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Presidential Address

Cardiac surgery in the 21st century: the future is now?[1]

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1. Introduction

As a general rule, a Presidential Address is an inaugural and prospective speech. But in our Association, as in many others, it is a Farewell Address in which I have chosen to speak only about the future.

On a human life scale, the history of cardiac surgery already seems far off; in 1996, Alejandro Aris [1] reminded us of the hundredth anniversary of this fascinating adventure. Modern cardiac surgery is barely more recent; how many advances were achieved in open heart surgery since the Gross atrial well technique [2] and the first cross-circulations until the development of cardiopulmonary bypass, 50 years ago. Myocardial protection, new technologies and biomaterials allowed to approach, with a wonderful intrepid boldness and an increased safety, almost all surgical cardiovascular pathologies. How much effort was needed to reduce by a few percent mortality and morbidity related to approach of a mythical organ for which the results are never half-way.

Yet cardiac surgery which could be considered as having arrived, if not to its completion, at least to its adult age, is experiencing, at the dawn of the 21st century, deep upheavals which do not call its existence in question again, but forebode a change in the way we have considered it, up to now. This specialty, to which most of us are devoting their professional life, runs the risk of its practice becoming fundamentally different from the time being. The passion for cardiac surgery cannot fail, especially because of the challenge of life over death, but surgeons are suddenly faced with techniques literally inconceivable some years ago. The advent of the year 2000 is a less critical turning point than previously passing through the second millennium, but to predict the future for the oncoming century is still a perilous exercise. However, it appeared to me that this new millennium is more a symbol than a threat, when, in addition, our specialty has been, within one century, extraordinarily full of inventiveness, feats, and genius, and I could let myself to go into desultory thoughts about our near future.

During the first decades, ‘the surgeons were really kings’ [3]; our current concern is to know whether we will simply remain surgeons.

‘To not anticipate is already to lament’, Leonardo da Vinci said. So I will try to anticipate rather than to venture predicting. To go from the more simple to the more complex, I have organized my Address according to the three following steps: (1) The future is already here; (2) Will ‘now’ be the future?; (3) Where next – and how?. I will obviously not be exhaustive, and I will abide by some topical aspects that I have chosen arbitrarily.

2. The future is already here

2.1. Ageing, epidemiology of cardiovascular diseases, and interventional cardiology

It is obvious that population demographics and epidemiology of cardiovascular diseases are in the process of making a radical change.

Life expectancy increases by a quarter of a year every year and we have gained 25 years of life within one century. Biologists and geneticians claim that the human race is programmed to live 120–150 years, and some of them have proposed an age of 400 years, which would make the oldest French woman Jeanne Calment, who died last year at 122, to be a somewhat premature death. Just to emphasize the genetic involvement for longevity among multifactorial explanations, we should remember this small threadworm whose life expectancy was increased from 45 up to 80 days just by X-ray radiation. In France, in 2010, there will be 150 000 centenarians; John R. Wilmoth, demographer at Berkeley University, foresees

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that in the States, for births after 2050, life expectancy could be 85 for males and females taken together, compared with 76 in 1995. But if we wish to prolong life, we should begin to make old age tolerable. Tomorrow cardiac surgery will face older and older patients, and octogenarians and nonagenarians will represent the common stock of our coronary and particularly of our valve patients. As a matter of fact, it would be illogical, even for economical reasons, to participate in increasing longevity without tackling unavoidable coronary and valve pathologies related to extreme ageing.

This fear should not slow down research to decrease cardiovascular mortality. Whereas there is an emerging epidemic of CHD in developing countries [4], on the contrary, in Western Europe, the established market economies can each claim a steady decline in CHD mortality rate of 1–2% per year [5]. Rises and falls in CHD can be largely explained in terms of the usual relevant risk factors, but also by different levels of genetic-environmental interaction in different populations. Consequently, primary and secondary prevention should be a priority, since aortic atherosclerotic plaques have already been identified in foetuses.

Statin trials [6] have demonstrated clinical benefit from cholesterol reduction. More attractive is dietary prevention, in terms of selection rather than deprivation, which will be developed by Serge Renaud in his *Science Lecture* [7]. Pharmaceutical laboratories have already tried to enter this market, fortunately without great success, sadly reducing the *French Paradox* to pills [8], and the *Cretan diet* to flasks [9]. Otherwise, what would remain of flavours, tastes and pleasures which certainly participate in the environmental and psychological protective effects. Consequently, in Western Europe, a significant progressive decrease will be observed.

This decline will become more marked because of the constant agressivity of interventional cardiology and the permanent advances in cath-lab technologies for coronary diseases. The residual monopoly of coronary artery surgery is likely to be broken into, not only by an intrepid boldness in ostial PTCA including left main stenosis, but particularly by at least three recent techniques which could increase the field of application of PTCA. (a) The effective prevention of coronary restenosis due to intimal hyperplasia by immediately post PTCA beta radiation or brachytherapy. (b) The reduction of in-stent restenosis by pre-interventional determination of plasma activity and D/D genotype of the angiotensin-converting enzyme significantly associated with intra-stent tissue proliferation. Avoiding stenting or intra-stent brachytherapy appears to be an efficient prevention. (c) Last, but not least, is the worst to come, with the so-called PICAB [10]. This interventional procedure aims to create, upstream and downstream coronary artery stenosis, by means of an extendable needle catheter and channelling devices, a coronary A–V fistula. Then the proximal and distal parts of the adjacent coronary vein are isolated with occlusive devices, and the coronary vein plays the role of a venous in-situ coronary artery bypass. Still currently experimental, this astonishing technique is giving evidence of the inventiveness of our colleagues.

2.2. Surgery of cardiac arrhythmia

Treatment of cardiac rhythm disturbances has almost totally escaped from surgery. Radio frequency catheter ablation techniques are currently able to cure non-invasively almost all atrial arrhythmias, AV nodal reentrant tachycardias, ectopic nodo-hisian fibres, all types of accessory pathways, and most ventricular tachycardias. New energies and catheters are continuously developed, which have a few current limitations to be solved, not due to an insufficient knowledge of mechanisms, but to a lack of appropriate catheter design.

Then the question is: what is still remaining of cardiac arrhythmia surgery, except the surgeon?

The Cox–Maze as an isolated procedure could remain a preferable alternative, but in fact the only cardiac arrhythmias likely to be surgically treated are the severe ventricular tachycardias related to postinfarction akinetic plaques or aneurysms justifying a Dor or Jatene procedure, or chronic atrial fibrillation associated to mitral valve disease, likely to be cured with a Mini–Maze or a simple left atrial procedure [11].

2.3. Stentless bioprostheses and new mechanical valves

Stentless bioprostheses are part of our present and demonstrated a better haemodynamic performance than most stented bioprostheses or mechanical valves. But will their durability be improved? Hypotheses of benefits from unstenting and antimineralization process will be verified only with time. In elderly patients, current mean durability of stented xenografts is approximately 13–15 years. In different recent reports, a standard bioprosthesis was demonstrated functioning well 19–21 years after implantation [12,13]. Consequently, any triumph is premature, and it is for the stentless side to top this challenge.

On the other hand, mechanical valves are far from throwing in the sponge. It is still quite possible to improve the bileaflet concept and design, to optimize hydrodynamics and haemodynamics, to minimize the hinge mechanism to reduce stagnation areas, to equalize the velocity profiles to decrease or suppress the downstream shear stresses, and to use new material such as glassy carbon, non-porous, nonwettable and thus more blood compatible, to coat substrates such as titanium. The main goal is to reduce the thrombogenicity to a such low level that the lowest possible anticoagulant therapy could be safely used.

2.4. Endovascular surgery

This new and promising chapter in the approach of high-risk aortic lesions is perhaps more questionable in the treatment of carotid atherosclerosis.

2.4.1. Thoracic aorta

Surgical repair of aortic arch aneurysms became a safe procedure with predictable results. On the contrary, replacement of the descending thoracic aorta remains a high risk procedure with the constant threat of paraplegia. In elderly patients with co-morbid factors, endovascular stent-grafts represent a real advance. The recent results reported by the Stanford group [14] do not underestimate the difficulties of this technique which concerns, up to now, only patients unsuitable for a conventional surgical approach; however, they demonstrated the technical feasibility and an acceptable mortality and morbidity, which compare, for non-comparable patients, with the best surgical series. No doubt this technique, if it shows good long-term results, will be, in selected patients, the treatment of choice.

2.4.2. Abdominal aorta

In standard-risk patients, the surgery of abdominal aortic aneurysms is a safe and expeditious procedure. But in high-risk patients, abdominal aortic stent-grafts are also an interesting alternative. Adequate anatomy and configuration of two or three vascular necks are of major importance. Preoperative imaging using spiral CT Angiography and 3D reconstruction [15] allow to choose an adequate stent-graft size and length before the procedure. Future devices with thermal memory materials and even differential thermal or electrical memory components will allow almost an infinity of different shapes to be constructed with one device. But it is not known yet if the endoluminal exclusion of an aneurysm will be durable and comparable to open surgical exclusion.

2.4.3. Carotid artery angioplasty

Carotid artery dilation and stenting are current alternatives to endarterectomy. But from a surgical viewpoint, the concept of introducing guides, balloons, and stents in the carotid lumen, littered with atheromatous and cruoric material, is somewhat terrifying. Nevertheless the Birmingham–Alabama group [16] reported in 1997 a hopeful experience in high-risk patients, with a 7.9% combined incidence of stroke and deaths, versus 18% in the NASCET study of high-risk patients with significant coronary disease. In fact, combined CABG and carotid endarterectomy have a mean stroke and mortality rate of about 5–6%. Thus, the relative roles of these methods must await the results of prospective randomized trials studying comparable patient subsets. However, the rapidly evolving technique of carotid stenting will benefit from the availability of low-profile embolic capture devices. Consequently, future indications for carotid endarterectomy could be limited to combined carotid and coronary surgical procedures, unless both these revascularizations would be performed by cardiologists, or as a part of hybrid revascularization.

2.5. Off-pump CABG

If one considers that in some patients, the surgical risk comes more from cardiopulmonary bypass than from median sternotomy, and that, in some developing countries, all the coronary patients could not be offered the cost of balloons, stents and ECC, then myocardial revascularization without cardiopulmonary bypass is fully justified. All the more because, 20 years ago, Benetti in Argentina [17] and Buffolo in Brazil [18] revived Kolessov's attempts [19]. Many recent reports from these authors, and also from India and Turkey demonstrated that it could be a safe and effective procedure in a special 20% subset of surgical patients. Apart from these medical and economical considerations, the competition of PTCA and coronary stenting stimulated Calafiore [20], Subramanian [21] and others in developing MIDCABG on the beating heart. In developing countries, it is obviously better to revascularize off-pump than not to revascularize at all. In the other situations, the fundamental questions to be addressed, before this technique could be widely adopted, is whether comparable accuracy and long-term anastomotic patency can be regularly achieved as with arrested heart. The only long-term comparison was recently reported by Steve Gundry and the Loma Linda group [22]: no differences in deaths or symptomatic status between techniques but twice as many recatheterizations and three times as many reoperations to achieve these results in patients undergoing the off-pump technique.

2.6. Web side story

The worldwide extension of cardiac surgery gave rise to an international community of cardio-thoracic surgeons. The emergence of the Internet literally changed the amount of time for, and the possibilities, of transfer of knowledge. The CTS net is the living application of this technology. I will not dwell more on this fascinating subject. Both the themes of Globalization [23], and International aspects of cardiac surgery [24] have been treated in a masterly manner by Bob Replogle, and Thomas Pezzella, respectively, in the *Annals of Thoracic Surgery*.

My only concern is that our major annual meetings could be replaced by virtual meetings. Less travel expenses obviously, but the necessary direct relationships would be limited or abolished. Virtual communications would reduce the transfer of knowledge to technology and science. 'Science without conscience is only ruin of soul' said, in the 16th century, a well-known Mayor of Bordeaux, Michel de Montaigne. Outside the meetings, direct and friendly contact with colleagues, living initiation to other cultures, discovery of people and cities in our old Europe (and we have yet to discover many of them) are of invaluable benefit. The Internet is a fantastic tool, but a Presidential Dinner through the Internet would be a curious experience. So virtual meetings can be useful for a 1 or 2-day symposium on a specific topic, but don't let technology infringe on humanity.

2.7. The industry-media-patient-surgeon 'dubious' square

The emergence of mini-invasive cardiac technology which we will further develop showed up a new phenomenon which is the industry pressure on media and patients, as well as on surgeon's thinking and acting. Development of new devices for approach, exposure, stabilization, visualization, cardiopulmonary bypass and introduction of robotics were partly suggested by surgeon's needs, but for most of them, imagined, proposed and provided by the industry. Under patients' and industry pressure, the surgeons are likely to become imprisoned by their competition with cardiologists and between themselves too. Industry rushed into this field with an expensive armamentarium, all the more expensive for being disposable. Fashion and media-driven pressure on patients make the surgeons no longer free to choose their procedures. It is all the more obvious that when surgeons achieve MICS without resort to specific instrumentation, they become less interesting for the industry.

But there is also a more serious threat. Surgical research runs the risk to become under influence. This burning theme was exposed in the last July issue of the *Journal of the American Medical Association* [25]. Medical and surgical research cannot be isolated from its economical context. To remain unbiased when research is suggested and supported by the industry, and to publish scientific results without overstating their true range is not that simple.

What about the early reports, which have appeared in mass public media, of new attempts which did not undergo the proof of time, and for which reported data appear incomplete or scientifically light?

Finally, I cannot find a better expression of this dilemma than the aphorism Gerald Buckberg delivered as a conclusion to a recent lecture in Bordeaux: 'Ideas define technology, but technology does not or should not define ideas.'

3. Will 'now' be the future?

3.1. Indirect myocardial revascularization: TMLR vs. angiogenic therapy

The so-called transmyocardial laser direct revascularization is a typical example of a new technology where application preceeded explanations. This accounts for the uneasy feeling of surgeons when industry strongly recommended this technique to be applied to patients with severe refractory angina, unsuitable for CABG or PTCA. The Vineberg operation could effectively support the hypothesis that myocardial revascularization could be achieved by laser-induced myocardial transmural channels. Laser was effectively demonstrated to be able to relieve intractable angina in these patients. But channels patency was not consistently proved and it seemed unlikely that TMR followed the mechanisms and reproduced the reptilian heart model of myocardial perfusion. Then it would have been more appropriate to call this technique LAR or laser angina relief. Animal experiments showed that clinical improvement could be also due to a possible myocardial denervation, more evident by epicardial than by an endocardial percutaneous partial transmural approach. But this is probably not the only mechanism involved, because it would be disappointing to change patent clinical into silent ischemia. All these disturbing controversies led to consider that human experiments were untimely. Finally, neoangiogenesis which could be a non-specific response to myocardial injury stimulating inflammation, or due to growth factors from the initial thrombus filling non patent channels, remains a satisfactory response to the claimed goal of revascularization. The recent method proposed by the Boston group [26] of combining TML to direct myocardial injection of the gene for VEGF-1, effectively appears to be the most appropriate combined approach.

However, these studies were preceeded by clinical applications of research on growth-factor-induced angiogenesis. Following the promising results of VEGF administration to patients with severe peripheral vascular disease, Sellke from Boston [27], and particularly Schumacher from Fulda [28] reported, in coronary patients unamenable to complete revascularization, the angiographic preliminary results in man of intraoperative local administration of human basic growth factor FGF1 produced by genetic engineering. The induced neoangiogenesis due to newly grown capillaries is more than obvious, and offers bright future perspectives for treatment of ischemic myocardial diseases, despite the warning of cancer researchers who, on the contrary, want to starve tumors by stopping the generation of new blood vessels [29].

Whatever the approach, thoracotomy or thoracoscopy, for either gene therapy combined with laser, or isolated administration of growth factors, the future of either one or both methods will depend on their respective efficacy, harmlessness, durability of action, ease of use, and finally their cost.

A common problem remains unsolved: what is really the functional value of this induced revascularization and its connections to the coronary network, when it is well known that native coronary collaterals do not follow the same vasoreactivity criteria as native coronary arteries, and that under exercise, vasoconstriction can surpass the desired and desirable vasodilatation?

3.2. Hypertrophic obstructive cardiomyopathy (HOCM): resection or infarction

In the Ross procedure, septal infarct resulting from injury to the first septal branch is generally responsible, at the very least, for an unfavourable outcome. But cardiologists never lacking in imagination and boldness to find an alternative to cardiac surgery induced, by selective intracoronary alcohol injection, localized septal infarction to get a non-surgical septal reduction for HOCM. Since the pioneer of this method, Ulrich Sigwart [30], does not hesitate to occlude not only the first major septal branch and even a second or third septal artery, we should certainly reconsider our old and certainly incorrect concept of the importance of these arteries. Short-term results of this so-called transcoronary infarction-ablation of septal hypertrophy showed few complications, no mortality, and significant reduction in LVOTO. Among other arguments, are the avoidance of ECC and a surgical mortality of at least 5%, from two already old reports dating from 1988 and 1989. However, cardiologists acknowledge that surgical resection is undoubtedly a successful palliation able to provide a durable improvement. But they fail to refer to more recent major surgical contributions from Turina [31] and Schulte [32]. In these series including patients operated on in the 60s, perioperative mortality currently decreased to 2.8% or even 1.7%, while actuarial survival at long-term follow-up was over 70%. Cardiologists are advocating that their technique can be applied in selected patients, but don't define their selection criteria, while surgery concerns patients of NYHA 3 or more. LVOT gradient eliminated during long-term follow-up cannot obviously be compared with the 3-month follow-up residual gradient in interventional series. Consequently, Morrow's septal myectomy remains the gold standard and should be applied earlier to preserve LV function. In the immediate future, TASH could be acceptable for lower degree HOCM patients, on the condition that there are the same low risks as in early reports, and long-term results similar to surgical results. Surgery will remain the ultimate or last hope, in the worst conditions.

3.3. Minimally invasive cardiac surgery and robotics: thoughts about a revolution

> '*Things should be made as simple as possible, but not simpler*' (Albert Einstein).

Mini-invasive cardiac surgery could have been a reasoned and reasonable evolution of conventional surgery, with the commendable aim of privileging the patient's instead of the surgeon's comfort, but without altering the safety and efficacy rules. The first step would have been minimizing the injury to access the body, by limiting skin and skeletal trauma. But it was also true that cardiopulmonary bypass, despite its current technological advancements, remains a non-physiological situation likely to induce general and visceral side-effects, particularly for patients at high-risk for aortic manipulation, cannulation and cross-clamping.

Consequently, stricto sensu, MICS should be cardiac surgery combining a small approach and no ECC. Only off-pump CABG and more recently MIDCAB meet these criteria. It is however a more demanding technique and, notwithstanding its cosmetic, psychological and medical advantages, three main concerns have been raised.

First, the technical accuracy of distal anastomosis on a beating heart despite pharmacological and/or mechanical stabilization, and not only early, but long-term patency.

Second, the issue of total revascularization, which was some years ago an intangible dogma, needs to be readdressed; could optimal not be complete revascularization unless combining MICS for LAD revascularization with PTCA for the remaining coronary arteries. Until the recent advances in cath-lab technologies to avoid post PTCA or intrastent restenosis, the obvious background was that PTCA of the circumflex or right coronary artery had a better prognosis than in the LAD. But, as was outlined by Neal Salomon [33]: '*Does a surgical approach to a 'culprit' lesion have any place in a patient with multivessel disease*?'.

Finally, the concept of learning curve needs to be clarified. It is a light argument, from experienced and skilful surgeons, to explain that early results for anastomosis could not be as accurate as the gold standard of well established conventional surgery with which it is to be compared. In optimal patients with excellent ITA and LAD arteries, in whom almost 100% optimal anastomosis and patency are expected, it is difficult to accept anything less; the learning curve should not be at the patient's expense. Moreover, nothing guarantees that this so-called new concept of a learning curve could not apply to, and be the same for each new patient. In fact, to be consistent, MICS would have to carry matters to an extreme, which is that totally thoracospic surgery will be the only truly microinvasive operation. These means are going to be supplied by robotics, which alone is able to provide the steady picture, videodepth perception, improved instrument stability, computer-direct motion, tactile feed-back, allowing precise coronary anastomosis because of virtual stillness, and even remote surgery. One more step is then the use of automatic suture stapling, one-shot vascular anastomotic devices, laser welding, or gluing of the coronary artery to the arterial conduit anastomosis. Thus, it will be demonstrated that the *Brave New World* of Aldous Huxley was not only a science-fiction story. These technologies will need a new gesture or gesticulation training, very far from the Greek etymological meaning of surgery. This new surgery will not really be directly made by man's hand, what '*Χειρουργία Αχειροποίητος*' exactly means.

MICS is then considered as a revolution, and no other new technology, not even ECC, gave rise to such media-driven enthusiasm, criticism, industry-driven meetings, editorials of the pros and cons, letters to the editor, scientific papers but also popular press articles, and advertising from industry as well as from surgeons. In fact, there is nothing new except video-assisted cardiac surgery and robotics.

Each revolution conveys advantages but also excesses.

This laxity is particularly obvious in the other fields of cardiac surgery, in which the 'terrifying' cardiopulmonary bypass remains unavoidable, and in which partial or ministernotomy demonstrated that there was no limitation to surgeons' imagination. Most of these approaches are defendable, as are the small posterolateral thoracotomy or the subxyphoid approach for congenital defects repairs. When ministernotomy allows using standard retractors and instruments, conventional cannulation and bypass, approaches to cardiac structures and myocardial protection, it is a real advance in terms of cosmetic skin incision and thoracic deformity, especially in children. However, in every case, patients' pressure for 'incisionless' operations and improved cosmetic results must be balanced against the overall safety of the procedure. One per cent death for ostium secundum ASD repair would be totally unacceptable.

But the main concern when ECC is needed is to come back to peripheral cannulations that were abandoned for evident non-physiological and iatrogenic reasons. Who could seriously defend that endovascular catheters for retrograde cardioplegia and pulmonary vent, and that the endoaortic clamp, which is nothing else than a 'chimney sweeping', are not maxiaggressive. It is not defendable that side-effects of technology such as air embolism, despite the 20-year-old technique of carbon dioxide intrapericardial infusion, are the price to pay for smaller skin incision.

It is our responsibility to define the right indications for this evolving technology, to keep cool, and to resist temptation and undue pressures. 'Cardiac surgeons have always been at the vanguard of the ethical application of new techniques to enhance patient care' [33].

We should hope that we will continue to be so.

4. Where next – and how?

4.1. Intrauterine correction of foetal cardiac lesions

Intrauterine repair of some cardiac defects detected by foetal echo, as soon as a mean gestational age of 20–24 weeks, could theoretically allow prevention or improvement of the resulting anatomic and physiological disorders.

Ultrasound guided foetal balloon valvuloplasty was recently attempted in 14 human foetuses with severe semilunar valvular obstructions, at 30 weeks' mean gestational age [34]. Technically successful procedures were achieved in only seven of them, without atretic valves. All survived the procedure, but results of this multicentric experience are very poor, with at least 77% early mortality. Always enthusiastic cardiologists expect future cath-lab technical advances and more careful selection might improve outcome. By comparison, a surgical approach in low weight neonates or infants as reported by Hanley [35], gave a 9.8% early mortality and 9% late mortality in survivors, while Griepp recently reported [36], in the same subset of patients, a 83% hospital survival.

Experimental studies of foetal circulation, carried out by Champsaur [37], Hanley [38], Sakata [39] and others, led to consider foetal surgery as a possible future, but the current major challenge of this surgery in humans remains the preterm labour, occurring 100% of the time after hysterotomy. Tocolysis has never been achieved up to now, because of ineffective tocolytic therapy.

Another concern is the resort to foetal cardiac bypass which needs miniaturized circuits and pumps, currently under evaluation. But whatever bypass is used, the resulting placental dysfunction makes a long-term total extrauterine support, using an artificial placenta, mandatory. Even if these multiple problems were solved, it is not yet proven that semilunar valvular obstruction relief could allow a decrease in LV hypertrophy or enlargement of a diminutive right ventricle, which could be a concomitant feature of these valvular defects.

At last, from an ethical viewpoint, we should endeavour to give the human foetus the same consideration and humane care as applied to experiments in compliance with '*The Principles of Laboratory Animal Care*'. So the most reasonable policy, up to now, is the neo-natal surgical approach of echocardiographically detected foetal cardiac defects.

4.2. New materials and tissue engineering

4.2.1. New materials

Much of modern technology would not exist if it were not for the invention of materials nature never thought of. The 21st century will continue to take advantage of all these breakthroughs, but the science of advanced materials is not going to stop. Ceramics, carbon nanotubes inside a metal ceramic alloy, all light and tough materials, have to be tested to assess their bio and mainly blood compatibility.

Most exciting of all, however, is the prospect that scientists will finally unlock the secrets of biological materials which can outperform anything humans have dreamed of: spider silk, abalone shells, or chitin are being analyzed to define their possible use. Having spent this century improving on nature, engineers may be spending the next hundred years letting nature improve on technology.

4.2.2. Tissue engineering for creation of autologous viable conduits and cardiac valves

Except for the Ross procedure, all currently available RV to PA conduits, or valve substitutes, present well-known drawbacks likely to limit their durability and longevity, especially in the paediatric age group. In the ongoing search for an ideal conduit or valve substitute, the only promising answer is tissue engineering, to construct tissue from their cellular components. This fantastic concept utilizes a synthetic biodegradable scaffold, first seeded with fibroblasts, and subsequently seeded with endothelial cells forming a cellular monolayer coating around the scaffold. Such living autologous tissue engineered conduits or valve leaflets have been shown functioning well in animal pulmonary circulation. The construction of three-leaflet valves only depends on the shape of the scaffold. Early results reported by some of the leading groups in cardiovascular tissue engineering, such as Vacanti and Mayer in Boston [40,41] and Turina in Zurich [42], allow us to expect that in the near future the designed and constructed autologous pulmonary conduits or valves based on this concept would be a dramatic improvement over the substitutes currently available, with respect to longevity, function, and ability to grow. Endovascular implantation in descending thoracic aorta, for non-surgical patients with aortic insufficiency, could not be considered as a utopia. But that is another, and already old story referring to Gordon Murray [43].

4.3. Genetic revolution and gene therapy: between hopes and disappointments

Genetic research is one of the great human adventures of the end of this century, and undoubtedly a wonderful hope for the near future. Adult and paediatric cardiac surgeons are obviously concerned by this revolution from a scientific and practical viewpoint.

The goal of the Human Genome Project is to find, by the year 2005, not only the location of 100 000 or so genes, but the exact sequence of their constituent chemical parts. In their race to map the human genome, scientists are finding human genes at the rate of more than one a day. From a recent genetic atlas, it is clear that the more complex the organ or tissue, the more genes are required.

The second step was to identify those mutant or missing genes implicated in various diseases, especially adult or congenital cardiac diseases.

Hypertrophic cardiomyopathy, Marfan's syndrome, and coronary artery disease risk factors such as familial hypercholesterolemia or an anomaly of the angiotensin-converting enzyme were identified as genetic disorders.

In congenital heart defects, apart from the Noonan or Holt Oram syndromes, conotruncal malformations are associated with microdeletion of chromosomal region 22 q 11, which were found in 5% of tetralogy of Fallot (TOF) patients, and in 60% of familial forms of TOF [44,45].

Up to now no gene was identified to be responsible for primary dilated cardiomyopathy.

The difficulty of screening these gene anomalies is due to the fact that, in many diseases, many genes in many chromosomes are concerned. For cystic fibrosis, 350 mutation sites have already been counted.

The first consequences of this genetic revolution are genetic counselling and prenatal diagnosis. But when the issues are genetic screening and abortion, ethical values often clash with practicality and parental rights.

The basic goal of this revolution is gene therapy; the most direct approach is to find a healthy copy of the missing genes and insert them into the patient's affected tissue or cells, and somehow get them to express themselves. A retrovirus or adenovirus used as a vector for delivering genes to the lungs of cystic fibrosis patients is potentially dangerous and should be rendered harmless. Among other disadvantages of adenoviral-mediated gene transfer are the cytotoxicity, limited duration of expression, and the inability to administer a second dose because of an immune response; but DNA can also be injected directly into cells, and other vectors can be used, such as liposomes or artificial chromosomes.

But despite more than 200 clinical trials currently underway around the world, there is still, up to now, no unambiguous proof that gene therapy has cured, or even helped, a single patient. The most commonly used genetic treatments for cystic fibrosis and muscular dystrophy have run into a dead-end. On the other hand, it is illusory, either in the short- or long-term, to imagine a gene therapy of congenital cardiac defects, since they are associated with structural genes expressing very early in the embryo, with an incompletely formed heart 30 days following fertilization. At the very least, a preimplantation could be considered, as a selection more than a therapy.

Finally, gene therapy, as experimentally demonstrated, could be used in heart and lung transplantation to modify antigens on the cell surface of donor organs, involved in the rejection process. Intracoronary infusion of recipient HLA-genes [46,47] or adenovirus-mediated gene transfer to the lungs by way of the airways [48] could reduce immunosuppression and rejection frequency, as well as to prevent transplant arteriopathy in heart, or obliterative bronchiolitis in lung transplantation.

But the best practical achievement of gene therapy is animal genetic engineering, allowing transgenic organs to be transplanted into human patients. This will be the last issue of this address.

4.4. Xenotransplantation

Because of the absolute and relative scarcity of human heart donors, the only non-mechanical, biological alternative to cardiac allotransplantation is xenotransplantation. It would be hubristic of me to try adding anything else to the superb review on Cardiac xenotransplantation by Verdi Disesa [49], in the December 1997 issue of the Annals.

Hopes are coming from genetic engineering; the production of transgenic pigs, the most adapted animal from an anatomical, physiological and possibly ethical viewpoint, expressing genes for many major complement inhibitors likely to reduce or to limit the rejection process, is offering incredible prospects.

Disappointments for near future transplants of porcine hearts into humans come from the warning of virologists that even the cleanest pigs could bear bacterial or, more dangerously, viral organisms, some of which would be difficult to identify because the viruses themselves are unknown. Other endogenous retroviruses are included in the pig genomes. Consequently immunosuppression may potentially allow a zoonotic virus to be responsible for a new human epidemic. Microbiologic screening of donor animals and sterile breeding could provide virtually germ- or virus-free pigs. Production of an original perfectly transgenic and germ-free pig, then reproduced, in my opinion, by cloning instead of natural reproduction could help the clinical introduction of cardiac xenotransplantation. But our enthusiasm should be moderated: in 1995, Jeffrey Platt from Duke University predicted he might be ready to do xenotransplants into humans in 2 years [50]. Other scientists optimistically think that xenotransplantation could start in 2002 and to be routinely used in 2010. But how close is this goal really? We should not forget that the genetically programmed life expectancy of a pig is optimally 15–17 years. Moreover, despite the fact that a pig is likely to develop atherosclerosis, the main cause of natural death in pigs is lung viral disease. Finally, we do not know exactly what will be the function in a standing being, of an organ working in a four-legged animal: this point remains a physiological uncertainty. However, I am strongly convinced that the pig is the future of man, that xenotransplantation, within 20 years, will be the future of cardiac transplantation, and that pigs will together justify Auguste Preault's aphorism ('*Every man has in his heart a sleeping pig*'), and replace the dog as man's best friend.

5. Conclusion: the Art of the Fugue

I wish to close this general view with an allegory. I have had, from the very beginning, a great devotion to Johann Sebastian Bach, whose works have been said to represent by themselves a Europe of musics [51]. Thus, I have chosen the last masterpiece the great master wrote down as a striking symbol of our past, present, and future. The Art of Fugue, this hitherto unsurpassed, unique product of harmonic ingenuity, containing every kind of counterpoint and canon in one and the same theme, assumes an outstanding musical, mathematical, metaphysical in Goethe's opinion ('*Conversations of God with Himself, just before the Creation*'), and even, as Yehudi Menuhin said, '*cosmic*' dimension.

This musical last will and testament of Bach was planned to include 24 fugues. He had finished three-fourths of the twenty-first three-part fugue when a severe eye disease prevented him from quite completing the work, and obliged him to undergo two disastrous cataract operations which hastened his death. A deep-rooted but probably wrong tradition has it that when Bach felt death close upon him, he sent for his son-in-law, the musician Altnikol to dictate to him the conclusion of this fugue. But the 21st fugue breaks off in the middle of a bar, just at the point where the third of the three themes, which, for the first time in one of his works, spells out Bach's name in the musical notes B flat, A, C, H (or B natural) is combined with the other two. So this fugue was left unfinished when Bach breathed his last.

The beginning of cardiac surgery can be considered as the initial theme of a work of art and genius which was developed, until now, with more and more complex variations, as are the fugues. Then we are at the middle of the unfinished bar.

But Bach also conceived to conclude his great work with a second three-part fugue and two other still more grandiose quadruple fugues, all four parts of which were to be inverted, and thus, as the most eminent masterpiece, to form the keystone of '*Die Kunst der Fuge*'.

Nothing could better symbolize that many variations in cardiac surgery remain to be developed, undoubtedly more complex and sophisticated, and that the future of cardiac surgery has never looked brighter.

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