Research and surgery

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ABSTRACT

RESEARCH AND SURGERY

The science and practice of medicine and surgery have experienced an unprecedented development since World War II: antibiotics, blood banks, cardiac surgery, artificial organs, organ and tissue transplants, total joint replacement, total parenteral nutrition, or minimally invasive surgery. Paradoxically, during the last two decades of the past century, public recognition of physicians has decreased, while a series of distortions have occurred: increased healthcare costs, questioning of academic medical centers, litigation for medical errors, or an increased popularity of alternative medicines. The growing complexity of biomedical research in the constantly changing era of molecular biology has led to an skeptical attitude about whether clinicians, and particularly surgeons, may continue to contribute to medical advances. The study of the history of contemporaneous medicine shows that several of the most significant achievements are due to surgeons. There is no doubt that science and clinical practice will be able to adapt themselves to these times of change and will continue to generate important findings. Medical and surgical practice of today is determined by the scientific research of yesterday; tomorrow will not be different.

Keywords: Medical management. Academic medicine. Medical technology. Technological transfer.

"***I would suggest that the whole imposing edifice of modern medicine, for all its breath-taking success, is, like celebrated tower of Pisa, slightly off balance***".
Charles, Prince of Wales.

At a time like this, when healthcare professionals have been refused to take important decisions affecting medical care and when intellectual mediocrity conspires, consciously and unconsciously, to reduce physicians to mere providers of accountable care units –products-, it is becoming increasingly difficult to maintain healthcare, teaching, and research quality. This represents exposing patients to an unforgivable risk[1].

CHANGE IN PERCEPTION OF MEDICAL PRACTICE

Lewis Thomas[2] suggested that it was not until the decade from 1910 to 1920 that patients started to derive benefits from their meetings with doctors. Treatments only started to be effective following discovery of sulphonamides first, and antibiotics some years later. This lifted medicine to the leading positions in public recognition but, paradoxically, has not remained there. The trust in medical profession has decreased as the capacity to cure increased.

A simple way to document this increase in the power of medicine is the change occurred in the mortality rates of US soldiers injured in combat in the last wars where the US have been involved[3]. From World War I to the Vietnam war, mortality from head trauma decreased from 13.9% to 3%; in chest injuries, mortality decreased from 24% to 7%, and in colonic injuries from 66.8% to 6.5%. Before the Great War, a colonic injury was unavoidably fatal. Changes occurred in life expectancy are probably the best way to illustrate this phenomenon. When my parents were born, in the first decade of past century, life expectancy of citizens in developed countries was approximately 50 years, while my grandsons are expected to live 80 years. This represents a 30-year increase in four generations. Neanderthal men barely lived 25 years; 125,000 years were required for life expectancy to be increased in 25 years, and another 30 years have been added in only a century. How has this been possible? Of course, and first of all, because of hygiene and health measures, but also, as stated by Lewis Thomas, "because of the brilliant advance in our understanding of the basic mechanisms of diseases and to the surprising adaptation of technology to medicine"[4].

However, saturated by the spectacular achievements of medical science, the public started to receive terrifying news about medical errors, that started to be a favorite objective of communication media. The catalyst probably was the coverage by the New York press of the case of Libby Zion, a young patient whose death at the emergency room of a New York hospital in 1984 was inappropriately attributed by the media to the lack of sleep of a resident[5]. In 1999, the Institute of Medicine studied the prevalence of medical errors and estimated that they caused 98,000 deaths per year in the US[6]. Even if the most favorable figures are managed, the death rate from medical errors at US hospitals is higher than the rates from traffic accidents, breast cancer, or AIDS. The most common problems arising during clinical care occur at operating rooms, intensive care units, and emergency rooms. Errors do not only have significant financial costs, but are also burdensome in terms of loss of confidence in medicine by the general public and loss of satisfaction of patients and healthcare professionals. How many medical errors are made at our hospitals? Investigating why errors occur is medical scientific research, and more than that. When mishaps occur because of medication errors, for instance in an intensive care unit, those responsible for designing the curriculum of pre- and post-graduates and continued education programs should investigate the root of the error[7].

"We are indeed in the midst of a revolution, and we all know that those running our healthcare programs are not even remotely interested in medical teaching or research. At some time in the mid 80s, the business world realized that what we call today "healthcare" was a billionaire industry that was badly managed and ready to be conquered. Business made a move: capitalization of the impressive investment made in the past by society in education and research, and rapid reconversion of hospitals with a CEO –chief executive officer- at the front"[8]. The situation in Europe is quite different, as the leading role is not played but the business world, but rather by the world of policy, that shares the underlying philosophy. Organizational charts of university hospitals are headed by a manager –the person responsible for administrative management of a company or institution- appointed by politicians to manage –to take actions intended to achieve something- waiting lists (the single and omnipresent indicator of healthcare policies- and "days' shifts" (a word clearly expressing the situation reached). Thus, the question is whether Academy –healthcare, teaching, and research quality- has a place today in the so-called academic or university healthcare centers[9], because academic medicine is defined as the ability of the healthcare system and clinical care to think, study, research, discover, evaluate, innovate, teach, learn, and improve.
However, all politicians and the different professionals in the health system should also bear in mind that health, medical, or clinical care of tomorrow of tomorrow will depend on today's training and research. In this regard, mention should be made of the words by the French politician Pierre Mendès-France: "The Republic need scientists; their discoveries, the prestige they imply and their

applications are all part of the greatness of the country". Similar convictions have been voiced by other statesmen[10]; by contrast, the members of our parliament barely say anything about this subject. Would our politicians entrust the responsibility of commanding the flagship of our fleet to a "manager"[11]. One thing is intelligent use of resources, and another thing is empty economicism.

However, the lack of concern of our civil society for science also plays a role[12].
Academic or university medical centers –at least according to the inscriptions in the façades of our hospitals- are responsible for providing an exemplary healthcare to patients, teach medicine to students, train future professionals, and provide new knowledge through research. However, centers have instead become dispensaries and solvers of problems that are more social than medical. The system should be reinvented, because neither reforms nor reorganizations are sufficient. When complex problems are found, there is a trend to adopt simple solutions. Henry Mencken[13] said that "a simple and erroneous solution exists for each complex problem". There is no simple solution; there are so many factors involved, that a future to come cannot be predicted from disenchantment.

Richard Anderson[14] characterized recent historical medical developments by decades: the 60s was the decade of clinical innovation; the 70s, the decade of clinical expansion; and the 80s, the decade of financial restrictions. For the 90s, Alexander Walt[15] coined the term «**dis**-decade». This term summarizes a motion for the rejection of a bill: «Medical education: a continuum in **dis** array + **dis** affected public (lack of humanism) + **dis** spirited residents (service versus education) + **dis** functional government (declining financial resources) + **dis** organized specialty movement (fragmentation) + **dis** couraged faculty (relative value of surgical education) = decade of **dis** enchantment».

LABORATORY, CLINICAL PRACTICE, AND COLLABORATION

Before World War II, biomedical research in general, and surgical research in particular, were financed by institutional and private funds. There were virtually no grants from the government in the US, not to say in the rest of the developed world. In 1949, Vannevar Bush, Director of the Office of Scientific Research and Development, achieved substantial involvement in scientific funding of the government through the NIH (National Institutes of Health, Bethesda, USA). The Bush doctrine, defined in 1945 and greatly conditioning the future of the NIH, was to prioritize basic over clinical research: "Progress in the treatment of diseases will result from essential discoveries in subjects unrelated to disease"[16]. Enthusiasm for basic research was strengthened by publication of the DNA structure by James Watson and Francis Crick[17] in 1953, that marked the beginning of the era of molecular biology.

James Shannon[18], a follower of the Bush doctrine who directed the NIH during the 50s and 60s, persuaded the political leaders that the best strategy for curing diseases was to elucidate the underlying molecular bases of pathophysiology. Shannon argued that, like researchers of the premolecular era, molecular biologists, after elucidating the basic mechanisms of disease at their laboratories, would return to the bedside of patients with their discoveries and would translate them into new, effective treatments. Clinical research in general, and surgical research in particular, were very far from the scientific interest of the NIH, that opted for basic research in accordance with the Bush-Shannon doctrine. Research by surgeons was aimed at solving specific problems found during patient care, and despite the fact that they worked at a supramolecular level, with no federal help in most cases, they made very significant contributions to the solution of complex healthcare problems.

In his 1999 presidential speech to the American College of Surgeons (ACS), James Thompson[8] spoke of the most important surgical contributions in the last fifty years of the molecular era: cardiac surgery, vascular surgery, effect of hormones on cancer, metabolic response to trauma, burns, and sepsis, chemotherapy clinical trials and conservative surgery in breast cancer, total parenteral nutrition, artificial organs, and organ transplantation; total joint replacement, fetal surgery, or stereotactic neurosurgery may be added to this list. On his part, John Bell, Regius Professor of Medicine at Oxford and molecular biologist, talking about discoveries in molecular genetics with a greater potential of clinical application during those same years, recognized that molecular biology had not had the expected impact on clinical practice to date. Genetics and molecular medicine will not be, of course, the response to all questions about human health, and even less a key for optimizing clinical practice. Reductionism associated to molecular genetics will identify the parts of those problems, but their joint consideration to understand malfunction of those complex systems requires a much more integrated strategy than the one predominating today[19]. Thus, while basic science in the first fifty years of the biomolecular era is fascinating and has a tremendous future, it should come to no surprise that very few patients have benefited from it.

The paradox of the poor clinical impact of molecular research may be explained by the weak point in the Bush doctrine: governmental support to research focused on basic science only. In 1979, James Wyngaarden, director of the NIH, detected in physicians interested in scientific research a lack of concern for clinical problems; he said that physicians interested in clinical research were a species in danger of extinction[20]: “The reasons why interest of young physicians has decreased are complex. An important reason is re-evaluation of objectives of society after the Vietnam conflict. A reconsideration of interests that has led to place more emphasis in medical care for unprotected segments of our society rather than in basic biomedical research, in order to improve health and conquer disease […] A second major factor is the instability of governmental support to biomedical research […] A third factor is revision of the curriculum [… whose] result is that many professionals reach the end of the residency period without any firsthand knowledge of laboratory work… Another significant influence [… is that] a significant percentage of young physicians who in the past would have subordinated the economy to the curiosity for research are now victims of the so-called “resident-fellow-Porsche-syndrome” […] There is ample reserve of scientific knowledge in biology and medicine, and the opportunities for its application to unsolved medical problems have never been so evident. Progress is ongoing, and the moment should not be lost”.

This Wyngaarden essay was followed by other similar papers. In 1984, Gordon Gill wrote that “the first factor for the change [occurred] was practical and financial […] academic hospitals started to recruit more clinicians and less researchers […] The second factor was maybe more profound. The nature of molecular biology and true basic science changed with the development of recombinant DNA technology; the change was so fast that, without time to react, the revolution bypassed the medical world […] The role of the academic departments of medicine and physicians changed. Their current role is to apply the advancements made [at laboratories], to verify their efficacy and safety in clinical practice […] molecular biologists now dominate the whole biological science […] Many clinicians interested in research have been seduced by the power of molecular biology and have left clinical research. These physicians prefer to present their papers at the meetings in Cold Spring Harbor, the height for basic scientists, rather than at the Sheraton in Washington DC, that houses every year the ASCI/AAP/AFMR meeting[21]. The contribution of a third factor, as compared to the previous ones, is more difficult to delineate […] A tide of anti-intellectualism extends through Western countries […] Students of medicine are beginning to go during the summers to the most depressed areas, rather than to laboratories”[22]. Despite all, there were optimistic voices. Thus, for Robert Glickman, clinical research “is not dead, and we will not leave it die”[23].

“In my presidential speech, I will move away from the traditional philosophical discourse. I will instead take this opportunity –wrote Joseph Goldstein in relation to his speech before the 78th Annual Meeting of the American Society for Clinical Investigation[24]- to describe a recently identified clinical syndrome. This devastating disease afflicts our most brilliant and promising clinicians-scientists; it is a condition that disables them at the very time of their maturing as researchers. The syndrome is called PAIDS (Paralyzed Academic Investigator’s Disease Syndrome)». PAIDS is the inability of a researcher to capitalize on an original observation. The pathophysiology is defined by Goldstein in four words: lack of adequate training. He also dared to prescribe treatment: solid training in basic science and technical courage. The first part is obvious. Technical courage is self-confidence and the sense of adventure emerging from that training; it is the courage to use new techniques to answer new questions; it is the courage to avoid fossilization in what one already knows.

The intended Shannon’s model of a physician-scientist who translated his/her discoveries in molecular research to the patient bed did not work. Basic researchers shut themselves in the laboratory instead. The prediction that NIH funding would potentiate science was right –oncogene identification and tumor-suppressing genes are examples of success-, but the concept of Shannon that the same scientist who made such findings would apply them in clinical practice was wrong. In addition, as basic science progressed and became ever more interesting, physicians who had approached it eventually settled down in laboratory projects and deserted clinical practice.
The above-cited Goldstein article appears to have been written from a “Shannonist” nostalgia. A little over ten years later, this time with Michael Brown as co-author, he addressed the subject again, but from a different perspective[25]. In 1986, Goldstein illustrated technical courage by referring to three illustrious physicians –three giants of biomedical research- who had practiced it: Archibald Garrod, the father of biochemical genetics; Karl Landsteiner, the father of immunochemistry; and Rudolph Schoenheimer, the father of molecular biochemistry. All three did clinical practice and laboratory research at the same time.

Goldstein and Brown (JG and MB, from the University of Texas Health Science Center in Dallas, Texas, were awarded the Nobel Prize of physiology or medicine in 1985 for their discoveries related to the regulation of cholesterol metabolism) suggested that physicians interested in research, once they have completed their basic training, may consider three types of studies: basic research, disease-oriented research (DOR), or patient-oriented research (POR). The first two options are open to both biologists and physicians, while the third option is restricted to physicians. The distinction between DOR and POR is important because while basic research and DOR thrive, POR languishes. DOR is research aimed at understanding the pathophysiology or treatment of a disease, but does not require direct contact between patients and scientists. Materials from patients may be used, but not patients as persons. POR is performed by clinical physicians who watch, analyze, and treat ill people. As a golden rule, researchers are doing POR if they shake hands with patients during the research, and that direct contact requires placing patient dignity before any other consideration[26].

Many eminent scientists, including the Nobel Prizes Arthur Kornberg (in 1959, DNA polymerase), François Jacob (in 1965, *lac* operon), and Daniel Nathans (in 1978, restriction enzymes), were physicians trained in a clinical setting –as interns and residents in medicine or surgery- who subsequently devoted themselves entirely to basic research. Landsteiner, Schoenheimer, and Oswald Avery performed DOR. Avery, a clinician stimulated by patients with pneumococcal pneumonia, studied the mechanism by which avirulent pneumococcal strains were transformed into other virulent strains; the result was the discovery that genes consisted of DNA. A similar case is that of the abovementioned Goldstein and Brown who, spurred on by the case of a six-year-old girl with homozygous familial hypercholesterolemia, eventually buried themselves in receptor-mediated control mechanisms of cholesterol metabolism. On the other hand, POR's father was Garrod. Based on his observations in patients with alcaptonuria and in collaboration with William Bateson, a basic scientist working in the genetics field, he suggested that congenital metabolic errors are caused by genetic defects affecting enzymes that catalyze key metabolic steps in a given biochemical pathway. His conclusion, in 1908, that genes encode for enzymes was reported 35 years before the same phenomenon was discovered again in *Neurospora* by George Beadle and Edgard Tatum, who were awarded the Nobel Prize in 1958 for their work. There are many contemporaneous examples of POR of the type conducted by Garrod: Allen Steere and Steve Malawisa (Lyme disease), Michael Gottlieb (AIDS), William Waddell and Richard Loughry (cyclooxygenase inhibitors prevent colon cancer), or Barry Marshall (*Helicobacter pylori* causes gastroduodenal ulcer). The abovementioned researchers and others successfully doing POR usually share four Ps: patients, patience, passion, and poverty (in research grants). Because of their transfer of knowledge to the patient bedside, this type of clinical investigators have also been called POCTIs (patient-oriented translational clinical investigators)[27].

Goldstein and Brown gave an explanation for the seduction of basic research: "It is easy to have success in basic research, that is also more simple to do than clinical research. Basic scientists may choose a problem ready to be solved because new tools are available or because another researcher has made a finding that unblocks the experimental jam […] which makes it relatively easy to anticipate and perform the new experiment. This kind of basic research, while not revolutionary, provides definitive results […] that may be published in reputed journals, which will qualify researchers to obtain grants […] Basic science proceeds by abstraction […] The complexities of integrated organs and organic systems […] are deliberately excluded […] By contrast, the complex world of diseases is the obligate focus of clinical scientists. Clinical researchers are not free to choose their objectives. They must play with what nature offers them. A rheumatologist does not work with rheumatoid arthritis out of mere interest, but because patients suffer it […] Clinicians rarely solve the problem with the same brilliance as basic researchers do".
Alvan Feinstein[28] and Gordon Williams[29] think that Shannon was unwary in assuming that after the training that would allow scientist physicians to make basic discoveries, these same physicians would apply their findings to solve the problems of their patients. Though they were physicians, they had been trained in the "reductionist school". The reductionist strategy addresses cells and molecules, and is not a good approach to pathophysiological problems, which have no interest for reductionists. Complex processes occurring in living organisms can only be understood through an integrating approach. Human diseases occur in organisms and systems, rather than molecules, which do not fall ill. Reductionists are not interested in gross conditions such as blockade, spasm, ischemia, or decompensation; engulfed in basic problems, they rarely come close to clinical practice for answering problems related to patients.

Wyngaarden, Feinstein, Williams, Goldstein and Brown, and others[30] have voiced their concern about the danger of extinction of scientist physicians dealing with clinical problems, demanding a special training and support to clinical and translational research for their rescue. The model proposed by all of them is that basic research continues to be conducted by basic scientists, regardless of whether they come from medicine, biology, chemistry, or physics, but full time. The resulting findings must be taken by other different researchers, specialized clinical researchers who will do the translation. There is growing consensus in that an individual should not act as a basic and clinical researcher at the same time; no individual should know "everything"[31].

A way to POR salvage is collaboration, but not a large scale –macro networks-, but a simpler collaboration between two individuals ensuring cross-fertilization[32] or cross-breeding between disparate fields. An intimate, close collaboration that allows them for covering together what they could not individually cover. Both collaborators should be trained in medicine and science, which will allow them to be in both sides at the same time, though one in the clinic and the other in the laboratory. They may even exchange roles periodically. This is the type of collaboration practiced by Brown and Goldstein. Peer collaboration of two people, each playing a permanent role as a clinician and a scientist, may be more "normal" and even more potent. This type of collaboration has borne major fruits, as in the mentioned case of Garrod and Bateson. Two examples are given below: corticosteroids and *in vitro* fertilization (IVF).

The history of cortisone started in the 30s and involved two pioneers: a clinician, Philip Hench, and a chemist, Edward Kendall. In 1929, Hench, a rheumatologist at the Mayo Clinic, noted that some of his patients with rheumatoid arthritis experienced a marked improvement when they were pregnant or had jaundice. Hench thought that these two conditions induced the production of an anti-inflammatory factor that he called "anti-rheumatic substance X", and concluded, after several unsuccessful therapeutic trials, that the common denominator in pregnancy and jaundice was an increased cholesterol concentration in blood, and that the source of the pretended substance X had to be the adrenal gland, that was rich in cholesterol. In the mid-30s, Hench began to collaborate with Kendall, a chemist from the same institution who had isolated thyroxin from the thyroid gland and was at the time occupied in isolating adrenal substances that kept adrenalectomized dogs alive. By 1934 Kendall had been able to isolate 28 compounds, six of which showed activity in bioassays and were called compounds A-F. Ten years of work and the handling of 150 tons of bovine adrenal glands were required for characterization of these compounds. The first purified steroid, compound A (11-dehydrocorticosterone) was ineffective in Hench clinical trials. In 1946, Kendall isolated compound E (cortisone) that turned out to be the anti-inflammatory substance X in dog trials. Kendall was unable to synthetize a sufficient amount of product to be administered to patients. The problem was solved after a collaboration agreement was reached with Merck & Co Inc, whose chemists, under the direction of Lewis Sarret, designed a process for chemical synthesis of cortisone consisting of 37 chained chemical reactions, the most complex chemical synthesis ever carried out by any pharmaceutical company. In 1948, Merck scientists were able to produce several grams of cortisone, a sufficient amount to treat a rheumatoid patient with 100 mg/24 h IM for nine days. Treatment success was unquestionable. Hench and Kendall presented their work at the 1949 annual meeting of the AAP. After the presentation, Walter Bauer, head of medicine of the Massachussets General Hospital and one of the most respected clinicians in the world, remarked that he had not seen such an effective treatment in his whole professional life. Cortisone would not have seen the light without the collaboration of a clinician, a scientist, and the contribution of a third element that plays an increasingly leading role, a pharmaceutical company. This is a good example of how to get maximum returns from scientific effort[33].

The second example selected of an effective collaboration was the one that allowed for clinical application of the *in vitro* fertilization technique. In 1937, John Rock anticipated the possibility of IVF[34]. His article inspired Gregory Pinkus, who later became internationally famous because of his role in the development of the contraceptive pill, to perform IVF with rabbits, while Rock and Miriam Menkin achieved in 1944 the division of a human oocyte into two cells. The revival of IVF as a treatment for infertility occurred in the 60s thanks to the work of physiologist Robert Edwards, to whom a gynecologist, Molly Rose, provided ovarian tissue from patients undergoing laparotomy. When the problems posed by hormonal regulation were solved, Edwards became conscious that for IVF to become a clinical reality, an alternative method for obtaining ovules was required. The answer was laparotomy, that had been introduced in England by Patrick Steptoe while Edwards achieved his first successes with *in vitro* fertilization of human ovules. In April 1968, Edwards

moved with all his equipment to the hospital where Steptoe worked. In 1971, resources were centralized at Cambridge. In November 1973, Edwards reported his first eight unsuccessful attempts at human IVF. Louise Brown, the first test tube baby, was born in July 1978.
The traditional scientist physician should not be yearned for. Judith Swain[35] wrote: “Physicians who compete with basic researchers should share their time in research, teaching, and clinical practice, and stand out in all three. On the other hand, clinical medicine is not an activity that may be performed part-time”. Ronald Arky[36] had a similar opinion: “At the end of the 40s and the beginning of the 50s, the trivalent rugby player started to wane; players who could run, pass and kick, and score were being replaced by specialists in each of these skills. Similarly, in medicine there were in the past trivalent physicians: researchers, teachers, and clinicians. I would be surprised that there were today a few, or even any, of such trivalent physicians”. A similar reflection was voiced ten years ago by Robert Conter[37], and twenty years ago by Bernerdine Healy[38].

In surgery, the reductionist trap, that causes research to address molecules rather than diseases or patients, did not have a great incidence. First, because surgeons always think as pathophysiologists: blockade, spasm, ischemia, and second and unfortunately because surgeons rarely have time to become experts in molecular biology[39]. Wiley Souba[40], in “reinventing for the future”, states that “research initiatives will be programmatically organized […] If “pedestrian” biomedical research survives, it will be on a minimum scale”.

SURGICAL RESEARCH

Surgeons are often accused of paying little attention to the academic aspects of the profession, particularly research. In 1947, Edgard Churchill, an outstanding figure of Harvard surgery, said that if surgeons stopped to create their own new knowledge and to develop new treatments through research, they would become simple technicians at the orders of their internist colleagues[41]. Surgery is something more than skill.

If, despite everything, surgeons attempt to approach research, they should get round a number of difficulties: basic scientists, who think that the scientific background of surgeons and the time they have available are inadequate to approach a research project seriously; academic internists, who think the same as basic scientists; scientific committees, full of basic scientists and internists; financing agencies, that require a participation time impossible to take away from their surgical dedication; and selection methods, that cause a paper published in a surgical journal to be at a clear disadvantage as compared to another paper published in *Cell*, *Nature*, or *Science.* As mentioned by Judah Folkman[42], an additional deterrent element for scientific success, as important as the former or even more, is the surgeon's personality. The prototypical model of surgeon usually includes the following characteristics: decision, confidence, and the capacity to act rapidly, if necessary, before having all data. All these characteristics are necessary at the emergency room or the operating room, but do not form the best formula to do science. However, surgeons anticipated translational medicine, as shown by a few examples. Cardiac surgery. Alfred Blalock and his assistant Vivien Thomas attempted to develop a model of pulmonary hypertension in dogs. For this, they anastomosed the subclavian artery to the pulmonary artery. The attempt failed, because pulmonary circulation rapidly adapted to the sudden increase in blood flow without increasing pressure. Years later, Blalock had the opportunity to turn the experimental failure in a clinical success. When the pediatric cardiologist Helen Taussig suggested that an increased flow in the pulmonary artery could benefit “blue babies” with Fallot’s tetralogy, Blalock rescued his experimental model with full success. He performed the first surgical procedure on November 29, 1944[43]. The development of a heart-lung machine or extracorporeal circulation by John Gibson will be discussed at the end of this chapter.

Vascular surgery. Early vascular anastomoses were performed a little over one hundred years ago by Mathieu Jaboulay and his student Alexis Carrel, who is credited the most important innovations in vascular surgery, including some that were contributed by others. Carrel's success was due to the fact that he indeed introduced a completely new vascular suture method and to the scrupulousness of his technique, that prevented postoperative vessel bleeding and thrombosis. After failing to pass the entrance examination to occupy a position of surgeon in his country, Carrel emigrated, first to Canada and, on the next year, to the United States. In 1912, he was awarded the Nobel Prize of physiology or medicine for his work[44]. The whole work of Carrel, done in animals, was cast into oblivion for 40 years, until vascular surgery was started in humans. Early repairs of aortic aneurysms were performed at the beginning of the 50s. Initially, arterial defects were repaired using fresh or preserved homografts that usually degenerated, with sometimes calamitous results. Major vessel surgery had to wait to the development of artificial prostheses, which resulted from an accidental observation made in 1952 by Arthur Vorhees. The autopsy of a patient undergoing cardiac surgery a few months before showed that a poorly placed suture crossed the ventricular cavity. The suture, covered with endothelium, mimicked a normal valvular tendinous cord. Vorhees though that if the endothelium had covered the suture, it would also cover an artificial prosthesis, and put the idea into practice. Voorhees and Arthur Blakemore constructed prostheses and successfully grafted them into patients[45].

Endovascular surgery. Until the beginning of the 90s, vascular surgeons saw with indulgence how interventional radiologists performed procedures based on endovascular catheterization, such as balloon dilation of stenotic arteries and stent placement to prevent restenosis. In 1990, when Juan Parodi[46] introduced treatment with transfemoral intraarterial prostheses for abdominal aortic aneurysms, vascular surgeons realized that if they did not learn the skills required to perform those procedures, they risked to lose a significant segment of their professional practice to the hands of radiologists. This short story serves as an introduction to two "distortions": the label of the technique and the role of instrumental offer.

Interventional radiology, invasive cardiology (or neurology…), or trace-free surgery? The corresponding "specialists" use the same facilities and procedures, but at different plants of the hospital. This increases expenditure -waste is not investment- and decreases their experience –despite meta-analyses, that turn into alchemy-. The whole situation is nothing but a conflict of interests, as mentioned in the previous paragraph. Reinvention –rather than reform- of the curriculum first, and specialist training programs later, should be the rationalizing tool.

Modern vascular surgeons have acquired adequate skills to place stents and perform other endovascular procedures. It should therefore come to no surprise that public enthusiasm to replace major vascular surgery by other less aggressive vascular procedures has been similar to the hearty welcome given to laparoscopic cholecystectomy. And as occurred with this latter procedure, this enthusiasm makes randomized studies impossible. However, transition to endovascular procedures has not been as sudden as in the case of laparoscopic surgery. One of the reasons is the wide variety of devices. Surgeons collaborate with many manufacturing companies in an indiscriminate multitude of clinical trials that strive to show the advantages of each device. Every device should achieve approval by the Food and Drug Administration (FDA). FDA approval or rejection of devices usually means their global acceptance, or otherwise, before they may be used outside clinical trials, and only half a dozen devices have been granted approval. The approval process is burdensome, but has the merit of requiring follow-up of health outcomes, a requirement that does not apply to other procedures, such as laparoscopic surgery. On the other hand, despite the decrease in early intra- and post-operative morbidity of endovascular procedures, there are significant disadvantages. An experience of five decades showing the efficacy of standard or open vascular surgery is difficult to overtake. The different endovascular devices or closed procedures, though guided by image, differ in important characteristics, such as the anchoring mechanism or structure. As a result, they have different hemodynamic and biological profiles. Only long-term monitoring and follow-up will confirm that endovascular devices have a durability similar to the already consolidated procedures under conditions of biological normality. Such long-term monitoring is uncomfortable for both patients and surgeons. There is no doubt, however, that endovascular procedures have revolutionized vascular surgery and are an example of modern clinical research by surgeons.

An advertising campaign that flooded bus shelters and subway stations of our towns represented another example of commercial pressure. A multinational company specialized in electromedicine advised public transport users to use its novel “medical tricorder” for imaging examinations. How could hospitals and clinics refuse to buy such a tool, that was requested by an user demanding the best, particularly if communication media certify daily the efficacy of the device for solving the most intricate problems of media idols. Evaluation of technologies is research[47].

Minimally invasive surgery. This procedure has probable changed the life of surgeons more than any other. In September 1985, Eric Muhe successfully performed the first laparoscopic cholecystectomy in Boblingen, Germany[48]. Two years later, Phillipe Mouret significantly improved the procedure in Lyon. Laparoscopic surgery was popularized at community hospitals, rather than academic centers, where surgeons were initially reluctant to use the new technique. Widespread acceptance was due to patient demand based on their perception of less postoperative pain, a shorter hospital stay, and shorter periods of postoperative incapacity for work. While this perception was subsequently supported by several studies, the influence of communication media and patient preference, and the enthusiasm of surgeons for using the most novel procedures –also distortions- may jeopardize randomized studies to compare the results of open versus minimally invasive procedures. It should be noted, however, that there is no argument to question that minimally invasive surgery is one of the main contributions of clinical surgical research in recent decades.

Robot-assisted surgery and cybersurgery[49]. The abovementioned unstoppable advancement of surgery also runs parallel to that of other technologies that are already at hand. *Cybersurgery* is a term that covers and describes a new concept of surgery. A new word with which surgeons may understand and reconsider their job in the information era. Cybersurgery integrates, within the scope of surgery, both an emerging complementarity between clinicians and machines –particularly computers- and various digital technologies. Cybersurgery also symbolizes a new and true revolutionary option that combines the paradigm of information whereby bits replace atoms and molecules, the three-dimensional visualization provided by new medical imaging technologies, and virtual reality from integrated technologies. Young surgeons –*nintendo* surgeons[50]- are better prepared for these new technologies because their haptic capacities have been enhanced by video games during their childhood and adolescence. Cybersurgery is the complete synthesis of all those components, that are already almost here: Chirobotics –“chiro” + (ro)botics-, artificial intelligence, high performance computing, telepresence, or Internet. As in previous revolutions –asepsis, anesthesia, etc.-, the result of integration will be far higher than the sum of the parts.

Total parenteral nutrition. In 1938, Isador Ravdin and Jonathan Rhoads were studying the unfavorable impact of protein malnutrition on the course of wound healing. For the next 25 years they pursued the objective of achieving a positive nitrogen balance in patients unable to eat. For this, they used different approaches, including rectal infusions of glucose and alcohol or intravenous administration of gelatin and fat. When Ravdin retired, Rhoads continued research helped by a large group of assistants. Stan Dudrick, a resident working at Rhoads laboratory, conducted the decisive experiment. Francis Moore, the main competitor in that line of work, described the experiment years later: “Finally, his team […], including Dr. Wilmore, Dr. Vars, and Dr. Dudrick, conducted that simple experiment in dog pups that provided the world the modern intravenous nutrition and that gibberish term, total parenteral nutrition. It was an experiment that required no statistics. It was not complex. They were simple and direct, straight to the problem and very, very aggressive. They did not need great numbers. All they did was to show that pups grew normally when fed by the intravenous route only”[51]. Luck partly contributed to success. One of the collaborators, Harry Vars, was an excellent biochemist –prepared the intravenous nutritional solutions- and a great inventor; he devised a harness that allowed for continuous intravenous infusion for months. In addition, a resident in urology who came to the hospital for a rotation period knew a procedure for percutaneous catheterization of the subclavian vein and taught it to Dudrick. This provided the key for maintaining a continuous intravenous infusion of a hyperosmolar solution with no risk of thrombosis.

Transplantation. In the first decade of the 20th century, Alexis Carrel showed the technical feasibility of organ transplantation. After World War II, Francis Moore, head of surgery of Peter Brigham Hospital at Harvard University, encouraged one of his residents, David Hume, to attempt kidney transplantation in patients with end-stage renal failure, despite persistent failure in dogs. In 1947, a team formed by Charles Hufnagel, a hospital surgeon, Ernest Landsteiner, head of urology residents, and Hume transplanted a kidney from a cadaver into the antecubital fossa of a female patient with acute renal failure secondary to septic abortion. They anastomosed kidney vessels to the brachial artery and vein. The ureter drained directly into a reservoir. The kidney functioned for 48 hours, and was removed on the third day. The patient recovered[52], but died nine months later from the hepatitis transmitted through the blood transfusions received. This case was an exception, as all other attempts failed because of the lack of immunosuppressive therapies. When Hume was mobilized as surgeon for the Korea War, Joseph Murray, a plastic surgeon, was appointed as responsible for the transplantation program In 1954, Murray was lucky. The first fully successful kidney transplantation was performed on December 23 of that year. Donor and recipient were monozygous twins whose immunological identity had been confirmed by skin cross-grafts. A team headed by Joseph Murray performed the procedure in the same hospital[53].

Clinical trials in cancer. In 1966, Charles Huggins was awarded the Nobel Prize of physiology or medicine for his discovery, in the decade of 1940, of the influence of hormones on cancer, though other surgeons have noticed that relationship. In 1786, John Hunter had noted that bilateral orchidectomy caused prostate gland atrophy in animals[54], an effect that was again highlighted in 1983 by J William White, from Pennsylvania University. White published two years later his experience with castration in 111 patients who had experienced symptoms of prostatic hypertrophy, reporting improvement in 51 of them. Approximately one third of White patients had prostate cancer[55]. Oophorectomy as treatment for breast cancer, for which Huggins is often cited, was also used before his 1942 paper[56]. In 1896, George Beatson, from Glasgow, was the first to report that oophorectomy cause regression of metastases[57], an effect that was soon confirmed by others. The study by Huggins –a surgeon and specialist in urology, trained at Michigan University, who moved to Chicago University, where he worked as surgeon and directed and worked at the Ben May Laboratory for Cancer Research- of the relations of tumors to the endocrine status of the body was scientifically sophisticated and rigorous, and led to the understanding of estrogen receptors and to modern treatment of breast cancer with estrogen receptor inhibitors.

With the background of the very detailed observations by Huggins and though it may seem that the concept of controlled clinical trial has nothing to do with them, surgeons were among the first to conduct large-scale multicenter trials to compare treatments for important human diseases. Since the beginning of the 20th century and under the influence of Billroth, the practice of surgery was governed by anecdote and prejudice. Soon after 1950, surgeons became conscious that application of the scientific method could help them design clinical trials by which the results of different surgical procedures could be compared. Henry Buchwald and Richard Varco[58] undertook in 1963 a large clinical trial to test the effect of partial ileal bypass on cholesterol metabolism, and Marshall Orloff[59] started in the same year a series of controlled clinical trials to study patients with bleeding esophageal varices. However, the most influential clinical trials addressed treatment of breast cancer. From 1900 to 1970, surgeons followed the concept of William Halsted that breast cancer metastatized almost exclusively by the lymphatic route. The indicated surgical procedure was therefore *en bloc* excision of the primary tumor, pectoral muscles, and regional lymph nodes, i.e. radical mastectomy. At the end of the 50s, Bernard Fisher, from Pittsburgh University, questioned that assumption and stated that the roles of blood and lymphatic vessels in breast cancer extension could not be separated, and that metastases were governed to a great extent by genetic factors of cancer cells themselves. Fisher, with the help of the NIH, undertook in 1971 the clinical trials aimed at assessing the health outcomes of patients with advanced breast cancer treated by radical mastectomy or tumor removal. To the great surprise of most surgeons, the very large controlled studies of the National Surgical Adjuvant Breast and Bowel Project directed by Fisher showed that tumor excision and irradiation was as effective as radical mastectomy for the treatment of breast cancer[60]. A series of prospective, randomized clinical trials sponsored by the American College of Surgeons were subsequently conducted in different types of cancer.

Molecular research. The January 1992 issue of the journal *Archives of Surgery* included a comment by Edward Passaro, entitled “Molecular biology: the message, its language, and the surgeon”, that started: “The message is there, but is not easy to read. It simply is, and says that molecular biology dominates the process of the fundamental change in our concepts and treatment of the disease [...] The pity is that not many surgeons understand that language, the implications of the message, or even its role in conversation […] It is true that such a deep message has been written in an arcane language: cosmids, YACs, centimorgan, RFLPs, telomers, or contigs are not in the surgeon’s jargon […] But just as surgeon needs molecular biology, molecular biology also needs surgeons […] Surgeons have access to human tissues. Such access is critical in molecular biology, and can only be made by surgeons. It is not a coincidence that a part of the most imaginative and incisive researches in molecular biology of cancer has been directed by surgeons… We need to known that language […] We need to speak it. They need to hear us”[61]. In the next year, the same journal started a series under the general title “Surgeons and molecular biology: a happy cohabitation”[62] to commemorate the fortieth anniversary of the discovery of DNA structure. The journal editor wrote: “Clinicians and basic scientists need each other […] Surgical practice of today is determined by yesterday’s basic research; tomorrow will not be different. Most current surgery departments understand the need for molecular biology to have a greater presence in their programs”. One of the articles in the series had the suggestive title “Should surgeons clone genes?"[63]. “Surgeons are routinely exposed –wrote the members of the surgery department of Pittsburgh University- to certain clinical problems at the patient bedside before which only the surgeon is able to ask relevant questions”. Thus, it was surgeons who, answering these questions, have made relevant contributions to the angiogenesis process in cancer[64] or to the pathophysiology of multiorgan syndrome through the concept of “cytokine storm”[65]. It was also a surgeon -Thomas Starzl, who started the first stable program of kidney transplant first, and liver transplant later- who promoted research in gene knockout to produce matching animals for xenotransplant by silencing the galactosyltransferase gene, responsible for the antigens responsible for hyperacute xenograft rejection[66]. And it was also a surgeon -Steven Rosemberg, from the National Cancer Institute at Bethesda, a pioneer in immunotherapy, was the most quoted clinician in the field of oncology in the 1981-1998 period- who promoted the most ambitious programs in oncotherapeutic gene therapy, mainly against melanoma[67].

SURGICAL RESEARCH, QUESTIONED

The following sentence appeared in the October 27, 1983 issue of the N Eng J Med: “The year of laboratory work that is still part of some surgeon training programs […] is a loss of time”. This was a statement by Dr. Robert Petersdorf, who was at the time dean of the school of medicine of California University at La Jolla. Why then do research in a surgery department; is it worth the effort? It is indeed. First, for the same reason that some years ago surgeons were set to opening the doors to clinical transplant, or to treatment of major trauma, or to total parenteral nutrition, or […] Another reason is, simply, curiosity. There is however another more important reason, because during professional training, particularly in surgery, there is a especially weak point: the difficulty to teach residents how to think critically and how to evaluate results without prejudice. It is at the laboratory where a rigorous analytical attitude may be taught and learned. If a resident would only do that, to get rid of dogmatism -with no publications or papers and without returning there-, a stay of a few months, not to say one year, would have an inestimable value in the training of future specialists. “The art of surgery is too powerful and too dangerous to leave it in the hands of a surgeon that only uses his cerebellum”40. It is impossible to predict whether a research will provide added value, but if surgeons and researchers work together, the chance will increase.

Richard Horton asked[68]: “How does surgical knowledge advance?” A publication[69] reporting the results of a randomized study comparing cholecystectomy performed using laparoscopy or through a reduced laparotomy partly answers this question. The design of this study, including adequate sample size, randomization at the operating room, and blinding of the procedure performed (identical dressings in both patients groups), sets a new standard for surgical clinical trials. The way in which authors answer their question –laparoscopic surgery has no obvious advantages-, that may influence standard surgical practice, is the exception, rather than the rule, in surgical research. The study reveals significant aspects about why surgeons investigate, how do they do it, what criteria they use to judge the validity of their data, and how their experience compares to the rest of the medical community. “In order to have a clear idea of what “surgical research” means” –wrote Horton-, I read the first 1996 issue of nine non-specialized surgery journals”[70]. This represented 215 articles, of which 175 reported original research results. Only 12/175 (7%) provided data collected from a randomized clinical trial. The most common research method were series of cases (80 studies, 46%), followed by experimental studies on laboratory animals (31, 18%). The significance of case series in surgery is beyond doubt, and it seems reasonable to wonder whether this study method may be trusted to provide a valid result. Horton was categorical: “according to the conventional epidemiological method, the answer is no”.

Case series have as advantages that they have a low cost and are rapidly achieved and easy to perform; they generate valid hypotheses for subsequent research; and they sometimes contribute unique facts that allow, for instance, for defining new diseases (e.g. AIDS[71]). However, case series provide the weakest evidence to assess the efficacy of a treatment or establish a cause; some critics do not even consider them research *stricto sensu.* Thus, if half the surgical research is based on case series and this type of study is the most vulnerable to criticism, it should be inferred that a significant proportion of publications in the field of surgery have a questionable value. What arguments may be use to attenuate concern about case series? While randomized controlled trials are assumed to be the gold standard for assessing the effectiveness of clinical treatments, maybe surgeons do not contemplate such trials as an acceptable approach to solve problems related to surgical treatment, among other reasons because standardization of surgical procedures is one of the greatest difficulties when designing randomized protocols.

Will research in surgery have a future? Today, surgeons do not appear to see this question as something key in their practice. Competence, training, and organization appear to be the main concerns. However, if case series predominate, standards to publish them should be defined. To maintain their academic reputation, surgeons should find ways to collaborate with epidemiologists in order to improve the design of case series and plan randomized studies. In addition to safety and efficacy studies, more pragmatic studies are required to assess the efficacy of new surgical procedures using standardized and widely proven treatments. Unfortunately, evidence suggests that the quality of surgical studies is inadequate. In a review of 202 randomized controlled studies comparing surgical treatments, the mean score was 0.40 in a scale ranging from 0 to 1.0[72]. John Hall and Jane Hall[73] reported similar conclusions after evaluating 619 surgical clinical studies published from January 1990 to December 1999: only 33% of the trials published (202/619) had a valid design. "Our study suggests –they wrote- that most surgical studies published ignore basic aspects of randomized design". Another publication stated that most surgical studies lack, above all, the rigor required in a trial of the characteristics noted[74].

In order to get round the pointed deficiencies, the Clinical Epidemiology Group of the surgery department of Toronto University wrote a series of articles about research in surgery[75]. "The frontiers of surgery have advanced over time as the result of a combination of observation and application of science to clinical problems", stated the editor's note. "Today, surgical research reflects the wide spectrum of research in medical science, from molecular genetics and biology to use of randomized clinical trials to answer clinical questions. This marked growth and vigor of surgical science has caused data interpretation to become more complex, which has led [*Surgery*] to publish a series of short articles about interpretation of data resulting from research in surgery". The first article in the series addressed "measurement" in surgical clinical research[76]: "To measure is the basis of scientific research. In surgical clinical research, measurements are used to assess patients and the procedures and treatments they undergo. In addition to standard laboratory measures, such as blood glucose or urinary electrolytes, surgeons are usually interested in measuring complex events such as severity of a disease, dysfunction of an organ, or quality of life. Accurate measurement of such complex clinical events is one of the challenges in surgical clinical research".

The situation is however rapidly changing. The journal *Surgery-Devoted to the art and science of surgery,* an official publication of the US *Society of University Surgeons* and one of the most prestigious surgical journals, has been including, since the abovementioned initiative, an increasing number of research contributions that are distributed in very specific sections of the journal: *Clinical research review, Evidence-based surgical hypothesis, Short research review, Surgical outcomes research*, or *Surgical research review*. Among the different modalities, "health outcomes research" (HOR) is given an increasing attention[77]. HOR is focused on evaluation of the quality and effectiveness of medical care, while incorporating the patient's perspective as the perceived health status. HOR results help better understand diseases and their clinical treatment, and should be incorporated into the process to assess the effectiveness of healthcare services in order to improve their quality. The intended objective is a "medicine based on health outcomes and as a logical and desirable evolution of evidence-based medicine"[78]. HOR represents a wide group of research methodologies in the different facets of the healthcare system, each with different traditions and scientific foundations. Many HOR studies mimic studies in traditional clinical research, with which they share some basic objectives: to describe the different outcomes of a treatment in patients, to identify prognostic factors, and to assess the relative efficacy of alternative treatments. Both types of research may consist of experimental designs (e.g. randomized, controlled trials) or observational studies (series of cases, cohort studies, and case-control studies). Despite this overlapping between research studies of medical care outcomes and clinical studies, outcomes are assessed at patient level, while incidence rates refer to healthcare systems or populations cared for.

To summarize, HOR studies are focused on specific aspects related to the patient. In fact, research on medical care outcomes was given this name because it addresses things that are important for patients (e.g. nocturia, sexual function, or continence following prostatectomy), rather than the effects of treatment on physiological aspects (e.g. urinary flow). Patient studies, evaluated using increasingly complex methods, cover a wide spectrum of aspects of patient satisfaction and functional status[79]. Many indicators are available for evaluation of the different diseases, such as the symptom index for patients with benign prostatic hyperplasia of the American Urological Association[80]. However, the most commonly used assessment tools are those referring to the physical, mental, and social wellbeing of patients and that are evaluated using generic data, such as the Medical Outcomes Study 36-item questionnaire[81]. Although related to patient's functional status, these indicators (utilities) reflect how patients feel and how they rate different care processes. These indicators are therefore quantitative expressions of patients' quality of life and preferences, and are usually combined with life expectation indices to compute quality-adjusted life years (QALYs), an index commonly used in decision analysis and cost-benefit analysis[82]. Indicators usually have a poor correlation to functional status or the traditional symptom indices. For instance, patients with similar symptom indices from a given disease differ in their indicators for the same symptoms. In addition to patient-focused outcome studies, there are studies comparing the effectiveness of actions of the different healthcare systems –e.g. between hospitals- and exploring the reasons for the differences[83].

Individual outcome results rarely are robust enough so as to guide clinical decisions. Even intelligently designed studies, such as randomized and controlled clinical trials, leave many unanswered questions about clinical efficacy. To face such problems and add value to the information provided by individual results, the clinician has two main tools, meta-analysis and decision analysis. Meta-analysis is a biostatistical tool to combine and jointly analyze the results of multiple clinical trials, provided they are well conducted[84]. Decision analysis is an increasingly popular tool to evaluate therapeutic alternatives that is viewed as a "black box" by most surgeons. While this analysis may be used to improve decision taking in a particular case, it is generally used to answer generic clinical questions (e.g. in what subgroup of patients is cryoprostatectomy effective?) and in economic evaluations (e.g. what is the cost-benefit of cryoprostatectomy?)[85]. Simple decision trees and Markov models represent the extremes of a variety of decision analysis models[86].

Despite their wide dedication to surgical practice, surgeons, as executors of the medical action, have usually had a very limited role in the modality of health outcomes research. There are however several reasons for the opposite situation. First, surgeons should respond to the growing consumerism of medical care. Patients demand information about therapeutic alternatives and their efficacy, and are also increasingly involved in decision taking (see endovascular surgery and minimally invasive surgery in previous paragraphs). Many patients want to know the clinical and technical competence of their physicians, that may now be found out in the communication media in certain countries -the US Freedom of Information Act, FOIA-. The *Newsday* weekly magazine published the mortality rates of each of the surgeons performing myocardial revascularization in the state of Mew York[87]. Surgeons, if they participate in this process, will be able to ensure that

data are adequately taken and that any adjustments required based on disease severity are made before a public dissemination difficult to control *a posteriori.* Surgeons also need to respond to public administrations, that strongly emphasize cost containment, but are less concerned about quality issues. The most important thing may be that surgeons have a professional obligation to involve themselves in outcomes research. As scientists, surgeons are responsible for assuming leadership in evaluation of surgical practice and application of results to clinical decision taking. They will thus help avoid that healthcare quality is compromised in the cost control process.
In his 1958 presidential lecture to the US Society of University Surgeons, Francis Moore said: “There is an unsolved conflict of interest in academic surgery, […] the conflict between the operating room and the laboratory […] between clinical pressure and patient care and the search for science. Few academic surgeons have not suffered this conflict. Even though university surgeons build a bridge between the laboratory and clinical practice, colleagues at both sides tell them they are not in any side. Scientists reproach them not to do enough science, while clinical surgeons say that they do not have worked at an operating room for a sufficient time. They are therefore bastards, and should learn to live with it. However, all advances in surgical science since Vesalio, Hunter, Lister, Halsted, or Cushing have been made by those who opted for taking such an uncomfortable stance”[88].

IN SUMMARY, WHAT IS RESEARCH IN SURGERY?

Discussion of a clinical case is the most simple modality of clinical research and naturally has an educational character. Most clinical cases are simple phenomenological observations, but they sometimes change clinical practice because of their direct clinical relevance. An example of this is the incidence of a clinical case reported by EJ Kosnick y WE Hunt[89] on the treatment of cerebral vasospasm following a subarachnoideal hemorrhage caused by rupture of a vascular aneurysm. Clinical research also frequently provides technological improvements that have a rapid impact on surgical practice. For instance, description of bone wax by Victor Horsley in 1892 allowed for easy control of bleeding from trabecular bone. Orthopedic surgery and neurosurgery would have barely progressed without this simple technique, that took up a quarter of a page in the *British Medical Journal*[90].

But let us take a closer look to the most complex techniques, since case series or HOR have already been discussed. After two years as intern physician at Philadelphia Hospital, where he started out in clinical research protocols –effects of potassium chloride versus sodium chloride in the diet of patients with severe hypertension-, John H Gibbon (1903-1973) moved in February 1930 to the medicine school of Harvard University as research fellow in surgery, joining the laboratory of the Boston City Hospital directed by Edward Churchill, head of the Harvard Surgical Teaching Service at that hospital. Churchill told him his first research work: to measure pulmonary artery pressure with a femoral arteriovenous fistula open and closed. Gibbon found that, when the fistula was open, the increase in pulmonary artery pressure was very mild, as compared to the significant increase in pulmonary blood flow, measured using Fick’s principle. In June 1930, Dr. Churchill took charge of one of the surgery departments of Massachussets General Hospital. Gibbon installed himself in an experimental research laboratory located in an old building. The idea to construct a heart-lung machine arose in February 1931 as a result of the circumstances surrounding the death of a patient because of a massive pulmonary embolism. During the long night of agony of the cyanotic patient until she died after undergoing a pulmonary embolectomy –no such operation had been successful at the time-, Gibbon considered the possibility of drawing blood from her distended veins, removing CO_2, oxygenating blood, and reinjecting it into the patient’s arteries. In the spring of that year, Gibbon married Mary Hopkinson, an assistant technician at Churchill’s laboratory, and returned to Philadelphia for his residency in surgery. He spent three and a half years practicing surgery in the mornings and doing research in the evenings. With Eugene Landis –who would eventually occupy the chair of physiology at Harvard-, Gibbon studies the effects of temperature and tissue pressure on fluid movement through the wall of human capillaries. “Often, my mind –said Gibbon[91]- wondered about the possibility of temporarily replacing cardiopulmonary function by a machine […] I realized that such a project required full time, and a lot of time”. Gibbon returned with Churchill, who did not show any interest in the possibility of an artificial heart-lung, but never hindered in any way its development. Even less enthusiasm was shown by the great friend of Gibbon, Walter Bauer –who would eventually occupy the chair of medicine at Harvard, and who was alluded to in relation to the cortisone study-, who told him that if he wanted to make an academic career in surgery he should undertake less ambitious projects that he could rapidly publish in the usual scientific journals and irrespective of results. The only one who showed interest and gave him complete support was Eugene Landis: “if you think you can make it, it is worth trying”. “I saw no reason why the project could not be successful –wrote Gibbon-, and I therefore decided to carry it out, despite the total lack of enthusiasm by all others”. In a little over one year, they –Gibbon and his wife, and the Harvard department of engineering- were able to maintain for almost four hours the cardiorespiratory functions of cats in which the pulmonary artery had been occluded using a rudimentary heart-lung machine. Results of those experiments were published in 1937[92]. In 1935, after completing one year in Harvard, Gibbon returned to Philadelphia and continued his work at the Harrison Department of Surgical Research of the Pennsylvania University medical school. In 1939, the favorable results allowed him to suggest that “it is conceivable that a diseased mitral valve may be exposed for surgical manipulation under direct vision, which would substantially expand the fields of cardiac and thoracic surgery”. Gibbon continued to work at that department, now with a scholarship from the Josiah Macy Foundation. World War II interrupted work. After four years as army surgeon, Gibbon took up again the project at the Jefferson Medical College in Philadelphia. It was the time to take the definitive step. Gibbon got in touch with Thomas Watson, IBM’s president. “I will never forget my first meeting with Mr. Watson at his New York office -continued Gibbon-. He arrived with all my publications. He shook my hand and sat beside me. He said the idea was interesting, and asked me how could he help me. I remember that I answered him stammering that I did not want any money for my idea, or to make money out of it. He told me I should not worry. I then explained him that what I needed was engineering advice for the design and construction of a machine effective enough as to be used in human patients. He replied: “All right. Tell me where and when should engineers go to discuss the project with you”. Since then, IBM not only provided all necessary advice, but paid for the construction of the successive machines that allowed for progress over the next seven years”. The crucial experiment was carried out in April 1951; one of the machines successfully maintained for 96 min the cardiorespiratory functions in a 9.5 kg dog with both caval veins totally occluded. The dog fully recovered after surgery. The project culminated on May 6 1953 with the successful closure of an interatrial septal defect in an 18-year old female patient who remained connected to the machine (Heart-lung machine Model II, IBM) for 45 min and was totally dependent on it for 27 min. From February 1931 to May 1953: twenty years after an idea. From 1953 to 2007: benefits for countless patients. This is surgical research! And the same applies to cardiac valves, joint prostheses, cardiac pacemakers, and other devices, all of them achieved through technological developments that have been the result of collaborations between the industry and clinical surgeons; good examples of translational research[93].

EPILOGUE

In the 21th century, the capacity for continuous discovery in basic science should be maintained. However, the potential benefits of such discoveries will not be realized without a greater concern for clinical practice and prevention. Research provides the foundations of our scientific knowledge; the challenge in the future will be to translate that knowledge to expand the capacities of daily practice. Academic centers have to play a central role to prime a long-term basic research that makes possible innovation in the future; and this should be done fostering clinical research, which will allow for translating new discoveries into clinical practice, evaluating the current clinical practices, and answering what should and what should not be done in medicine: patients are the beginning of the end of a discovery process[94]. "If I am optimistic –said Abba Eban, an Israeli diplomat- is because of my conviction that men and nations behave wisely once they have exhausted [and failed with] all other alternatives"[95]. As may be read in the hall of the NIH clinical center:

«*Hospitals with traditions of excellence have demonstrated abundantly that research enhances the vitality of teaching, teaching lifts the standards of services, and service opens new avenues of investigation*»[96].

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11. El portaaviones «Príncipe de Asturias» tiene una dotación de 830 tripulantes y 29 aeronaves. Su comandante es un capitán de navío.

12. Pedro G.ª Barreno. Informes, manifiestos y pactos de Estado, por la Ciencia. Arbor 2004; 177 (698): ix-xliii. Frente a los «pactos de estado por la ciencia», reiteradamente firmados por investigadores —¡pues faltaría más!— de nuestro país y sin otra firma de adhesión, los ejecutivos de dieciséis compañías americanas, líderes mundiales en tecnología, firmaron un escrito urgiendo al gobierno a continuar su apoyo tradicional a la investigación básica y aplicada universitaria. El «anuncio» apareció en The Washington Post, el cinco de mayo de 1995, con el título «*A Moment of Truth for America*». En el texto puede leerse: «*Imagine life without polio vaccines and heart pacemakers. Or digital computers. Or municipal water purification systems. Or space-based weather forecasting. Or advanced cancer therapies. Or jet airliners. Or disease-resistant grains and vegetables. Or cardiopulmonary resuscitation […] This partnership-the research and educational assets of American universities, the financial support of the federal government and the real-world product development of industry-has been a critical factor in maintaining the nation's technological leadership through much of the 20th century. Just as important, university research has also helped prepare and train the engineers, scientists and technicians in industry whose discipline and skill have made technological breakthroughs possible. It has sparked innovation and prudent risk-taking. And as a result of the opportunity afforded such skilled workers in our technologically advanced economy, many disadvantaged young people have used high-tech jobs as a stepping stone to more productive and satisfying lives. Unfortunately, today America's technological prowess is severely threatened. As the federal government undergoes downsizing, there is pressure for critical university research to be slashed[…] For all these reasons, it is essential that the federal government continue its traditional role as funder of both basic and applied research in the university environment… As we reach the final years of the century, we must acknowledge that we face a moment of truth […] As the Congress makes its decisions on university research, let there be no mistake. We are determining the 21st century today*». Ver: Tercera Encuesta Nacional de Percepción Social de la Ciencia y la Tecnología, realizada por la FECYT en colaboración con el Centro de Investigaciones Sociológicas; en: www.fecyt.es. Redacción. Percepción de la ciencia, ¿un paso atrás? SEBBM 2007; 151: 26-28.

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