

Harvard Medical School
The Warren Alpert Foundation Prize 2011
Bioengineering and Its Impact on Cardiac Surgery
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Mr. Chairman, Dr. Cohn, Dear Colleagues, Ladies and Gentlemen, it is a great honour indeed to receive the Harvard Engineering Award of the Warren Alpert Foundation. Je vous suis très reconnaissant. Merci beaucoup.

Let me introduce first my hospital in Paris ...and my research team of the Biosurgical Laboratory with my wife, Sophie, Dr Juan-Carlos Chachques and Dr Philippe Menasché as senior researchers. They are all proud to receive this award.

Cardiac surgery, my discipline, is only sixty-years old. It would not exist without the contribution of science and engineering. All the instruments, devices and machines we use in our daily practice have been conceived by surgeons and developed by engineers. They ensure a biological function and work in a biological environment justifying the term "bioengineering".

There are two types of bioengineering depending upon the materials used: mechanical or biological. They may be complex devices such as the heart-lung machine developed by John Gibbon with his wife Mary, and IBM-engineers ...or simpler devices such as the artificial valve first developed by surgeon Albert Starr and engineer Lowell Edwards. Whatever their structure and function, they all require blood compatibility.

What is blood compatibility? It's common knowledge that when one sustains an injury the simple compression of the wound for a few minutes will stop the bleeding. The reason for this is the formation of a clot which obstructs the bleeding vessels. In this particular circumstance a so-called white clot predominantly involving the platelets of the blood. Similarly, when a foreign material is implanted within a vessel or the heart, the contact of the material with the blood triggers a cascade of coagulation factors leading to the formation of a red clot composed predominantly of red cells fibrin and other blood elements. The systematic use of blood thinners does not completely eliminate the risk of clot formation and, at the same time, increases the risk of haemorrhage for a total incidence of complication of 2 to 6%/patient/year. This is the main difficulty we face when using prosthetic devices with blood thinner adjuncts: an excess of blood thinner leads to bleeding while an insufficient amount leads to clot formation. This dilemma is the nightmare of the surgeon after prosthetic valve implantation. Another difficulty is the fact that the clot has the tendency to migrate within the circulation, producing severe organ damage. This is what happened to one of my early patients, an Egyptian artist, in whom I had implanted a Starr-Edwards mechanical valve and who, three months later, presented with a cerebral embolism. A

clot, formed at the valve, had migrated into his brain producing a severe paralysis. The same valve, that saved his life, impaired his quality of life, so much so that he could no longer paint. Research in Medicine is often triggered by emotional circumstances. This patient made me decide to devote my research to the challenge of valve thrombogenicity.

The first difficulty at the beginning of a research is to get on the right track. In the early sixties, several surgeons, notably Ross in London had shown that aortic valves retrieved from cadavers and implanted in the aortic position - the so called homografts - functioned well and did not trigger clot formation. This was paradoxical since the main component of a valve is collagen, and collagen is known to trigger clot formation. This could be the track I was seeking to orientate my research. I began by collecting aortic valves from human cadavers but I was soon confronted to a French law which banned retrieval of human tissues during the first 48 hours after death in order to give enough time to oppose tissue harvesting. After such a delay, many valves were infected and not suitable for use. Valves retrieved from animals would get around this difficulty, but attempts by Carlos Duran in Oxford, using pig valves transplanted in animals of different species had failed due to severe immunological rejection. The solutions for this new obstacle could be, either to treat the patient with immunosuppressive drugs or to treat the valve with chemicals to reduce its antigenicity. The first solution was not attractive because of the constraints and risks associated with immunosuppressive drugs. The alternative had already been attempted, but only to sterilize the valve using glycerol, ethanol or formaldehyde and the results had been disappointing in the mid term.

During my residency rotation in orthopaedic surgery under Robert Judet, the pioneer of the artificial hip with Marius Smith-Petersen, I had been struck by the fact that the skin he used to replace cartilage in arthritis of the knee did not trigger immunological rejection although skin is known to be one of the most antigenic of tissues. I inferred that the reason for this surprising tolerance could be the fact that the skin had been treated in a mercury solution that was only intended to sterilize it before implantation. My hypothesis was validated by animal implantation of pig valves preserved in a mercury solution. Not only did these valves function well but they also retained their valuable, although mysterious, capacity of not triggering clot formation.

In 1965, because of the pressing need for non-thrombogenic valves in youngsters and childbearing women, our group began to implant mercury treated porcine valves (in other words xenograft valves) in patients in whom anticoagulation was contraindicated. Satisfactory early results were marred after a few years by two complications: immunological reaction and collagen denaturation. The long-standing hypothesis of tissue graft regeneration propounded by Nageotte had unfortunately not been confirmed by the facts. I wrote at that time: «The theoretical possibility of graft regeneration by host cell ingrowth failed to materialize. Cellular infiltration proved to be more harmful than beneficial, as the cells invading the heterologous grafted tissue were most often inflammatory in nature. A method of tissue conditioning should be developed which would prevent inflammatory reactions and collagen denaturation». This new challenge required much more expertise in chemistry and immunology than that which I

had acquired during my medical studies. Although I was already an active cardiac surgeon, I decided to spend two days a week at the Faculty of Science. This change of environment and complementary training led me to explore all the existing chemical methods of tissue fixation. The turning point was the discovery in 1968 of the dual effect of glutaraldehyde on pig valves. This chemical effectively prevented collagen denaturation by intermolecular cross linkages and minimized immunological reaction. Cross linkages were established by the 2 terminal aldehyde groups of glutaraldehyde covalently bound to the free aminogroups extending from the collagen molecules. I was a bit lucky because only glutaraldehyde, which is a 5 carbon chain dialdehyde worked, whereas neither the two-carbon chain dialdehyde (Glyoxal) nor the four-carbon chain dialdehyde (succinaldehyde), nor other dialdehydes worked as well. Most important was the fact that the glutaraldehyde-treated tissue retained its non-thrombogenic capacity. Although reinforced by cross linkages the tissue remained a delicate structure submitted to high pressures and shear stress constraints. In addition, the anatomy of the pig valve which differs from that of the human valve raised serious difficulties at surgical implantation. These problems led me to design a variety of metallic supports fitting in the human aortic root and flexible enough to reduce the stress. A fabric sewing band was added to facilitate surgical implantation. After all these artefacts, clearly the term “graft” was no longer appropriate to define this new type of valve substitute. I proposed the term “bioprosthesis”, which indicates both the biological origin and the prosthetic fate of these new valves. «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 prevention of host cell ingrowth and the unfailing stability of the chemically treated biological tissue». The first valvular bioprosthesis, home made, was successfully implanted in 1968 in a woman who could not receive blood thinner. This case was followed by 10 successful implantations. As I did not apply for a patent, several medical industries could manufacture several models of bioprosthesis without limitation. Edwards Laboratories were the first to do so, thanks to Albert Starr who introduced me to the company, thereby displaying remarkable generosity, as this new valve would eventually compete with his own mechanical prosthesis. Over the next six years, valvular bioprostheses were used with increasing frequency in clinical practice. Observation in some patients during this six-year period showed that collagen denaturation and immunological response had been almost completely eliminated. However, an unexpected complication, tissue calcification, that compromised long-term valve function, emerged after seven years, particularly in patients younger than 60 years of age.

The challenge of tissue calcification opened a new period of my research. I returned to the laboratory and found that the factors playing a role in calcification were 2 fold hemodynamical and biochemical. For help, I head hunted my wife Sophie Carpentier away from Professor Jérôme Lejeune, her former mentor in genetics (who discovered of the cause of Down’s Syndrome). We thought to improve the method of glutaraldehyde fixation by first adding calcium-mitigating adjuncts mainly surfactant and later on by heated glutaraldehyde fixation.

To minimize mechanical factors, and in particular reduce flow turbulence, I improved the valve design and introduced the pericardial valve model. These improvements led to a near doubling of the average durability of the bioprosthesis in patients over 65 years and extending its indications to younger patients. As a result, the number of bioprostheses implanted worldwide increased and rapidly exceeded that of mechanical valves because of the superior quality of life they provided due to absence of blood thinners.

At the end of a lecture, someone often raises the question of future developments. What is the future of cardiac surgery? To answer this question, I have to refer to Richard Feynman, the Nobel Prize winner for his contribution to quantum electrodynamics. One Feynman's "*idée fixe*" was miniaturization. He is regarded as the father of nanotechnology. What has Feynman to do with cardiac surgery? Why do I evoke his name? First, because he wrote one of my favourite books: "The Pleasure of Finding Things Out". Second because in this book I found the answer to my question about the future of cardiac surgery. I quote: «Although it is a very wild idea, it would be interesting in surgery if you could swallow the surgeon». A wild idea indeed! But, listen: «You put the mechanical surgeon inside the blood vessel and it goes into the heart and "looks" around. It finds out which valve is the failing one and takes a little knife and slices it out».

Dick will be glad to learn that we have followed this advice. In a first step by reducing the size of the incision, and using video and computer assisted technology, then by taking advantage of another unique characteristic of the valvular bioprosthesis, its softness and pliability, we can now compress its supporting stent so as to reduce its size to the diameter of the femoral artery. Without anesthesia, the valve is introduced into the artery up to its normal position in the heart and there, secured to the surrounding tissue by restoring its normal size by balloon dilatation ...as you will see in this short movie. It is interesting to note that this ultra mini invasive technique, recently developed by Alain Cribier of the University of Rouen, would not have been possible if the valvular bioprosthesis had not been developed 40 years ago.

M. Chairman, it is time to conclude my remarks. Allow me to express to you, once again, how much I appreciate the honour of being awarded this prestigious Warren Alpert Foundation Award. And dear Colleagues, Mesdames et Messieurs, before being completely swallowed... let me thank you for your attention!