound phosphorus. In support of the above hypothesis, we have demonstrated, using a newly available technique called electron energy loss spectroscopy (EELS), focally high concentrations of intracellular phosphorus in unimplanted, glutaraldehyde-preserved porcine aortic valve and bovine pericardium, and the progressive accumulation of calcium in tissues that have been implanted (131). The formation of calcium phosphate deposits occurs at these cellular sites as early as two days following implantation in the rat subcutaneous model. It is unknown whether collagen deposits are related to contiguous cell-oriented mineral deposition, or arise independently.

Pathologic calcification in the calcific diseases (e.g., degenerative calcific aortic stenosis, atherosclerosis) and the normal calcification of skeletal and dental tissues share important features: 1) initial mineral deposits are poorly crystalline apatitic mineral, highly insoluble in body fluids at physiological pH, but able to proliferate in serum concentrations of calcium and phosphate; 2) cell and collagen crystal deposits are ultimately present, and 3) initial crystal formation occurs on cell membranes, usually in the form of extracellular vesicles (132,135–139). Interestingly, alkaline phosphatase, a matrix vesicle-associated enzyme critical to bone mineral nucleation, is present in both fresh and fixed bioprosthetic tissue, localized to sites where early mineralization occurs (140,141). Alkaline phosphatase further accumulates in porcine aortic valve tissue, in both subcutaneous and circulatory sites, concurrent with mineralization onset (141).

Enhancement of Bioprosthetic Valve Durability

Several approaches are under investigation to reduce bioprosthetic valve failure by modifying host, implant, or mechanical influences. Modifications in cuspal configuration, valve design and tissue pretreatment procedures might enhance overall durability through lower mechanical stresses, thereby lessening structural damage, as well as reducing calcification.

Strategies for prevention of bioprosthetic tissue mineralization involve modifications of either valve preparation details or the local environment of the implant (132). Mechanisms of calcification inhibition by antimineralization treatments (AMTs) considered and/or investigated, clinically and/or experimentally, include extraction of calcifiable material, ionic and/or macromolecular binding to nucleation

Table 6. Anticalcification Studies—Sheep, Mitral, 5 Mos

Treatment	Type	N	Ca (µg/mg)
Control (none)	PAV	22	99.8 +/- 11.1
Control (none)	BPV	17	104.3 +/- 9.1
Polysorbate-80 (PV2)	PAV	15	7.6 +/- 2.6
Polysorbate-80 (PV2)	BPV	11	55.2 +/- 12.7
Triton X-100, N-laurel sarcosine (PV2')	PAV	17	24.4 +/- 1.8
Polyacrylamide (PV3)	PAV	8	112.9 +/- 15.3
SDS (T6)	PAV	17	17.7 +/- 4.2
SDS (T6)	BPV	24	126.6 +/- 5.3
APDP	BPV	12	126.6 +/- 7.3
Toluidine blue	PAV	21	81.6 +/- 12.0

PAV, porcine aortic valve; BPV, bovine pericardial valve. Modified from M Jones et al. *J Cardiac Surg* 4:69, 1989.

sites, neutralization of critical cofactors, such as alkaline phosphatase (141), interference with calcium phosphate crystal growth, charge modification, alteration of interstitial tissue spaces by tissue compression or hydrogel infiltration, prevention of serum diffusion into cusps, and restoration of natural inhibitors. Diphosphonate compounds, used to treat metabolic bone disease, retard calcium phosphate crystal growth. In rats with subcutaneously implanted bioprosthetic tissue, either systemic therapy with ethanehydroxydiphosphonate (EHDP) or EHDP administered in the vicinity of the valve tissue from controlled-release drug delivery polymers loaded with the drug inhibit leaflet calcification (127–130). Cuspal modification by incubation in solutions of trivalent ions of aluminum or iron (Al^{3+} or Fe^{3+}) (131), elements associated with osteomalacia in renal dialysis patients (142), also inhibits mineralization. Our studies suggest that mitigation of mineralization derives from the association of aluminum or iron ions with devitalized cells, the sites of initial calcification (131). Although pretreatment in sodium dodecyl sulfate (SDS) also significantly inhibits calcification of porcine aortic valve tissue implanted subcutaneously in rats, results in experimental circulatory models have been inconsistent (143–146). Nevertheless, detergents, including SDS, are the only AMTs that have been demonstrated to be effective in circulatory implants (Table 6). Likely mechanisms of action of SDS could include the removal of phospholipids (Fig. 14), charge modification, or membrane-protein denaturation. Other compounds under investigation include covalently-linked protamine (147) and locally-administered phosphocitrate, a natural calcification inhibitor (148).

Preclinical determination of the efficacy and safety of AMTs includes four components: 1) initial qualification using heterotopic implantation (e.g., subQ in rats); 2) hydrodynamic/durability testing (e.g., pulse simulator, pulse accelerator); 3) morphologic studies of unimplanted material to assess treatment-induced degradation, and 4) valve replacement in an animal model. Clearly, however, bioprosthetic heart valve durability can be assessed with certainty only by long-term (>10 years) clinical evaluation. Efficacy and safety must be demonstrated for any strategy (Table 7).

Table 7. Bioprosthetic Heart Valve Antimineralization Treatments: Criteria for Efficacy and Safety

Efficacy
Effectively inhibits calcification
Valve has adequate performance (i.e., unimpaired hydrodynamics and durability)
Determination of specific mechanisms of action
Dose-response relationship established
Effect not lost or inactivated during function
Neutralized component not reaccumulated
Does not merely delay onset of mineralization
Safety: Does Not
Cause adverse blood-surface interactions
hemolysis
platelet adhesion
coagulation protein activation
complement activation
inflammatory cell activation
binding of vital serum factors
Enhance local or systemic inflammation
foreign body reaction
immunological reactivity
hypersensitivity
Cause local or systemic toxicity
Potentiate infection

Other Developments

Since aortic valve replacement with relatively small valves may leave unacceptable gradients, attempts are being made to develop a stentless porcine aortic valve bioprosthesis (149). Such a valve would be glutaraldehyde-pretreated using conventional technology, and implanted inside the aorta, thereby using the aortic root as the valve stent. This could not only greatly improve hemodynamics by allowing use of a larger valve but might improve durability by dampening cuspal mechanical stresses. Other developments include the use of low- or zero-pressure fixation and AMTs in commercial porcine valves presently in clinical trials (150,151) and a custom-fabricated autologous pericardial valve with a novel stent construction (152).

Modest development of mechanical prostheses with new designs, particularly those using pyrolytic carbon occluders, has continued over the past decade, but it is unlikely that radical design changes will be soon forthcoming. Modification of tilting-disk configurations has concentrated on enhancing opening to improve hemodynamics, developing more durable supporting structures for the poppet, and reducing thromboembolic risk by eliminating metallic struts from regions of stasis.

Attempts are being made to develop near-anatomic-configuration central flow trileaflet prostheses using synthetic polymers. Despite previous lack of success of synthetic trileaflet valves, due to poor tear resistance and calcification of the cusps (4,132), reconsideration of the concept is now encouraged by major developments in the technology of polymeric materials, with implanted polyurethanes and

other materials. Nevertheless, long-term durability limitations remain the major concern, with valve failures marked by tearing and/or calcification (153) (Fig. 15).

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