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Lasker Award to Heart Valve Pioneers

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This year, the Lasker Foundation recognizes Albert Starr and Alain Carpentier for their development of effective treatments for valvular heart disease. Their innovative work is a model of interdisciplinary basic and clinical research and has benefited millions of people.

On September 28, 2007, the Albert Lasker Award for Clinical Medical Research will be conferred on Albert Starr of the Providence Heart and Vascular Institute, Providence Health System, and the Oregon Health and Science University in Portland, Oregon and Alain Carpentier of the Hôpital European Georges Pompidou in Paris, France. They are recognized for developing effective treatments for valvular heart disease, interventions that save lives and dramatically improve the quality of life of nearly half a million patients annually.

The heart is a remarkable pump, rhythmically beating ~3 billion times without fail in the course of a normal lifetime, propelling oxygen, nutrients, and blood cells throughout the body and varying its output according to metabolic need. This astoundingly efficient mechanism relies upon four chambers that contract synchronously and the actions of four valves that provide directional blood flow (Figure 1). The right atrium receives venous blood from the systemic circulation, and its contraction passes blood through the tricuspid valve, filling the right ventricle; contraction of the right ventricle then sends blood through the pulmonic valve into the pulmonary artery and then the lung capillaries, where it is oxygenated. This oxygenated blood is returned to the left atrium, which passes blood through the mitral valve to the left ventricle that then contracts, pumping blood through the aortic valve into the arterial circulation via the aorta. From here, the blood passes into successively smaller vessels, ultimately delivering oxygen and nutrients to tissues; this blood then flows into the venous circulation, ultimately returning to the right atrium. The heart must pump continuously throughout life, and failure of this mechanism for even a few seconds results in loss of consciousness; failure for a few minutes results in death.

The four heart valves all open in response to pressure from the proximal side and close in response to pressure from the distal side, thereby producing directional flow. Should one of these valves fail to open properly, the flow of blood will be impaired and will only occur under higher pressure from the proximal side. Alternatively, should a valve become leaky, blood can flow in both antegrade and retrograde directions, with resumption of the necessary antegrade flow only when larger total volumes of blood are pumped.

Diseases of the heart valves were well-described as far back as the 17th and 18th centuries. It is now recognized that a variety of antecedent conditions result in valvular heart disease. These include rheumatic fever due to an aberrant immune response to group A streptococcal infection; abnormal development of valve structures resulting in congenital malformations; calcification of valves with aging; mitral valve prolapse; and ischemic heart disease. It is estimated that 15 million people worldwide have valvular heart disease due to rheumatic fever alone (WHO, 2004). The clinical consequences and natural histories of the stenotic and regurgi-

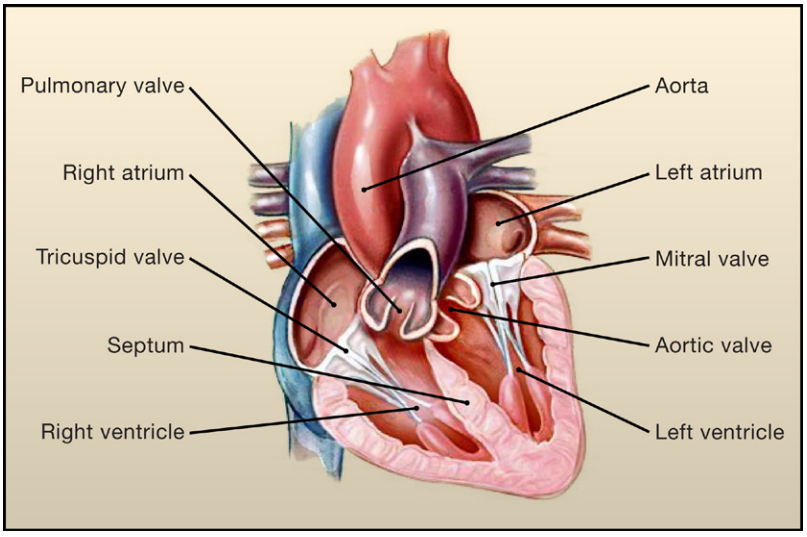

Figure 1. Anatomy of the Heart
This coronal section of the human heart shows the anatomic relationships of the four heart chambers, its valves, and the great vessels that receive the output of the right and left ventricles. Image courtesy of Edwards Lifesciences.

tant lesions of each valve (narrowing of the valve orifice and failure of valve closure, respectively) have been well described. If left untreated, valvular defects typically lead first to impaired capacity for exercise, then to overt congestive heart failure, then to death (Bonow and Braunwald, 2005). Indeed, this was the typical outcome of these disorders until the work of this year's Lasker award recipients.

Prior to the development of cardiopulmonary bypass in 1953, which for the first time permitted open heart surgery, the treatment of valvular heart disease was limited to desperate efforts to blindly open stenotic valves with a finger or a hooked knife in the beating heart; there were no effective therapies for regurgitant valves. With the advent of cardiopulmonary bypass, it was recognized that diseased valves might be surgically replaced; this initiated an aggressive search for a suitable mechanical valve.

Early efforts identified a number of daunting obstacles to success. First and foremost, the introduction of nonbiological materials into the cardiovascular system had a high propensity to induce thrombosis, resulting in obstruction of the valve orifice or the showering of emboli to distant organs, both with catastrophic consequences. In addition, the valve had to be remarkably durable, functioning without fail for the duration of the patient's life.

Into this setting, an innovative and accomplished mechanical engineer, Lowell Edwards, approached a young cardiothoracic surgeon at the University of Oregon, Albert Starr, with a proposal to develop an artificial heart. Starr, recognizing the enormous complexity of such an endeavor, persuaded Edwards to instead focus on valve replacement as a more tractable problem. Rapidly, they converged on a design for their artificial valve that was quite unlike the leafleted native valve. They designed a ball-in-cage valve in which the seated ball would be displaced to the end of its cage by pressure from the proximal side, allowing blood to flow, and then would become reseated in the closed position due to increasing pressure on the distal side, preventing retrograde flow. This very simple design (like one developed as a bottle stopper in the 19th century) had been adopted as a valve inserted into the descending aorta (Hufnagel, 1951) but largely had been abandoned. Nonetheless, the design was attractive for its simplicity and the hope that the constant movement of the unattached poppet (ball) might inhibit thrombus formation (Figure 2).

Figure 2. The Starr-Edwards Prosthetic Heart Valve

Two views of the valve are shown: one with the poppet (ball) seated in the closed position (left), and the other with the poppet displaced in the open position (right). Image courtesy of Edwards Lifesciences.

Starr and Edwards went through a number of design modifications and experimentation with different materials for the poppet, struts, and annulus. Promising surgical experimentation in dogs, along with development of regimens for pharmacological inhibition of thrombosis, led to the first artificial valve implants into humans within two years of the initial meeting between Edwards and Starr. The first patients undergoing valve replacement with the Starr-Edwards valve were carefully selected for having intractable congestive heart failure. A report of the experience of the first eight patients undergoing mitral valve replacement was published in 1961 and caused a sensation. Not only were there six long-term survivors, but recipients showed dramatic improvements in hemodynamics and equally dramatic symptomatic improvements, even returning to their normal daily activities (Starr and Edwards, 1961).

The Starr-Edwards valve quickly went into commercial production through a company founded by Edwards, and its wide implementation revolutionized the treatment of valvular heart disease. The Starr-Edwards valve is still in use, virtually unchanged since 1965, and has been implanted in over 250,000 patients (Gott et al., 2003). Edwards, who died in 1982, deservedly shares credit with Starr for his key role in the development and dissemination of prosthetic valve replacement.

The success of the Starr-Edwards valve spurred further development efforts, and there are currently five additional mechanical prosthetic valves approved for human use by the US Food and Drug Administration. Among these, the St. Jude bileaflet valve, first implanted in 1977, has become the most widely used prosthetic valve, with over 1.3 million valves implanted. Although this valve more closely mimics native valve function, randomized controlled trials have documented no significant differences in symptoms or outcomes between the Starr-Edwards valve and the St. Jude valve (Murday et al., 2003).

In addition to outstanding surgical skill, Starr also proved to be a superb clinical investigator. He pioneered the maintenance of a detailed registry of all his patients receiving valve replacement with careful monitoring of complications; the registry now lists 20,000 patients with up to 40 years of followup (Gao et al., 2004). The results have yielded a trove of clinical information documenting the early and late complications of valve replacement, permitting ongoing improvements in valve design and the treatment of recipients (Herr et al., 1965). Surgical mortality has been reduced to a few percent and more than 25% of prosthetic valve recipients survive for 25 years. The Starr-Edwards valve and other prosthetic heart valves have proved extraordinarily durable, with structural failure virtually nonexistent. Nonetheless, about half the deaths among valve recipients are due to complications of the artificial valve; chief among these

are hemorrhage arising from life-long treatment with anticoagulants, thromboembolism despite anticoagulant treatment, infection of the valve, and the development of leaks at the surgical margins.

The risk of hemorrhage and thromboembolism in patients with mechanical valve replacement led to the realization that development of biological or bioprosthetic valves free of these complications would be advantageous. Alain Carpentier, a cardiothoracic surgeon, and his colleagues in Paris recognized that xenografts of heart valves from other species represented a possible path forward. These heart valves had the obvious advantage of being well-adapted to their purpose, could be harvested under rigorously controlled conditions, and because of their natural nonthrombogenic properties might avoid the need for treating valve recipients with anticoagulants.

There were, however, several major hurdles to development. First, an abundant supply of non-human valves with size and hemodynamic properties suitable to the human heart would be required. After evaluation of a number of possibilities, the pig was identified as an attractive source: supply was abundant, and the valve size and hemodynamic properties proved well-suited to function in the human heart. This left two daunting problems: antigenicity of the xenograft and durability. Not surprisingly, the foreign antigens of a porcine valve had the capacity to incite a brisk inflammatory response, ultimately destroying the implanted valve. Moreover, because the implanted valve was biologically inactive, degradation of its collagen matrix with time drastically reduced its useful life after implantation.

Initial efforts to increase valve durability entailed treatment with mercury. These valves were the first xenografts implanted into humans, in 1965; unfortunately, they continued to elicit an inflammatory response, resulting in valve degeneration over short time periods (Binet et al., 1965). Recognizing the need for improved methods of valve preparation, Carpentier sought

Figure 3. The Carpentier Porcine Bioprosthetic Valve

The image shows a glutaraldehyde-fixed porcine valve mounted on a prosthetic stent. Image courtesy of Edwards Lifesciences.

training in chemistry to advance these studies, ultimately receiving a PhD from the University of Paris. Through experimentation with a variety of agents, he showed that cross-linking with glutaraldehyde offered virtual elimination of valve antigenicity (Carpentier et al., 1969) as well as dramatically increased valve durability. In addition, recognizing the key role of invasion of inflammatory cells at the surgical margin, Carpentier mounted the valves on a prosthetic stent, which reduced inflammatory reactions and also facilitated surgical implantation of the valve (Figure 3).

The first glutaraldehyde-treated valves were implanted into humans in 1968 and resulted in long-term survival without anticoagulation. The success of these xenografts was first reported in 1969 (Carpentier et al., 1969), and these valves were commercialized and made available for general use. Carpentier and his colleagues documented the long-term outcome of these patients (Carpentier et al., 1974). Compared with mechanical valves, these bioprosthetic valves did not require anticoagulation, eliminating the increased risk of hemorrhage and likely reducing the risk of thromboembolism. On the other hand, xenografts were not perfect: they were substantially less durable than mechanical valves, initially with an expected lifetime of about 15 years. Moreover, for uncertain reasons, xenografts in young people are prone to calcify, making them unsuitable for insertion in young patients. Carpentier has continued to refine the bioprosthetic valve to address these issues, developing a bovine pericardial bioprosthesis with greater durability (Perier et al., 1991) and developing high-temperature fixation procedures that have been shown to reduce valve calcification (Carpentier et al., 1998).

Despite all of these advances with valve replacement, Carpentier recognized the intrinsic superiority of the native valve to any replacement and observed that in many cases of degenerative mitral valve regurgitation, the primary problem was a dilated mitral valve annulus, with otherwise normal valve leaflets. Accordingly, he developed a prosthetic annulus (universally known as the Carpentier ring) and showed that its implantation can restore valve function with preservation of the native valve (Carpentier et al., 1971). This repair procedure has become the treatment of choice for most patients with degenerative mitral valve regurgitation.

Starr and Carpentier revolutionized the treatment of valvular heart disease. Their bodies of work are each extraordinary for their broad embrace of interdisciplinary research, combined with intuition, focus, and careful experimentation. Their efforts have had enormous worldwide impact, with ~450,000 patients benefiting from valve surgery each year. These interventions are life-saving and dramatically improve the quality of life of recipients. Starr and Carpentier are richly deserving recipients of this year's Lasker Award for Clinical Medical Research.

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REFERENCES

Binet, J.P., Carpentier, A., Langlois, J., Duran, C., and Colvez, P. (1965). C. R. Acad. Sci. Hebd. Seances Acad. Sci. D *261*, 5733–5734.

Bonow, R.O., and Braunwald, E. (2005). Valvular heart disease. In Braunwald's Heart disease: A textbook of cardiovascular medicine, Seventh Edition, Chapter 56, D.P. Zipes, P. Libby, R.O. Bonow, and E. Braunwald, eds. (Philadelphia: WB Saunders).

Carpentier, A., Lemaigre, G., Robert, L., Carpentier, S., and Dubost, Ch. (1969). J. Thorac. Cardiovasc. Surg. *58*, 467–483.

Carpentier, A., Deloche, A., Dauptain, J., Soyer, R., Blondeau, P., Piwnica, A., Dubost, C., and McGoon, D.C. (1971). J. Thorac. Cardiovasc. Surg. *61*, 1–13.

Carpentier, A., Deloche, A., Relland, J., Fabiani, J.N., Forman, J., Camillieri, J.P., Soyer, R., and Dubost, Ch. (1974). J. Thorac. Cardiovasc. Surg. *68*, 771–782.

Carpentier, S.M., Chen, L., Shen, M., Fornes, P., Matinet, B., Quintero, L.J., Witzel, T.H., and Carpentier, A. (1998). Ann. Thorac. Surg. *66*, S264–S266.

Gao, G., Wu, Y.X., Grunkemeir, G.L., Furary, A.P., and Starr, A. (2004). J. Heart Valve Dis. *13*, 91–96.

Gott, V.L., Alejo, D.E., and Cameron, D.E. (2003). Ann. Thorac. Surg. *76*, S2230–S2239.

Herr, R., Starr, A., McCord, C.W., and Wood, J.A. (1965). Ann. Thorac. Surg. *1*, 403–415.

Hufnagel, C.A. (1951). Bull. Georgetown Univ. Med. Center *5*, 128–130.

Murday, A.J., Hochstitzky, A., Mansfield, J., Miles, J., Taylor, B., Whitley, E., and Treasure, T. (2003). Ann. Thorac. Surg. *76*, 66–73.

Perier, P., Mihaileanu, S., Fabiani, J.N., Deloche, A., Chauvaud, S., Jindani, A., and Carpentier, A. (1991). J. Card. Surg. *6*, 589–594.

Starr, A., and Edwards, M.L. (1961). Ann. Surg. *154*, 726–740.

World Health Organization. (2004). WHO Expert Consultation, Geneva, 29 October–1 November 2001.