Members and guests of The Western Thoracic Surgical Association, I would first of all like to thank Don Doty for that outstanding introduction. It is much appreciated.

The dictionary definition of value includes (1) desirable use for an important quality, (2) having intrinsic worth, and (3) worth in money or goods. The measurement of value differs depending on one’s point of view. Measured by the cardiac patient, quantity of life and quality of life are important. Measured by the cardiac surgeon, the ability to give value to patients is important, and professional and personal relationships are certainly of value. When value is measured by the health care system, cost, outcome, and availability are the yardsticks.

Viability is (1) the ability to survive, (2) the ability to take root and grow, and (3) the quality of having real meaning or pertinence. Once again, point of view affects the measurement of viability. From the patient’s perspective, viability translates into active, meaningful survival and growth potential. To the surgeon, viability means professional development and personal fulfillment. To the health care system, viability is the cost-effective use of resources.

For our purposes, valves are defined as membranous folds or structures that permit blood to flow in one direction only. Many questions surround cardiac valves. What determines value in a replacement heart valve? Is valve viability significant? Is the ideal replacement valve made by man, by nature, or by some combination of both?

The historical perspective of cardiac valve surgery is important to the understanding of current practices and future possibilities. Valve stenosis was the lesion that was addressed initially. In 1914, Tuffier performed the first valve operation when he dilated a stenotic aortic valve with his finger.1 The patient survived the procedure but the long-term success of the operation is unknown.

As cardiac surgery progressed into the 1920s, Drs Cutler2 and Souttar3 both performed closed dilation of the mitral valve to relieve mitral stenosis. In the 1940s, Lord Brock4 developed his famous closed procedure for dilating the pulmonary valve, and Henry Swan5 used topical hypothermia and inflow occlusion to perform both pulmonary and aortic valvotomies. Drs Bailey6 and Harken7 achieved the first successful, classic, closed mitral commissurotomies using primarily finger fracture and dilation of the mitral orifice.

The need to deal with insufficiency of aortic and mitral valves led to the quest for the ideal replacement heart valve. Charles Hufnagel8 in 1950 devised a ball valve that was placed in the descending thoracic aorta of dogs and was found to provide some functional relief of severe aortic regurgitation. That same year, Charles Lam9 demonstrated that a homograft valve could be placed in the descending thoracic aorta and that the valve leaflets would function only if native aortic valve regurgitation was present. In 1956, Gordon Murray10 successfully implanted an aortic homograft in a human descending thoracic aorta as treatment for aortic valve
insufficiency. In the early 1950s, Walton Lillehei, Charles Gibbon, and John Kirklin all contributed much to the development of cardiopulmonary bypass,11-13 the prerequisite to open cardiac surgery, which was clearly a landmark in our specialty.

Mechanical valves were introduced for human use by Albert Starr with the collaboration of Lowell Edwards and resulted in the first prosthetic ball-in-cage valve,14 opening the door for other surgeons including Michael DeBakey, Denton Cooley, and Viking Björk to develop their own mechanical valve prototypes.15-17 A variety of mechanical valve types have been used over the years, including ball-in-cage valves, tilting disc valves, and valves that look more or less like toilet seats. However, the Björk-Shiley valve became the most common prosthetic valve choice for a number of years.18,19 In 1977, St Jude Medical (St Paul, Minn) introduced the bileaflet valve, and that has remained the gold standard for valve replacement therapy to the present time.20

Mechanical valves, however, do not always provide a permanent solution. Many valves fail. The failure mode can be different depending on valve type. Ball variance can cause failure21 and clots on the struts of the ball-in-cage valve can lead to thromboembolic complications,22 the Achilles heel of mechanical valves. The tilting disc valve can stick because of panus ingrowth and/or thrombosis.23

The actuarial late results for mechanical valves show that the overall complication-free survival is about 50% at 18 years after implant.24 However, most of the complications involve neither patient mortality nor the necessity to replace the valve. With mechanical valves, structural durability is no longer a significant problem. Unfortunately, even after 30 years of refinements, anticoagulation of mechanical valves still is necessary. Thromboembolic complications continue to be problematic and hemorrhagic complications occur with anticoagulation.25 In addition, prosthetic valve endocarditis, although uncommon, presents a very difficult clinical problem.26

In 1969, Alain Carpentier and colleagues27 developed the prototype porcine xenograft. Simultaneously but independently, Warren Hancock’s group developed a slightly different porcine bioprosthesis.28 Although these valves do not require long-term anticoagulant therapy, they predictably fail over time because of calcification and perforation or rupture of the leaflets. Actuarially, the freedom from thromboembolism of porcine valves without anticoagulation is similar to that of mechanical valves with anticoagulation. Freedom from reoperation at 15 years after implant averages only about 50%.29 There is an inverse relationship between patient age and porcine xenograft failure, with valve failure being more rapid in younger patients.30

In 1971, Marion Ionescu developed a valve constructed of bovine pericardium preserved in glutaraldehyde.31 Its fate was similar to that of porcine valves. Heavy calcification appeared on the leaflets and they became susceptible to tears, perforation, or both. Actuarially, only 40% of the valves remained functional 10 years postoperatively.32

At present, the technology that supports glutaraldehyde-fixed valves has reached a plateau. Efforts to address calcification have been only marginally effective. With no major breakthrough in sight, the limits of durability have been reached for glutaraldehyde-preserved tissue valves.33 The tissue calcifies rapidly in young patients, but the valves can be useful in elderly recipients or in some situations in which anticoagulation is contraindicated.

In 1962, Donald Ross34 developed the use of aortic valve homografts orthotopically. Shortly thereafter, Sir Brian Barritt-Boyges,35 Wilford Bigelow,36 and Mark O’Brien37 followed Ross’s lead and began implanting aortic homografts in the subcoronary position. Historically, many methods were used to preserve homograft valves, one of which included sterilization with antibiotics and storage at 4°C; if implanted in less than 4 to 7 days, the valve was considered a homovital graft. Other valves were treated with β-propiolactone, freeze-dried and lyophilized, and preserved with acid formaldehyde, glutaraldehyde, or electron beam irradiation. More recently, valves have been cryopreserved with liquid nitrogen. For practical purposes, the antibiotic-sterilized and the cryopreserved homografts are the only valves with significant long-term utility. Comparing actuarial freedom from valve-related events for the two methods of preservation, at 18 years’ follow-up, 76% of the cryopreserved valves survived versus only 36% of antibiotic-sterilized valves remained event free. Analysis of homograft aortic valves and patient age at operation reveals that fewer valves survive longer than 10 years in patients less than 20 years of age as compared with their adult counterparts.38

A review of homograft aortic root replacement reveals a similar pattern of valve failure in children, as only 45% of the valves remain event free at 10 years of follow-up.39 Aortic homograft failure is typified by extensive calcification of the aortic wall and leaflets. In fact, it is difficult to find a photograph of a failed aortic homograft because such homografts are removed as numerous small pieces of rock-hard, calcified tissue.

In 1967, Donald Ross40 performed the first pulmonary autograft procedure, the operation that now bears his name. The operation involves excision of the native pulmonary valve for reimplantation into the left ventricular outflow tract to replace the diseased aortic valve. The pulmonary valve is then replaced with a homograft; initially an aortic homograft was used, and now pulmonary homografts are commonly used. In the United States, Ronald Elkins began to perform this operation extensively in the early 1980s and has become the national expert on the pulmonary autograft procedure.41 Actuarial valve survival in the series reported
Discussion of the pulmonary autograft procedure mandates that we turn our attention to right ventricle–pulmonary artery conduits. Several types commonly have been used: (1) the porcine valved conduit, which is a glutaraldehyde-preserved porcine valve in a Dacron conduit; (2) the aortic homograft; and (3) the pulmonary homograft, which became popular after the development of cryopreservation. For porcine conduits in the right ventricular outflow tract, actuarial freedom from reoperation is 30% to 40% at 15 to 20 years, respectively. Analysis of freedom from reoperation by lesion reveals that the anomalies that require conduit implantation at younger ages display a more rapid failure rate. Again, the mode of failure involves calcification, pseudointima formation, and leaflet perforation or fracture.43

Aortic homografts implanted in the right ventricular outflow tract have similar late results, with approximately 40% actuarial valve survival at 10 years’ follow-up. Pulmonary homografts have proven more durable, with 80% actuarial valve survival at 10 years after implant.44 Pulmonary homograft valves therefore display good durability and hemodynamic performance. However, they also stimulate an immune response, and this undoubtedly affects their durability.45 Also, homograft recipients might become sensitized to the foreign tissue, which would make future cardiac transplantation more difficult and hazardous. The degree of immunosuppression that would be required to prevent this immune response is undesirable and no less hazardous than anticoagulation.

If we look for a moment at calcification of the native bicuspid aortic valve, we see that abnormal blood flow rheology results in wear and tear of the leaflets and predisposes them to calcification, primarily on the aortic side of the valve.46 This has technical implications for the implantation of tissue valves. Tissue valve implantation techniques vary in their reliability to produce an anatomically normal blood flow pathway. The distortion leads to turbulent blood flow, and abnormal blood flow predisposes to an inflammatory process that leads to calcification in the same fashion as occurs with a native bicuspid aortic valve. There are three techniques of reconstruction for the right ventricular outflow tract. In repair of truncus arteriosus, the proximal end of the conduit is placed on the surface of the ventricle, which results in a more tortuous blood flow pathway and greater turbulence. When the conduit can be placed partially into the native right ventricular outflow tract, as in tetralogy of Fallot repair, distortion is less. The most anatomic and least distorted application is found in the Ross procedure, in which the homograft is placed precisely in its anatomic location.47

With respect to the left ventricular outflow tract, the subcoronary implantation technique, although clinically reproducible by some surgeons, does not reliably create a normal hemodynamic pathway. Slightly more reliable is the inclusion cylinder technique. Certainly, the most reliable method of preserving normal anatomy and therefore normal hemodynamic flow across the valve is aortic root replacement with coronary artery reimplantation.48

Consider, for a moment, immunology and its relationship to implanted heart valves. One can reasonably assume that immunology is not relevant to mechanical valves. Some believe that it also is not relevant to glutaraldehyde-preserved tissue valves. However, a more careful exploration of the issue shows that although glutaraldehyde fixation kills the cells, it does not remove cellular proteins, and although collagen cross-linking masks antigenic expression, it also prevents repopulation by the host. Therefore, it is possible if not likely that glutaraldehyde-preserved tissue valves do elicit an immune response over time. Donor cell viability in a tissue valve also is significant in that it might stimulate an increased immune response, and viable endothelium is known to be a strong antigen in the clinical situation.49,50

In 2000, John Hawkins and his colleagues51 in Salt Lake City conducted an interesting study in patients undergoing pediatric cardiac surgery. They compared a group of children who received cryopreserved homograft tissue with a control group who underwent cardiac surgery but did not receive homograft tissue. They measured panel reactive antibody (PRA) levels before surgery and at 1 month, 3 months, and 12 months postoperatively. They found that the control patients had low PRA levels at all times. The homograft recipients had low levels preoperatively but rapidly increasing levels postoperatively; PRA levels peaked at 3 months and leveled off at 1 year at approximately 85%.

So, what is the current status of cardiac valve replacement? Clearly, the quest for the ideal replacement valve continues. A new bileaflet mechanical valve is available from ATS Medical, Inc (Minneapolis, Minn). It is similar to the St Jude Medical valve but has a different hinge mechanism that is theoretically less thrombogenic.52 Also available are a new pericardial valve53 and stentless porcine valves.54,55 The group in Boston is developing a synthetic scaffold to use as a matrix for cellular repopulation in vitro,56 and a decellularized tissue matrix valve of xenograft or homograft origin is being developed.

The natural matrix decellularization process includes a gentle enzymatic washing during which the cellular protein components of the graft are removed while the collagen matrix remains intact. No fixation or cross-linking of the collagen matrix occurs. The tissue is then sterilized with gamma-irradiation and cryopreserved. The principles of decellularization are (1) to preserve the biomechanical and biochemical properties of the matrix, (2) to presume that an
acellular collagen matrix is a poor antigen, (3) to assume that a matrix that is not cross-linked or damaged by an immune reaction is receptive to host recellularization, and (4) to conclude that a recellularized matrix should be durable for the long term.

An acellularized xenograft construct has been developed.57,58 Because of difficulty with decellularization of porcine myocardium, three size- and symmetry-matched decellularized, porcine, noncoronary cusp units can be sutured together longitudinally. The anterior mitral leaflet remnants are used to form the inflow conduit. These valves were implanted into the right ventricular outflow tract of weanling sheep. Compared with a fresh leaflet that shows normal cellularity, a decellularized leaflet shows no nuclear staining and therefore no cellularity. Recellularization with sheep cells began before 150 days and progressed to a near normal pattern at 336 days. In summary, the acellular xenograft is a stentless symmetrical design, has excellent hydrodynamic performance, has retained biomechanical properties, and is initially durable in xenogenic recipients including sheep and human beings. Leaflet recellularization has been demonstrated to occur spontaneously in vivo.

Decellularization of homografts59 was explored because homografts are more immediately available and do not have to go through the extensive premarket approval process that is required of composite xenografts. In vitro testing demonstrates that decellularized homografts are comparable with traditional cryopreserved homografts in conduit and leaflet strength, handling and suturing characteristics, and hydrodynamic performance. In animal studies, decellularized homografts in the pulmonary position exhibit normal function as demonstrated by echocardiography. They demonstrate spontaneous cellular repopulation of both leaflet and conduit tissues, and the new cells differentiate into a mature population of host structural and contractile cells. Procollagen staining reveals that the fibroblasts are functioning and synthesizing procollagen at 3 months and continuing at 6 months after implant.

Decellularized homografts have been implanted for 2 years on a clinical trial basis. The objective of the clinical study is to evaluate the graft’s hemodynamic function and to assess host immune response by measuring PRA levels at 1 and 3 months postoperatively. A negative PRA level is defined as less than 10%. A portion of this study includes 56 patients who had had no previous replacement valve and received a decellularized homograft. Fifty-one of the patients had a negative preoperative PRA measurement, 1 had a positive measurement, and 4 were not assessed. Postoperatively, 46 of the 51 negative PRA levels remained negative, 1 turned positive, and 4 were not measured. The patient whose readings turned positive had had multiple pregnancies and might have been sensitized by blood transfusions. In summary, a decellularized homograft is a collagen matrix that is not cross-linked and is devoid of cellular proteins. HLA antigen levels are reduced, thus decreasing or eliminating the host antibody response. Because there is no inflammatory response, the matrix remains undisturbed, allowing for host cellular repopulation, and host sensitization is reduced or eliminated.

In the current era, the economics of cardiac valve replacement60 cannot be ignored. Let us first examine mechanical valves. If we assume an average 25-year survival after valve replacement, the cost of anticoagulation per patient is approximately $13,500. Clinic visits, international normalized ratio measurements, and so forth amount to about $25,000 over the same period. A complication rate of approximately 4% per patient-year equates to 1 incident per 25 years at a conservative estimated cost per complication of $7500. Thus, the total conservative estimate of cost per patient lifetime is $46,000 after mechanical valve implantation. If 30,000 mechanical aortic valves are implanted per year, the attrition rate approximates the implantation rate, and the yearly cost is similar during the 25-year life span, the cost per year then amounts to 30,000 valves times $46,000 or $1.38 billion and the cost to the health care system over 25 years becomes $34.5 billion.

Let us also assess the economic impact of cryopreserved homograft implantation. In the United States, approximately 40,000 homografts have been implanted. A 75% late survival equates to 30,000 valves. Assume that 80% will require one reoperation and 40% will require a second reoperation. Hospital payments for the reoperations average $35,000, and physician payments average $5500. In a 25-year life span there are 36,000 reoperations at approximately $40,000 per operation or a $1.5 billion cost to the health care system.

Is there an ideal valve? It is possible. Tissue-engineered valves combine technology with nature. Value to the patient equates to enhanced viability that is achieved through normal cardiac function with growth potential and decreased complications and reoperations. The implication for surgeons is a reduced case load secondary to fewer reoperations, but we can tolerate that since it means that our patients are having better outcomes. With valve implants that require recellularization, the need to restore normal anatomy is more important and more technically demanding, but these valves might produce a lifelong solution for a patient who requires valve replacement.

Value to the health care system includes good patient outcome and substantial long-term dollar savings. Availability potential increases as we progress from a homograft matrix to a xenograft matrix and ultimately to a totally synthetic matrix. Although the ideal replacement heart valve is not yet a reality, the theoretical potential exists for the first time.

Presidential Address Clarke


