The artificial heart valve

Albert Starr

So much in life is determined by being in the right place at the right time, and by being prepared and bold enough to seize opportunities as they present themselves.

I was prepared in large part by Columbia University—as an undergraduate at Columbia College, then as a medical student at Columbia College of Physicians and Surgeons, and finally as a resident training in both general surgery and cardiothoracic surgery. A surgical internship at Johns Hopkins with the great Alfred Blalock provided a southern flavor to my Northeast background.

For the boldness, I owed my parents and my great teachers. At Columbia College, it was Lionel Trilling; at Physicians and Surgeons, it was George H. Humphreys III, Frank Berry and the master of surgical technique J. Maxwell Chamberlain.

With this background, I arrived at the right place—the University of Oregon Medical School, with its brand new University Hospital and frontier mentality—in August 1957 to start their program in open-heart surgery with the confidence, not unusual in a surgeon, that I could do anything.

The timing was also right; cardiac surgery was just getting started. The major focus was on the treatment of congenital heart disease. Surgeries for patent ductus arteriosus, coarctation of the aorta, and tetralogy with the Blalock Taussig shunt—all performed outside the heart—were in place. The first open-heart surgery using the heart lung machine had been performed by Gibbon[1] in 1953. In Minnesota, Lillehei and Varco in Minneapolis and Kirklin in Rochester were making steady progress in the same direction[2,3]. My job was to introduce their techniques to Oregon and achieve results similar to our great Midwestern centers as soon as possible.

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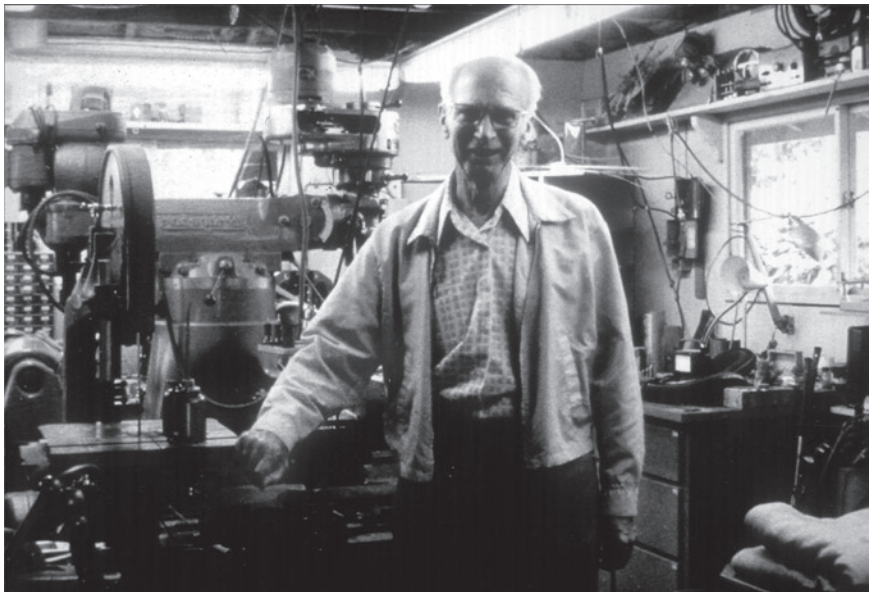

Figure 1 M. Lowell Edwards in his workshop near Mount Hood, Oregon, USA, in 1958.

In the fall of 1957 we opened an animal laboratory to perform studies on oxygen consumption during cardiopulmonary bypass, and to address surgical issues of atrial septal defect and pulmonary hypertension. When we treated our first patient in the spring of 1958, the operating room was our laboratory, and I became fully engaged in clinical work.

At that time I had a visitor, a retired engineer named M. Lowell Edwards (**Fig. 1**), who asked if I would collaborate with him in the development of an artificial heart. He was serious. I told him it was too soon, that we did not even have satisfactory artificial valves, and that simple vascular grafts were not yet fully satisfactory. The quality of valve surgery itself was still relatively crude for both closed- and open-heart techniques. But we made a deal. We would start the project by developing one valve at a time, taking the mitral first and later doing the heart. We shook hands. In the West that was it.

I watched him walk to his car through my office window. He was fragile with early Parkinson's disease and wore crumbled slacks, a sports shirt without a tie and a tan golfing jacket. I did not realize then that I was taking on an additional full-time job. Edwards would set a grueling pace. His background was in hydraulic engineering, and he designed many hydraulic debarking systems for the lumber industry. He had many patents, the most important of which was his fuel-injection system for rapidly climbing aircraft during World War II. His royalty income financed the Edwards Development Laboratory, a private engineering and research company in Portland, where his interests in fluid dynamics was now directed to the human circulation.

Animal studies and early design

Edwards and I met frequently to exchange ideas and plan our initial approach to the problem of mitral-valve replacement. This valve is attached to the heart in two separate locations—one to the mitral annulus and the other, through the chords, to the papillary muscle apparatus—and both move with ventricular contraction. Our first assumption was that lack of chordal support and a noncon-

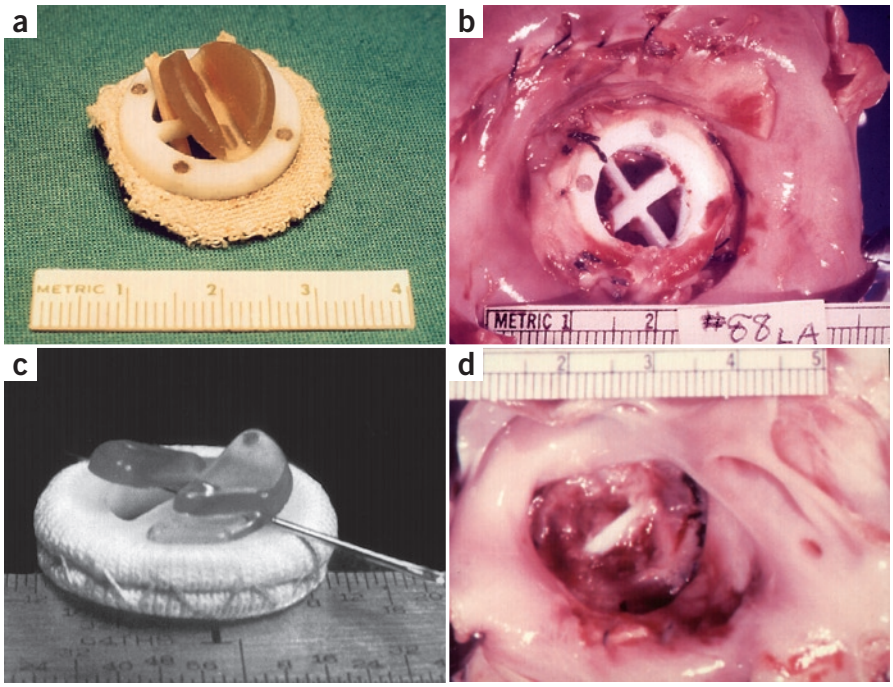

Figure 2 Bi-leaflet valve designs. (**a**) The first animal implant: a bi-leaflet valve with a Dacron single-layer sewing ring. (**b**) A left atrial view of thrombotic occlusion two days after implantation in a dog. (**c**) A modified bi-leaflet valve with enhanced sewing ring and rearranged leaflets. (**d**) Thrombosis two days after implantation of the modified valve.

tracting mitral annulus would not seriously interfere with ventricular function. We could therefore keep it simple by first removing the normal valve and attaching a valvular mechanism to the mitral annulus.

For the first implant we had to determine the size, shape and type of valvular mechanism and the materials to be used. The first valve design had a single-layer sewing ring of Dacron cloth attached between two layers of solid Teflon rings bonded together. Two Silastic leaflets were mounted on a cross bar (**Fig. 2a**).

Using this design, we performed a series of implants in dogs on cardiopulmonary bypass. We completely removed the normal mitral valve apparatus and attached the prosthesis using silk sutures. It was an immediate success, as most dogs survived the operation with good cardiac function. Unfortunately, all the animals died within two to three days from thrombotic occlusion (**Fig. 2b**). In addition, many had areas of prosthetic valve separation at the suture line due in part, I thought, to the stiffness and noncompressibility of the sewing ring.

We redesigned the sewing ring to consist of multiple layers of cloth to achieve compressibility, thereby enhancing tissue contact with the prothesis. For the next device, we mounted the leaflets such that the hinge areas were exposed to rapidly moving blood, hoping to avoid thrombus formation (**Fig. 2c**). We implanted several of these modified valves but observed the same thrombotic problem two to three days after surgery (**Fig. 2d**). However, periprosthetic leakage was greatly decreased. We analyzed the mechanism of thrombus formation at various intervals after implantation and found that the thrombus formed initially at the zone of injured tissue and directly extended onto the sewing ring without causing initial valve malfunction. However, it continued to extend onto the leaflets, preventing leaflet excursion and causing thrombotic occlusion.

These two sets of experiments, while not leading to long-term animal survival, gave us considerable insight into the scope of remaining problems and set us in the right direction with regards to sewing ring design. They also showed that mitral-valve replacement was possible with a rigid ring in the annulus and chordal attachments divided. However, we had to abandon the leaflet design and take a completely new pathway.

We considered the possibility of a ball design for the valve, hoping that thrombus formation would stop at the margin of the valve orifice and not interfere with valvular function[4]. Such devices had a history of use both industrially and medically. In the years before open-heart surgery, Hufnagel developed such a device to palliate aortic regurgitation in the form of an acrylic tube implanted quickly into the descending aorta using a nonsuture technique[5]. If a ball design could help us achieve longer follow-up than a few days, we might learn more about the long-term suitability with regards to ventricular function and late valve-related complications.

Our concept required complete reengineering of Hufnagel's device. What was the optimal ball valve diameter-to-orifice ratio, the optimal ball excursion, the cage material, the ball material, how many struts to avoid ball escape, the shape of the bearing areas, both on the orifice and the struts? It took three weeks from concept to an implantable device. The ball, initially made of acrylic, was quite noisy, but in its last iteration, coated with Silastic, was quite acoustically acceptable. Hemolysis was occasionally a problem, but thrombus formation was rare. Using the platform we had already established, we could incorporate such a design by using an open cage rather than an acrylic tube and the relatively quiet solid Silastic ball (**Fig. 3a**).

This new design had a profound effect on animal survival—we obtained full recovery from surgery. But at three to four weeks, all dogs died of thrombotic occlusion, except for one beautiful black Labrador retriever. Autopsy examination showed massive thrombus piled up on the sewing ring and finally reaching such thickness that it could fall into the orifice producing sudden obstruction. We were now at an impasse. The surviving animal fully recovered and was adopted by one of our team members (**Fig. 3b**). This dog helped keep the project alive.

Spring comes very early to Oregon, with cherry trees blooming in late February. In the spring of 1959, as I bounded up the stairs of the research building entrance at the University of Oregon Medical School, the blossoms caught my eye, my mind wandered, and I suddenly thought of the solution to the thrombotic problem[6]. Why not use a Silastic shield that could be retracted during implantation and then snapped into place to cover the entire zone of implantation (**Fig. 3c**)? Whereas the initial ball valve had an acrylic carved cage, the new design could be made of stainless steel and incorporate even further improvements in the sewing ring.

Implantation of this device started shortly thereafter and led to 80% long-term animal survival with no thrombosis. **Figure 3d** shows a clot under the shield but a perfectly functioning valve. We were at last on the right track. We could follow these animals for a few years, measuring cardiac and prosthetic valvular function and looking for late complications such as valve dehiscence and durability, hemolytic anemia, infection and other problems that could not be anticipated.

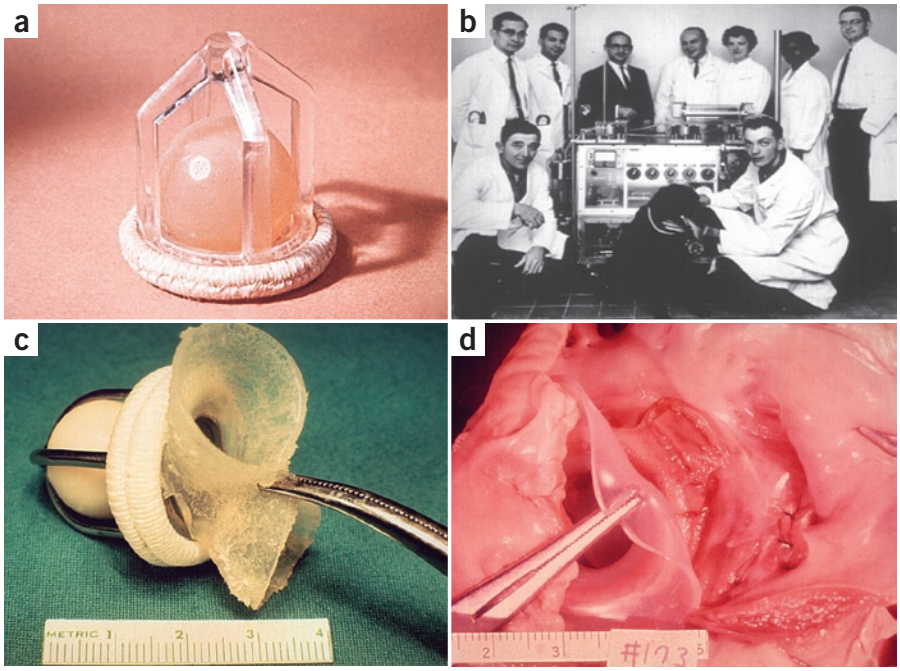

Figure 3 Ball valve designs. (**a**) First ball valve for animal implantation. (**b**) Sole surviving animal, surrounded by members of our team. (**c**) The shielded ball valve. (**d**) Autopsy specimen of a shielded ball valve showing a clot confined to the zone of implantation and covered by the Silastic shield.

From animal to human

Herbert Griswold, Professor and Chief of Cardiology, was aware of our experimental program but had not visited the laboratory until the early summer of 1960. He was amazed at what he saw: a kennel full of healthy and happy dogs that had had mitral-valve replacements. He had patients in the hospital in the terminal stages of heart failure with mitral-valve disease and urged us to change our plan to early human implantation. Our Professor of Surgery, J. Englebert Dunphy, said "Do it." Now we had to face the real world.

There was no precedent to follow, no involvement of the US Food and Drug Administration with implantable devices; legal issues of informed consent and liability had to be addressed, a company to manufacture the valve would have to be formed, technology transfer issues would have to be solved, and the first patient was already in the hospital. More importantly, we had two big clinical issues to address. First, should we use the unshielded valve that only yielded a single, precious survivor or should we use the shielded valve with an 80% survival mode and no thrombosis? Second, should we use anticoagulant treatment, how early after surgery, and with what medication? All of these issues were worked out in weeks.

We selected the unshielded acrylic Silastic ball valve for the first implant. Our logic was that, if it succeeded, we would have used the simpler device[7]. If it failed, we had the shielded valve as a backup. However, if we started with the more complex shielded valve and it was successful, how would we know if the simple device would have also been successful? What would lead us to even try the unshielded valve? Furthermore, in patients we could use careful anticoagulant treatment that was not feasible in dogs, and clotting in humans is much less aggressive than in dogs.

There also were ethical issues. As this was to be the first implantable life-support device of any kind in people, did we have additional responsibilities beyond the usual associated with open-heart surgery? From the beginning we committed ourselves to the lifetime follow-up of the patients, and to objective and scientific reporting of long-term results. The experiment would continue, but this time in humans. Patients would be selected only when there was no alternative therapy and a limited life expectancy—of weeks or months in the absence of treatment.

We also had to separate the business and professional aspects of the project. Edwards with three other investors formed a new company, Edwards Laboratories, now Edwards Lifesciences Inc., based in Anaheim, California, to manufacture artificial heart valves for human use—the first such company in the world. I remained in Oregon to continue the project as a consultant to Edwards Laboratories, but with no financial interest in the company and therefore no possible conflict of interest to question the credibility of our findings and recommendations. This is a decision I never regretted.

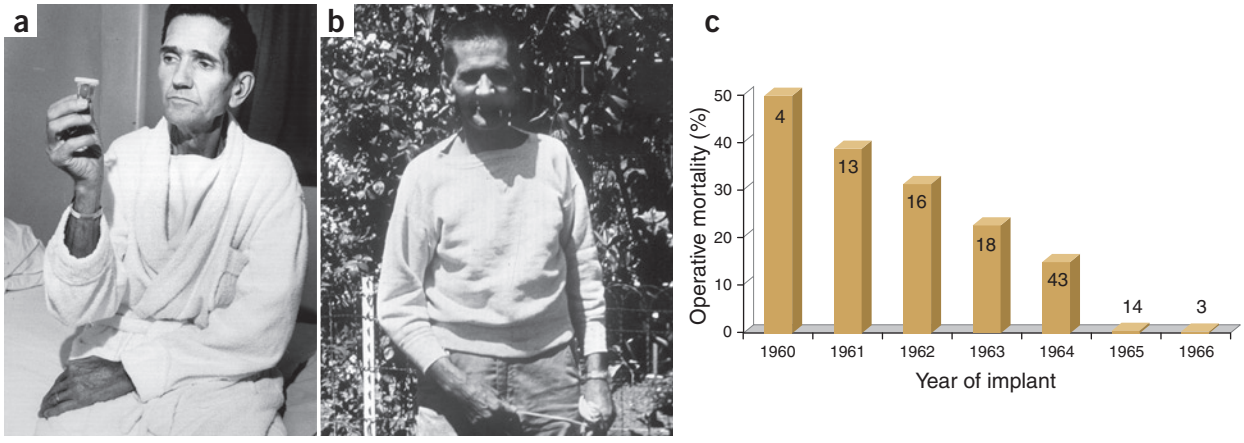

Figure 4 Success in humans. (**a**,**b**) The first surviving patient, holding a hand-made acrylic valve three weeks after the operation (**a**) and working in his garden nine years after surgery (**b**). (**c**) We experienced a rapid learning curve, reducing operative mortality to less than five percent within six years (number of isolated valve replacements are shown on the bars).

The human experience

A quick inventory of our capabilities in adult open-heart surgery at the time revealed almost no assets. We had an extracorporeal circuit that allowed cardiopulmonary bypass in adults, but little else. So we had to build the infrastructure for postoperative care, developing a multidisciplinary team of cardiologists, surgeons, hematologists, nephrologists, neurologists, radiologists and specialists in infectious diseases. We also had to develop the surgical technique: the incision, cannulation, myocardial and renal protection, and suitable suture material. Finally, we had to develop a database that would serve for lifetime follow-up of patient-related events and results.

We did all of those things, wrote many papers, gave many presentations and had many visiting surgeons from the United States and abroad. For the next few years, the surgical suite and the intensive care unit were literally a war zone. The generals, Griswold and Dunphy, had given us our orders. As in a theater of operation they supported our efforts, and as a young officer leading the battalion I would serve with equanimity.

The first patient, a young woman in her late 40s, was operated on in August 1960. She spent many months in the hospital in an oxygen tent with severe congestive heart failure due to end-stage rheumatic mitral-valve disease, and had two previous attempts at mitral-valve repair. The operation was easier than in the animal laboratory, and she was returned to a converted anesthesia wake-up area on a stretcher. She awakened from anesthesia late in the afternoon and her circulation was excellent. Howard Lewis, the Chief of Internal Medicine, visited the area. I watched him listen to the valve. He was a tall, thin, dignified man with a carefully trimmed moustache that twitched as he listened. He heard the opening snap followed by a louder, high-frequency closing sound. There were no murmurs. He thanked me—"Nice job, Al"—and left.

That evening I helped sit the patient up for a portable chest X-ray. The technician then brought in the X-ray and snapped it on the screen. There was an air fluid level in the right pleural space that we interpreted as a small hemopneumothorax. Later in the evening the patient was turned with her left side up. She died suddenly, losing consciousness immediately as if from a large stroke. We reviewed the X-ray. The air fluid was actually in the left atrium. The patient had died of air embolism. I was numb, but that night I slept. I would never let that happen again. The following month I presented our animal work at a special meeting in Chicago sponsored by the US National Institutes of Health[8]. There were no pathways more appealing than the one we were already on. I knew we were going to succeed. Griswold had the patients lined up.

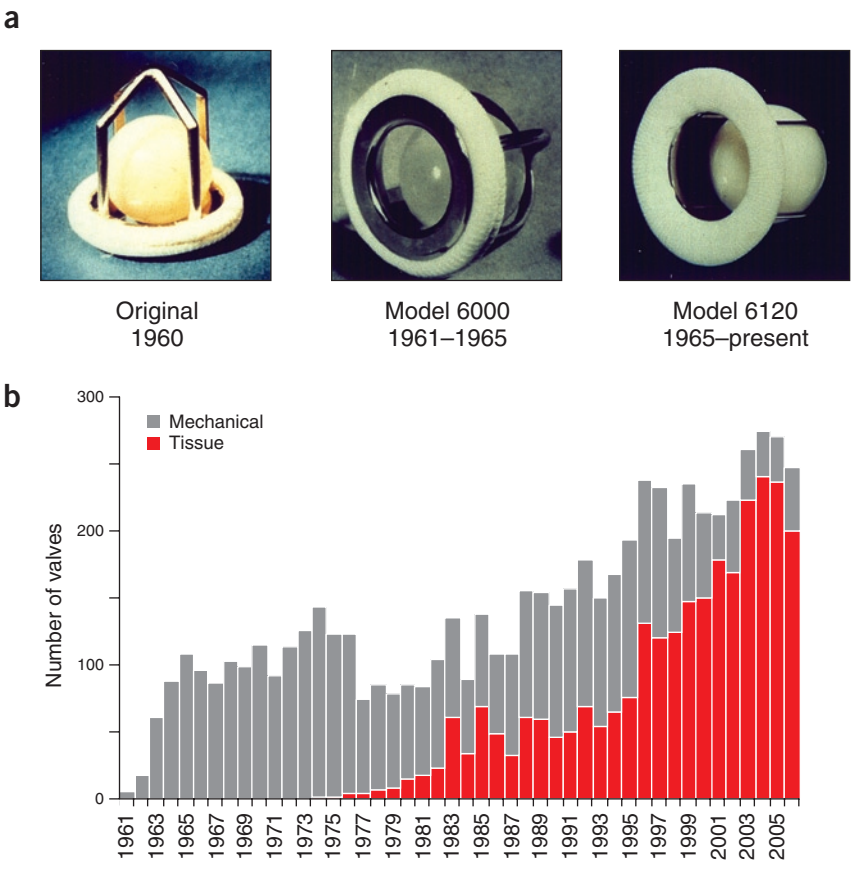

Figure 5 Later developments. (**a**) Three of the many stages in the development of the Starr-Edwards mitral Silastic ball valve. (**b**) Increase in use of tissue valves for aortic valve replacement, reaching ~80% in recent years. Data from a total of 6,648 patients treated at the Providence St. Vincent Hospital, Portland, Oregon, USA.

The second patient was a truck dispatcher from Spokane, Washington, who had two previous closed mitral commissurotomies for calcific mitral stenosis. Ralph Berg, who started open-heart surgery in Spokane and did one of this patient's commissurotomies, sent him in. He was our first survivor (**Fig. 4a**,**b**). In retrospect, we had produced a 'black swan'—an occurrence of low predictability and large impact[9].

The rest is in the medical literature; it tells a long story. The first clinical paper[10] became a classic[11] and was followed by many more publications[12–14]. Valve replacement became a frequent procedure, with a fall in operative morality from 50% to zero in the first six years with the original Model 6000 mitral valve (**Fig. 4c**), extending rapidly to the aortic and tricuspid valves. As clinical progress was made, valve design was gradually modified to improve function. By 1965, the mitral prosthesis design was complete (**Fig. 5a**).

For the first two decades, mechanical valves were primarily used, all requiring long-term anticoagulant therapy. It was for my good friend Alain Carpentier to develop an alternative tissue valve that would eventually become preponderant, with the tipping point[15] coming in the mid 1990s (**Fig. 5b**).

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I need to thank my colleagues and comrades in arms: J.A. Wood, my friend and partner who developed the fine details of operative technique necessary for successful outcome and who slept alongside our early patients in the intensive care unit; R. Herr; R. Kendall; and C. McCord. They were great cardiac surgeons who assisted on our early cases. They were the surgical core surrounded by cardiologists, nephrologists, neurologists and many other specialists who allowed heart-valve replacement to become a standard, low-risk operation with predictable outcomes. Most importantly, I must thank the patients, who trusted me.

COMPETING INTERESTS STATEMENT

The author declares competing financial interests: details accompany the full-text HTML version of the paper at http://www.nature.com/naturemedicine/.

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