The surprising rise of nonthrombogenic valvular surgery

Alain Carpentier

Surgery has always been regarded as an art rather than a science—the art of curing diseases by manipulating instruments with one's hands. In the past, progress resulted from the development of new ways of cutting, excising, resealing and suturing. Nowadays, this is no longer the case.

My own specialty—cardiac surgery—did not exist 60 years ago. Its spectacular development would not have been possible without the contribution of basic sciences and engineering. Surgeons who participated in its development had to master these sciences. A visit to a cardiac surgery operating room may give an idea of the influence of these disciplines.

In a 50-square-meter room, a patient is lying on the operating table with his chest open and his beating heart exposed to the dazzling light of three "suns of crystal", as Paul Valery named the operating lights hanging from the ceiling. Around the table, ten phantom-like people, dressed from head to feet in blue gowns, bustle about, exchanging few words. The patient's life hangs on sophisticated machinery. Multiple tubes, wires, catheters connect him to monitoring devices, automated drug-delivery pumps, a respirator and a heart-lung machine that provides adequate oxygenation and perfusion to the organs during the open heart procedure. In an adjacent room, laser systems, external defibrillators, counter pulsation pumps, ventricular-assist devices and computer-assisted instruments are ready to be used if necessary. Implantable devices such as pacemakers, defibrillators or cardiac-valve prostheses of different types are also available. So today, chemistry, physics, electronics and engineering do more for the success of a surgical operation than surgery itself.

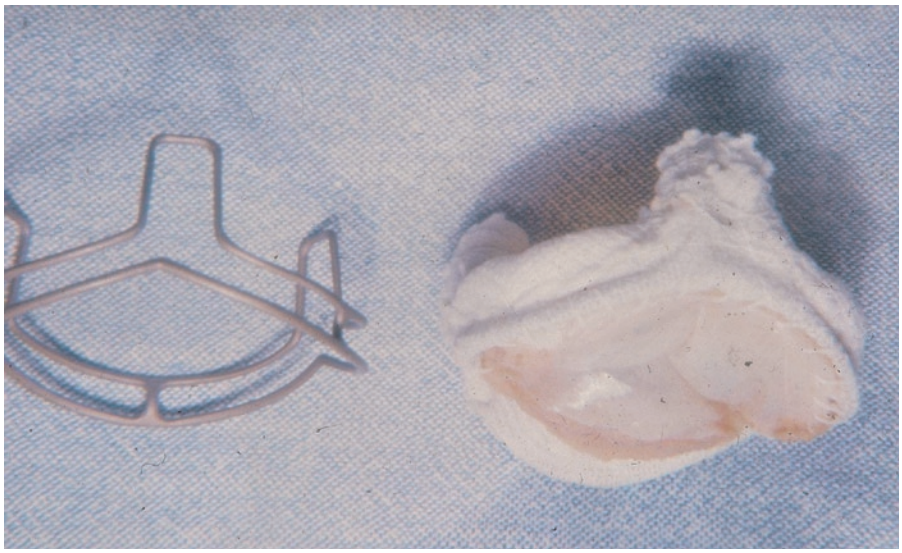

Figure 1 First (homemade) glutaraldehyde-treated pig valve implanted in human. Left, Teflon-covered stainless steel stent used to support the valve, preventing its deformation during implantation. Right, stent covered with Dacron fabric to facilitate fixation and host-tissue incorporation. The porcine valve has been sutured into the stent preserving a full motion of the leaflets, avoiding fibrous incorporation. From ref. 6.

The purpose of this brief description of my daily environment is to recognize the contribution of the sciences to surgery and to pay tribute to all the dedicated specialists, technicians and nurses who participate in this endeavor.

Progress in medicine is often triggered by emotional circumstances concerning a particular patient. John Gibbon's invention of the heart-lung machine was triggered by the observation of a young woman he took care of as a resident in surgery in the early 1930s. As she was dying from a massive pulmonary embolism despite his efforts, he thought that her life could be saved by oxygenating her blood if he had some sort of heart-lung machine. Educating himself in bioengineering, he spent ten years with the help of his wife Mary to build the first prototype, and an additional ten years before he could carry out the world's first open-heart procedure under extracorporeal circulation[1]. This seminal contribution opened a new therapeutic avenue: open-heart surgery, which saves over one million lives every year.

My own contributions followed a similar pattern. As a young resident of cardiac surgery in the early 1960s at Hôpital Broussais in Paris, I had been struck by an artist with a valvular disease. His life had been saved by the implantation of a valvular prosthesis, but three months later he presented with a cerebral embolism. A clot had formed at the site

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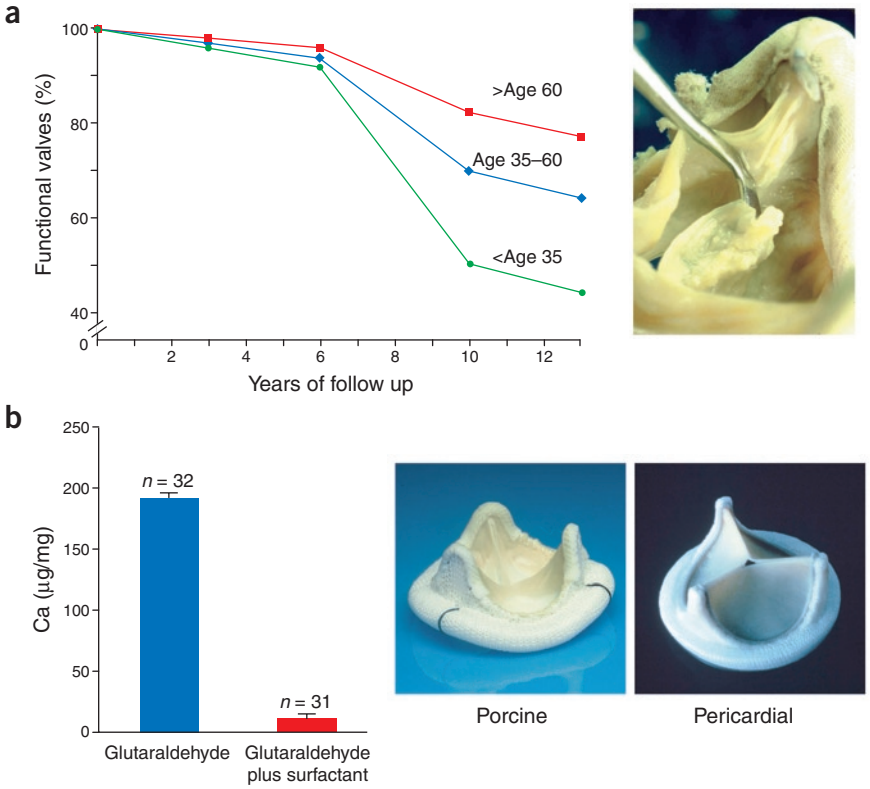

Figure 2 First- and second-generation bioprostheses. (**a**) Primary-failure curves of the first-generation bioprostheses. Failures began to occur 6–7 years after operation. Beyond seven years, the bioprostheses deteriorate further at different speed depending on the patients' age, indicated in years next to each curve. Data from ref. 8. The cause of failure was not immunological response or collagen degeneration but, unexpectedly, calcification, which lead to leaflet tear, as shown in the valve on the right, which was retrieved seven years after implantation. (**b**) Second-generation valvular bioprostheses were introduced in 1980. They were characterized by an improved glutaraldehyde process involving the addition of a surfactant to reduce calcification (left; data from ref. 9), and by improved designs using either porcine valves or bovine pericardial tissue (right). The *y* axis (left) represents the calcium content in micrograms of calcium per milligram of valve tissue in valves retrieved up to one year after subcutaneous implantation in rats. Owing to these improvements, their durability markedly increased—90% of patients over 60 years of age do not require a second surgery 20 years after the first operation.

of the valve and migrated to the brain, causing serious damage. The same valve that saved the patient had now affected the quality of his life to a point in which he could not paint anymore. At that very moment, I decided to devote my research to the challenge of valve thrombogenicity.

I can identify four periods in this research, which has spanned over 40 years from 1964 to the present time. The first period encompassed my attempts to develop valvular xenografts. In 1964, the first mechanical valve prosthesis, developed by Albert Starr and Lowell Edwards, had been in use for only four years[2]. The lives of hundreds of patients had been saved by this remarkable invention. But the risk of clot formation and the need for long-term anticoagulation to minimize that risk were severe limitations, particularly in children and for women of childbearing age.

In London, Donald Ross had shown that valves retrieved from human cadavers carried a lesser risk of clot formation[3]. As a young resident, I was asked to collect homograft valves from cadavers by my mentor, Jean Paul Binet, but I was soon confronted with a French law that did not permit tissue collection during the first 48 hours after death, to allow the family to oppose tissue harvest. As a consequence, most of the retrieved valves were infected and not suitable for use. This drawback stimulated me to revive the idea of using pig valves, which had been tried

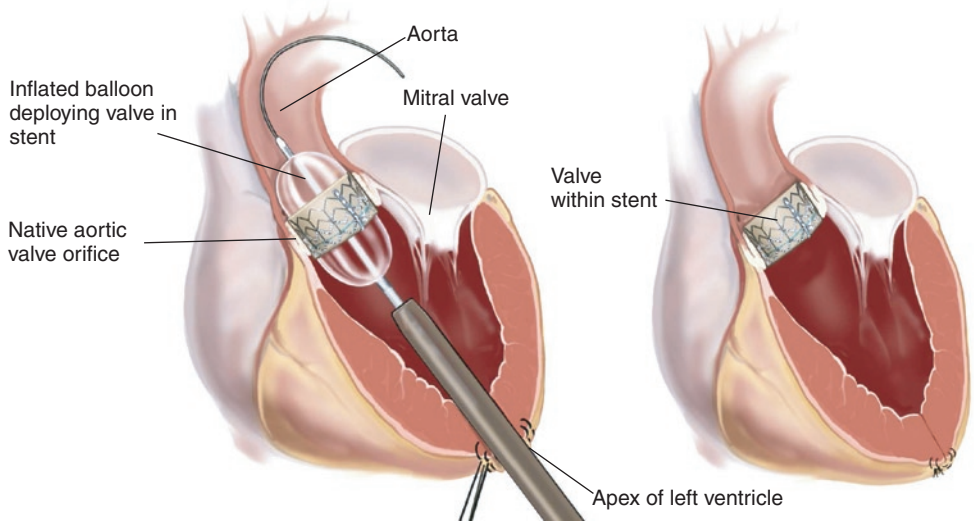

Figure 3 A bioprosthesis compressed within a stent can be introduced percutaneously or through the apex of the beating heart. Once in the proper position, the bioprosthesis is deployed by balloon dilation and automatically secured into position by hooks penetrating the native aortic valve orifice; the diseased aortic valve is laminated by the dilated stent.

experimentally in Oxford by Carlos Duran. The challenge remaining was the immunological response: porcine valves implanted in sheep were rejected in a few weeks.

The residency period is important in the education of a surgeon because it gives access to various disciplines. During my rotation in orthopedic surgery, I had the opportunity to assist Robert Judet, the inventor of the artificial hip. He used human skin to cover the cartilage of knees affected by arthritis. As the skin is highly antigenic, I was surprised to see little inflammatory reaction in these patients. I inferred that the mercury-based solution that was only intended to sterilize the skin before implantation had also the ability to minimize immunological reactions, most probably by killing cells and modifying some of the antigenic components.

This observation led me to treat the pig valves with a similar solution before their implantation in sheep. The results looked promising: not only did these valves retain their function, but they also did not trigger any clot formation, owing to their normal hemodynamic response and high biocompatibility. In 1965, because of the pressing need for nonthrombogenic valves, Jean-Paul Binet and I began to implant mercury salt–treated porcine valves in patients in whom anticoagulation was contraindicated[4].

Our excellent early results were marred by two complications in some patients after one or two years: inflammatory reactions and collagen denaturation. The long-standing hypothesis of tissue graft regeneration propounded by Nageotte and Bert[5] was not confirmed by the facts. I wrote: "The theoretical possibility of graft regeneration by host fibroblast ingrowth failed to materialize. Cellular infiltration proved to be more harmful than beneficial, as the cells invading the grafted tissue were most often inflammatory in nature. A method of tissue conditioning should be developed which would prevent inflammatory reactions and collagen denaturation"[6]. These new challenges required much more expertise in chemistry and immunology than what I had acquired during my medical education.

The second period of my research led to the development of the concept of the bioprosthesis. Although I was already an active cardiac surgeon in the service of Charles Dubost at Hôpital Broussais, I persuaded him (with some difficulty) to let me spend two days a week at the Faculty of Sciences. This complementary training and the development of my own research laboratory, which allowed me to work during the evenings and to explore all the existing chemical methods of tissue fixation, led to the discovery in 1968 of the dual effect of glutaraldehyde on pig valves: it prevented collagen denaturation by intermolecular cross linkages, and it reduced immunological responses. Its two terminal aldehyde groups and its five-carbon chain established covalent binding and cross-linkages with the collagen molecules. In addition, glutaraldehyde reduced the immunological response by cell fixation and by 'masking' the host antigenic determinants. It was interesting to note that neither the four-carbon chain nor the six-carbon chain dialdehydes worked. Most important was the fact that, similarly to that treated with mercury salts, glutaraldehyde-treated tissue retained its nonthrombogenic nature.

We mounted glutaraldehyde-treated pig valves into a stent to facilitate surgical implantation (**Fig. 1**). Clearly, the term 'graft' was no longer appropriate to define this new type of biological material. I proposed the term 'bioprosthesis', which indicates the biological origin and the prosthetic fate of these valves. The results of these research studies and the early clinical experience became public in the medical literature in 1969: "As opposed to a graft, the durability of which depends upon cell viability or tissue regeneration, the durability of a bioprosthetic tissue relies on the unfailing stability of the chemically treated biological material and the prevention of host cell ingrowth"[7].

As I did not apply for a patent, several medical industries could manufacture the bioprostheses without limitation. Edwards Laboratories were the first to do so, owing to Albert Starr, who introduced me to the

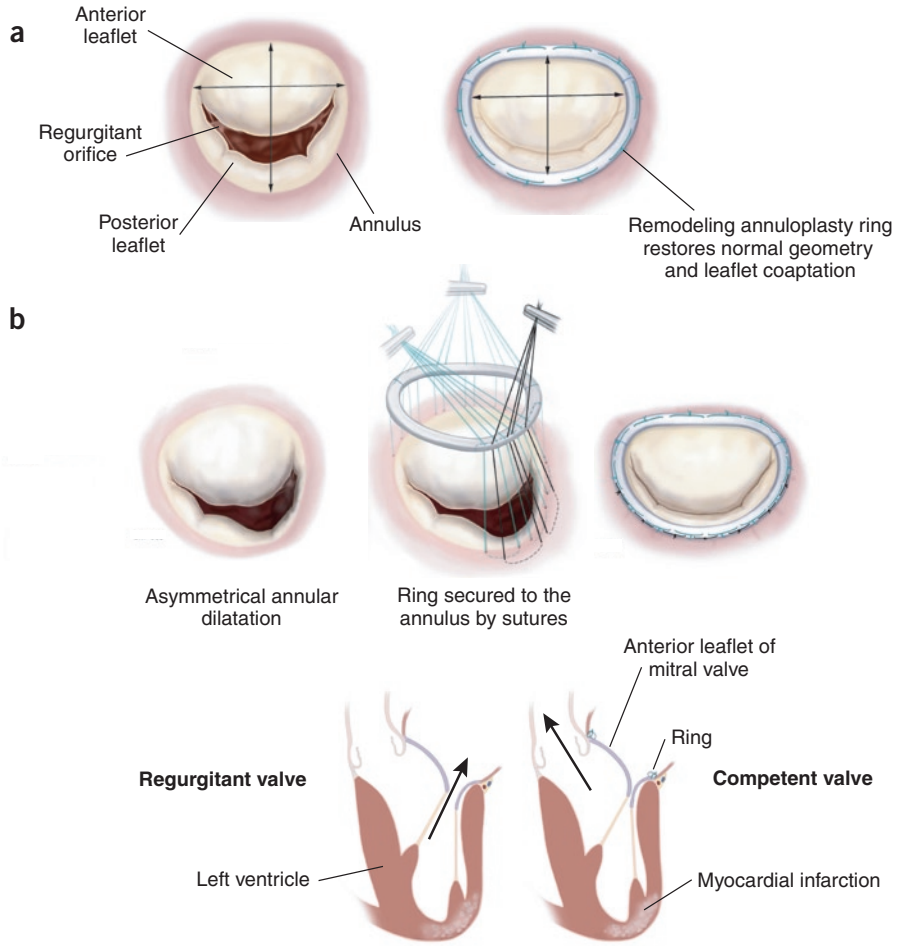

Figure 4 Valve reconstruction. (**a**) Surgeon's view of the diseased mitral valve before (left) and after (right) correction by a remodeling annuloplasty using suitably shaped and sized prosthetic rings. The regurgitant mitral valve shows a severe deformation of the annulus fibrosus, which attaches the two leaflets (left). A ring secured to the annulus remodels and stabilizes it, effectively restoring leaflet coaptation and solving the regurgitation (right). (**b**) Top, an example of ring implantation for mitral valve regurgitation due to myocardial infarction (asymmetric annulus). Bottom, hearts cut longitudinally show (left) the regurgitant mitral valve with regurgitant blood flow (arrow) and (right) the corrected mitral valve with blood flow now directed toward the aorta (arrow).

company—showing remarkable generosity, as this new valve could challenge his own prosthesis. Indeed, over the next six years, valvular bioprostheses were used more and more in clinical practice. Observations in some patients during this six-year period showed that collagen denaturation and immunological response had been almost completely eliminated. However, an unexpected complication emerged in patients younger than 60 years of age: tissue calcification, which altered long-term valve function (**Fig. 2a**)[8].

The new challenge of tissue calcification opened the third period of my research. I returned to the lab and, with the help of my wife, Sophie, tried to improve the method of glutaraldehyde fixation by adding calcium-mitigating adjuncts[9]. At the same time, I improved the valve design to minimize flow turbulence, an additional cause of calcification (**Fig. 2b**). These improvements led to a near doubling of the average durability of the bioprostheses and to extension of their indication to younger patients. Valve calcification remains a challenge, however, in very young patients and children. This last challenge occupies our current research, with promising, new glutaraldehyde-based processes[10].

Although the durability of valvular bioprostheses is limited, the number of bioprostheses implanted worldwide increases by three to five percent every year because of the superior quality of life provided by nonthrombogenic valves. In the near future, the use of bioprosthesis will allow surgeons to implant valves without extracorporeal circulation using noninvasive techniques through the apex of the heart (**Fig. 3**) or by simple catheterization through the skin[11], techniques that would not be possible with the current mechanical valves.

It is not surprising that patients choose valvular bioprosthesis for a better quality of life. What surprises me is that, after almost 30 years, glutaraldehyde remains as the unsurpassed element in animal-tissue processing.

The fourth chapter in my research—valve reconstruction—has unfolded in parallel to the first three. The Nobel Laureate André Lwoff used to say, "Disappointment in research comes from other people's discoveries." I have always thought that the best way to avoid disappointment is to challenge my own contributions. While I was developing the valvular bioprostheses, I was also trying to reduce the need to use them by developing techniques to preserve the patient's own valve.

In my early days as cardiac surgeon, I was struck by the fact that some retrieved valves, although severely regurgitant, had still a reasonably good configuration. Valve-repair techniques had been tried at the beginning of open-heart surgery, but had been abandoned because the results were unpredictable. Having the opportunity to carefully analyze these techniques during surgery, I found a common downside to them: they were only palliative. They corrected valve regurgitation by narrowing the fibrous annulus to which the leaflets were attached; that is, by producing a certain degree of valve stenosis. They did not restore the shape of the mitral valve orifice, nor a normal leaflet motion, nor a large and harmonious surface of coaptation between leaflets. This problem occupied my mind for several months.

One November evening in 1967, as I left Hôpital Broussais, I passed under the stone arch framing the iron gates and was struck by its similarity to the structure of the mitral valve. If the arch were partially destroyed, a good architect would restore its geometry using a support structure of appropriate size and shape, which would fit with the geometry of the gates. Clearly, a surgeon should do the same for the mitral valve! The concept of annular remodeling using a prosthetic ring (**Fig. 4a**) emerged from this vision. This device reshapes and stabilizes the structure that holds the valve, therefore restoring normal function. As the ring is readily covered by host tissue and the patient keeps the original valve, anticoagulation treatment is not necessary.

The introduction of remodeling annuloplasty allowed the development of complementary techniques of valve reconstruction (**Fig. 4b**)[12]. This so-called 'French correction', with a proven durability of up to 25 years, allows 50–90% of diseased valves to be reconstructed, rather than replaced with a bioprosthesis or a mechanical valve[13]. For the first time in the history of valvular diseases, patients could be cured for the rest of their lives.

ACKNOWLEDGMENTS

I would like to acknowledge my second family: the members of my research laboratory. As Diaghilev said to Nijinsky, I often tell them, "Surprise me!", and they do it. I am proud to mention among others the seminal contributions of J.C. Chachques to dynamic cardiomyoplasty, P. Menasché to cell therapy, N. Lila to the study of HLA-G histocompatibility antigen expression in transplanted patients, and E. Martinod, who first showed the surprising metaplasia of an aorta into a true neo-trachea when implanted into the tracheal environment. My final words are to express my deep gratitude to the Lasker Foundation for the honor of being distinguished with such a highly prestigious award that I share with all the members of my laboratory and my department of cardiac surgery.

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