

unmasked, rather than lose a contract.

Brian Strom, editor of *Pharmacoepidemiology and Drug Safety*, tells a story that raises similar issues. Strom's journal received a report from i3 Drug Safety researchers of an observational safety study of rosiglitazone (Avandia), Glaxo-SmithKline's antidiabetic drug. Hired by GlaxoSmithKline to evaluate Avandia's cardiovascular risks, i3 had found those risks to be intermediate between those associated with sulfonylureas and metformin, but it hadn't compared Avandia with the only other marketed drug in its class, Takeda Pharmaceuticals' pioglitazone (Actos). When Strom asked the authors to add this comparison, they said they couldn't, because the cohort of patients using pioglitazone in their database was too small in the period they focused on (2000 to 2004). Yet Takeda scientists later used the same database, for the period 2003 through 2006, to show that the risk of myocardial infarction was higher with Avandia than with Actos.<sup>5</sup>

Greg Koski, former director of the Office for Human Research Protections in the Department of Health and Human Services and now a leader in a movement to improve clinical trials, believes that the problems with CRO research are fixable, perhaps through a requirement for certification of researchers or research sites. But it's not clear who would make such a change happen. CROs "fly under the radar," says Michelle Mello, an associate professor of health policy and law at the Harvard School of Public Health, who notes that problems with CROs are even more difficult to detect now that many of their trial sites are in Eastern Europe, Russia, India, and Asia, where costs are lower and research subjects are more plentiful but where there is also less governmental oversight of clinical-trials sites than there is in North America. Although ACRO's Peddicord asserts that the CRO's "principal roles" are protecting research participants and ensuring the integrity of research data, critics are concerned that in competing for contracts, CROs are

spending too little and working too quickly to do good clinical research. Given the steady dominance of CROs in the clinical-trials domain, the current flaws in the model will need to be remedied. This will require some shift in focus — less single-minded attention to "deliverables" and "billable hours" and greater concern with the discovery of new knowledge.

Dr. Shuchman is a national correspondent for the *Journal*.

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## The Development of Prosthetic Heart Valves — Lessons in Form and Function

Elliot L. Chaikof, M.D., Ph.D.

The 2007 Lasker Award for Clinical Medical Research, granted in mid-September to Albert Starr and Alain Carpentier, recognizes their extraordinary contributions to the development of the prosthetic heart valve, which represents a milestone in the journey toward the fabrication of synthetic living tissues and organ sys-

tems. The prosthetic heart valve was built on a foundation laid down during the first half of the 20th century with the introduction of cardiac catheterization by André Cournand and Dickinson Richards, the development of innovative surgical techniques by Alfred Blalock, the invention of the heart-lung machine by John Gibbon, and

the discovery of heparin by Jay McLean and dicumarol by Karl Paul Link. In the late 1950s, as clinical practice was being linked more closely to the surgical laboratory and collaborations were established with those working in the nascent field of biomedical engineering, new intellectual and technical frameworks were cre-

ated for replacing dysfunctional organ components with biologic or synthetic prostheses.

Although the capacity to surgically correct valvular heart disease through valvuloplasty had been established by the 1920s, the results had been discouraging. Diseased valves were frequently both incompetent and stenosed. Moreover, attempts to surgically decalcify valves either did not sufficiently relieve the stenosis or destroyed the leaflets. C. Walton Lillehei, Henry Bahnson, and others tried to surgically attach individual polymeric leaflets, but the results were consistently poor because of subsequent stiffening, calcification, and rupture. New materials were clearly required.

In 1954, Charles Hufnagel and his colleagues described 23 patients with aortic insufficiency who had been treated during the previous 2 years by rapid insertion of an acrylic ball valve into the descending aorta (see diagram).<sup>1</sup> However, since the valve prevented regurgitant flow only from the lower body, cardiac work was only partially relieved and coronary flow was not improved. In addition, embolization and thrombosis of the valve occurred frequently, and the noise generated by the valve was disconcerting — reminiscent, according to some, of a ticking time bomb. Nevertheless, Albert Starr and Dwight Harken recognized the importance of this approach and the advantage of using durable, rigid components, and they persisted in developing a caged ball valve. On September 21, 1960, Starr performed the first successful orthotopic valve replacement in the mitral position, which was followed by Harken's implantation of a pros-

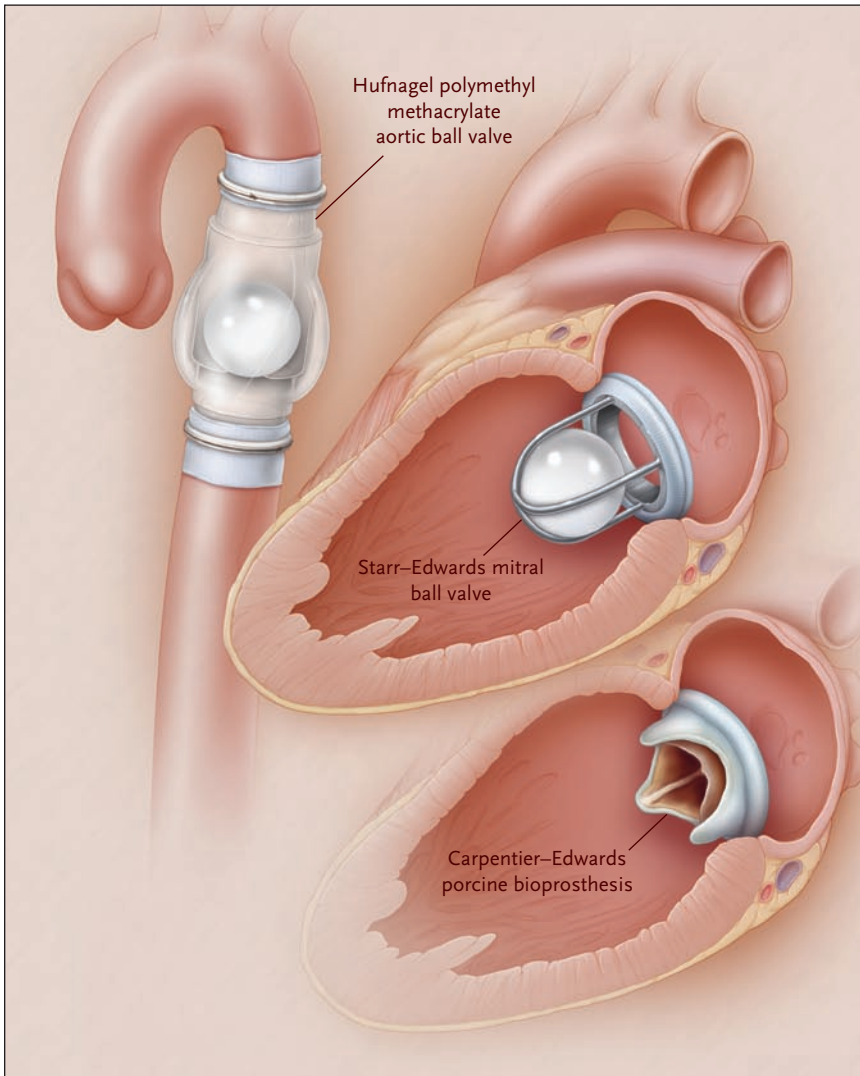
thesis in the aortic position.<sup>2,3</sup> Design criteria were formulated. The materials had to be chemically inert, compatible with human tissue, atraumatic to blood, and nonthrombogenic. They also had to retain their structural properties over many years and lend themselves to being engineered into a valve that was acceptable to patients, opened and closed rapidly in response to changes in the pressure gradient, and resulted in limited obstruction to forward flow and minimal regurgitation in the closed position. Finally, it had to be technically feasible to implant the prosthesis securely in an appropriate physiologic position.

Enthusiasm for mechanical valves was tempered by their association with persistent thromboembolic complications. The ball-valve prosthesis developed by Starr and M. Lowell Edwards, a mechanical engineer (see diagram), underwent various design changes after its introduction to reduce its thrombogenic potential. The amount of exposed metal was reduced, the material compositions changed, the surfaces coated with heparin, the design modified to facilitate retrograde flow that could "scour" the components, and the fabric altered in an effort to induce growth of endothelium. Some of these changes created new problems, including fraying of the fabric, excessive ingrowth of tissue, and obstructed blood flow. Overall, the embolization rate was reduced, but patients continued to require permanent anticoagulant therapy.

In concert, bench engineering, investigations in animals, and clinical studies emphasized the importance of hemodynam-

ics in valve design. The energy required to open the ball valve, as reflected by the pressure gradient, was substantial. An aortic valve that resulted in a large pressure drop with increased resistance to forward flow required greater left ventricular systolic pressure to drive cardiac output, with a commensurate increase in myocardial oxygen consumption. Moreover, centrally obstructive flow with large recirculation regions contributed to thrombogenic potential. Mechanical valves were refashioned in the late 1960s, when a tilting disk was introduced to minimize resistance to forward flow, decrease turbulence, limit regions of stagnation, and reduce shear stress. Although thromboembolism was not eliminated, anticoagulation requirements were reduced. In 1977, the ideal of central unimpeded flow was approached with the advent of the bileaflet valve. Despite improved hemodynamics and the application of thromboresistant alloys and advanced ceramics, the goal of substituting the use of antiplatelet agents for lifelong anticoagulant therapy remains elusive.

The hemodynamic and biologic advantages of cadaveric heart valves became evident in 1962 after Donald Ross implanted the first aortic-valve allograft in the subcoronary position, but their limited supply necessitated a search for other tissue substitutes.<sup>4</sup> In 1965, Jean-Paul Binet and colleagues presented their initial experience in five patients with mercurochrome-and-formalin-preserved heterografts: all five survived without anticoagulant therapy. Subsequent reports from Australia and Britain confirmed these satisfactory early results, but



### Three Stages in the Evolution of Prosthetic Heart Valves.

The Hufnagel aortic ball valve was designed for rapid surgical implantation in the descending thoracic aorta with the use of proximal and distal multiple-point fixation rings. A design breakthrough was achieved by Starr and Edwards, who engineered an integrated structure consisting of a stainless-steel cage, a fixation ring made from knitted Teflon cloth, and a heat-cured Silastic ball. Starr performed the first successful orthotopic valve replacement by implanting this prosthesis in the mitral position. Carpentier advanced the concept of a “bioprosthesis,” combining biologic and mechanical structures to create a tissue-based valve with low thrombogenicity. Long-term durability was attained through molecular re-engineering of the tissue by means of chemical treatment.

midterm durability was poor. In the late 1960s, Carpentier recognized that tissue stability required the prevention of both immunologic reaction and collagen denaturation. He postulated that washing a porcine aortic valve

in Hanks' solution and using an oxidizing agent would circumvent the immunologic burden by eliminating or camouflaging the valve's antigenic components. Further treatment with glutaraldehyde would prevent the dena-

turation of collagen by creating stable cross-links. Combining a valve treated in this manner with a fabric-covered metal frame would help to preserve the three-dimensional tissue relationships important to valve function and provide a sewing ring to facilitate surgical implantation. Carpentier referred to this stent-mounted valve as a bioprosthesis, a hybrid of biologic and mechanical structures, whose durability was based on the “unfailing stability of the tissue and not on regeneration by host cells” (see diagram).<sup>5</sup>

Despite the absence of a functional endothelium, clinical investigations confirmed that there was a low thromboembolic risk, which eliminated the need for anticoagulation. Central flow was achieved, but further analysis revealed substantial pressure drops attributed to the stent's restriction of leaflet opening, the stiffness of the fixed tissue, and the creation of artificial commissures. An appreciation of the interplay of hemodynamics, mechanical stress, and the biologic response in structural valve failure has guided efforts to reduce the late risks of structural deterioration, cusp rupture, and valve calcification. Alternative tissue substitutes such as bovine pericardium have been introduced; the assembly of the valve and individual leaflets has been altered to improve flow patterns; and stent materials have been modified or eliminated to reduce stress and pressure gradients. The recognition that glutaraldehyde promotes calcification has led to new fixation strategies that limit mineralization and optimally preserve molecular structure. Low throm-

bogenicity has been maintained and durability improved, but the risk of late structural failure remains.

Valve-replacement surgery has dramatically altered the natural history of valvular heart disease, affecting the lives of millions of patients. Limitations of the current technology will continue to drive the field toward new, minimally invasive and endovascular approaches for valve delivery. Valves that have the capacity for growth and self-repair, especially suited to the treatment of congenital heart disease, may be within reach through the application of tissue-engineering strategies. In addressing these needs or otherwise meeting the challenge of sustained valve perfor-

mance without thromboembolic risk, future solutions will probably combine more accurate computational tools that capture the complex environment of the prosthesis with molecularly engineered materials that have enhanced functionality and are assembled through microfabrication techniques. All of these developments will further the evolution of an advanced generation of heart-valve replacements whose form and function blur the distinction between the synthetic and the biologic.

Dr. Chaikof reports receiving consulting fees from Biolox, serving on the scientific advisory board of Intellectual Property Partners, receiving grant support from Boston Scientific, Gore and Associates, Aptus, Medtronic, and Merck, and holding eight patents on cardiovascular devices and biomaterials.

**An interview with Dr. Albert Starr, coinventor of the first successful artificial heart valve, can be heard at [www.nejm.org](http://www.nejm.org).**

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