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Special article

# Basic research at the dawn of a new century

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It is a pleasure for me to be here today and to have this possibility to address some of the students and faculty of the Universidad Autónoma de Nuevo León. I want to take advantage of this opportunity to tell you a few things about Basic Biomedical Research and discuss a couple of very serious problems that will confront all of us in the years to come and that will not be solved without the help and contribution of people like you, that is, people with your background and formation.

I believe it is the perfect time to bring up these matters because the advances that have occurred in the biomedical sciences these last 10 or 20 years are absolutely without precedent. If the first half of the century that just ended belonged to nuclear physics, with Einstein's relativity, Max Planck's quantum theory, Werner Heisenberg's principle of uncertainty or Ed Hubbel's red shift that gave us a measure of our universe, atomic energy and what not, there is no question that the second half belonged to biology. It gave us incredibly sophisticated new technologies, such as genetic engineering, including gene cloning, manipulation and expression, without which we would know essentially nothing about our genetic make-up, hereditary diseases such as muscular dystrophy, cystic fibrosis or diabetes, nothing about viral diseases such as AIDS or cancer. And with the pervasive presence of the computer that allow us to analyze and display data, store them and retrieve them at the touch of a button, today's investigator has at his disposal an incredible array of methodologies undreamed of just a few years ago.

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Many of these advances come from Fundamental Research, that is, research carried out for the sake of research as opposed, for instance, to applied targeted research, that is, studies specifically designed to solve a particular problem. Now, of course, there is absolutely nothing wrong with applied or targeted research as exemplified, for instance, by the superb work of French microbiologist Louis Pasteur or research carried out at the Bell labs or in countless Pharmaceutical or Biotech companies today. Absolutely nothing wrong as long as all the resources available to science are not funneled exclusively in that direction, i.e., for the support of a few preselected topics at the expense of all others.

This is because science is a vast, broad base enterprise in which every single advance relies on all the others. No single area can be developed alone, independently of all the others. Unfortunately, many administrations or government people don't seem to understand that one cannot solve a given problem by simply throwing millions of dollars at it. This is not how science proceeds because one cannot order at will, or buy a new discovery, simply because there is no way one can predicting when or from where it will come.

There are innumerable examples of which, I'm sure, many of you are well aware. There is the story of Gregor Mendel, a monk who was growing peas in the garden of an Augustinian monastery in Moravia in the middle of the nineteenth century. He wondered one day why some peas gave white or yellow flowers and others pink. Now, I'm sure that myriads of people over the centuries had noticed that peas came out with flowers of different colors but nobody had bothered to ask why. Not Mendel: not only did he raise the question, but he figured out a way to solve the problem. By carefully separating the seeds and keeping track of the different traits in the offsprings, he could formulate the basic laws of heredity and classical genetics, which, by the way, we now call Mendelian Genetics.

There is Willhelm Röntgen, a German physicist in Würzburg interested in what happened to electricity when it passed through vacuum tubes. He noticed one day that the flow of electrons, bouncing against the cathode, could light up a fluorescent screen standing some distance away. He further found that his mysterious rays (which he called x, not knowing what they were), could pass through solid objects, therefore paving the way to perhaps the greatest discovery ever made in the field of medicine. I mentioned these two examples because, if a granting agency such as our NIH (our National Institutes of Health) would have existed at that time, and he or Mendel would have applied for a research grant to do what they wanted to do, there is no chance in the world that their requests would have ever been approved. They would have said: what does the growing of peas or playing with vacuum tubes has to do with medicine?

Things haven't changed. Jonas Salk would not have been able to develop his vaccine against polio if others, (mainly John Enders) hadn't found ways to grow polio viruses in large amounts in various types of tissues, particularly monkey kidney tissue. At that time, in the early 40's, much of the money spent for the fight against polio was earmarked for the design and development of better iron lungs that became just about obsolete a few years later.

Finally, there are the countless discoveries due simply to chance that, of course, could never have been predicted. For instance, Sir Alexander Flemming discovered penicillin because, in a way, he was a sloppy microbiologist. Some of his bacterial cultures had been neglected to the point that they had become moldy. Until one day, he noticed that around one of these molds – a *Penicillium* (similar to the white or green mold you see on rotting lemons) there was a clear circle in which no bacterium would grow. He rightly surmised that antibacterial substance had been secreted by the mold which he could later isolate and named *Penicillin*. This is in fact the beauty of basic research when one knows where one starts from but never knows where one will end up.

But these discoveries did not spring spontaneously, out of nowhere, without a lot of observation and thoughts, a lot of effort and hard work, or without sacrifices. Knowledge can only be acquired at the expense of something, by paying a price for it one way or the other. For example, I am quite sure that when the early man acquired the intellectual abilities and skills to deal with his environment, he began to lose the acuity of certain of his senses: the sharpness of smell that most animals have or of vision and hearing that most display. A dog has about 1000 olfactive receptors (this is what will enable it to follow the trail of a single man in a crowd, by computing the input of a few molecules of odorants floating in the atmosphere); only circa 350 are left in humans. Perhaps he lost some instincts we wouldn't recognize or conceive today. Just like the blind person who, regaining his vision, would rapidly lose the sensitivity of some of the senses he had developed to cope with his condition.

There is nothing original or new in what I am telling you, or about this concept: one finds it mentioned time and again under different forms in various mythologies. For instance, it has been clearly told in the story of Adam and Eve one finds in the Old Testament. It is when they tasted the fruit of knowledge symbolized by the apple, that they lost their innocence and their paradise, their Garden of Eden. In fact, it is because of that that Eve was charged of having committed the Original Sin.

Likewise, one finds it mentioned in the ancient Teutonic and Scandinavian mythology, as so well told in the prelude of Wagner's *Götterdämerung* (the Twilight of the Gods: the last of Wagner's 4 operas retracing the saga of the Ring of the Nibelung). While spinning and weaving the cord of time, one of the Norns tells the story of the young God Wotan who appeared one day to drink at the spring of knowledge and wisdom. Wotan had to pay by giving one of his eyes. This is why, throughout the Ring of the Nibelung, you always see him with a black patch over one of his eyes. You cannot gain knowledge without paying for it.

But that's not all. Having now acquired knowledge and wisdom, Wotan breaks a branch of this huge Ash tree to fashion the spear on which he wants to carve the laws of the gods. But by breaking this branch, the wounded tree slowly withers, loses its leaves and finally dies. Let me read from the text because I believe it is pretty moving:

*In the long run of time.*
*This wound consumed the forest.*
*The leaves died and fell, the tree rotted.*
*Grief stricken, the well ran dry.*

What this tells us (and it is amazing to me that people living so many centuries ago already had this deep feeling, this understanding, this wisdom), that one cannot violate nature for whatever cause, no matter how worthy or virtuous it might be, without running the risk of affecting it one way or the other, sometimes wounding it if not destroying it altogether.

This is a warning that all research scientists should never forget, particularly today, when they are confronted by enormous problems that will not be solved without their contribution and their help. Furthermore, to solve them, they will be forced to make very difficult decisions, and choose between agonizing alternatives. And this brings me to the first problem I want to speak to you about, that is, the use of genetically modified plants as a means to deal with world hunger in the face of an ever growing population.

Indeed, nowadays, more than 3/4 of a billion people remain chronically undernourished and over 180 million children are on the verge of starvation. By the year 2020, enough food will have to be produced to feed an extra 2 billion people. But the agricultural environment has already been taxed to its limits and there are few realistic opportunities for opening up new land to agriculture. Soils are eroding and losing their fertility, precious water supplies are being squandered, fish stocks are declining world-wide and have already been depleted in many parts of the world oceans, and forests have been devastated by the push of urbanization, by wars, fires, acid rain, toxic wastes etc. And now, this new century will have to rely on biologists to feed a population that will exceed 8.5 billion in 20 years. The task will be enormously difficult because today, world population is probably increasing at least as fast if not faster than agricultural productivity. So, unless one can curb overpopulation world-wide (and I don't mean in developed countries only, but globally: after all, the world is a closed system and if there is an explosion of population in one of its quadrants, inevitably, it will spill over everywhere; even thermodynamics tell you that), frankly, I don't see how our civilization can survive without calling upon new technologies such as genetic manipulation of plants. Let me say a few words about that even though I am neither a plant geneticist nor a molecular biologist.

Okay, it is absolutely true and we all agree that modern agriculture has remarkably increased food production without having recourse to genetic engineering, but it has been able to do so only by the use of massive amounts of fertilizers and pesticides that are not only extremely costly (prohibited for developing countries) but are already causing a major pollution of our waterways and the environment. The huge concentration of nitrogen produced has resulted in an explosive growth of algae. When these bloom, they use up all the oxygen and suffocate marine life, creating "dead zones" in the oceans, graveyards of fish and plant life that threaten the health of the planet and millions of people who depend on the marine environment for their livelihood. So any further increase in food productivity can only be considered and accepted under conditions that would both conserve our natural resources and protect the environment. And here lies the problem because, frankly, I don't see that it can be done without taking advantage of molecular genetics, that is, by introducing new traits in transgenic plants. Not only has this technology allowed us to reduce heavy loses of crops due to predatory insects, pests and diseases, but it also has already enabled us to grow plants in very harsh environments, such as in soils of high salinity or under drastic drought conditions where no present plant would survive.

Of course, there is no question that absolutely rigorous and air-tight regulatory measures will have to be introduced, stringent guaranties of safety will have to be put in place to identify and monitor any potential health and environmental hazards, just as should be done for the introduction of any new technology. But I'm afraid that unless one can control the increase in world population, there is no alternative, unpalatable as this prospect might be.

Now, I am well aware that there is an enormous opposition (practically world wide) to the use of genetic engineering. These concerns are understandable and in good part justified, but there is another factor that has to be taken into consideration, that is, the fact there has been a distinct change in the way the general public perceives science today. In spite of the fact that no previous century has contributed so extensively to our health and well being, a great many people still express a very high level of apprehension and distrust toward science. Today, when a new discovery is announced, the first question that seems to come to their mind is “in what way might this discovery endanger the environment, menace our health or destroy our civilization altogether?” To such an extent that quite a few people seriously wonder whether humankind will be able to survive this third millennium. While some of these doubts may be justified, others are not. As my good friend François Jacob once said: “It is not science that is dangerous, it is ignorance”. Ignorance, indeed, and unfortunately the way some people might want to use science.

Naturally, no one can predict what the next millennium has in store for us, where it will lead us, because one cannot simply extrapolate the present. All that is absolutely certain is that the world that will surround us will be completely, totally different from the one we live in today. And it is no more possible for us to imagine that world that it would have been possible for Christopher Columbus a few centuries ago, to have imagined that thousand of people would be able to communicate with one another, or see one another, instantly and throughout the world. Or that man would walk on the moon or that he could have imagined atomic energy. One cannot imagine what one cannot conceive and it would be totally senseless, if not often silly, or even sometimes arrogant to try to do so.

Let me give you a few examples. Just a hundred years ago, at the turn of the century, William Thompson, perhaps the most reputed physicist of his days who became the first Lord Kelvin because of his studies on thermodynamics and absolute temperature that gave us the degrees that bear his name, namely “the degrees Kelvin”, President of the Royal Society, etc., made three astounding predictions:

**First:** that radio waves would be of little utility and therefore had no future.

**Second:** that no machine heavier than air would really ever fly, and

**Third:** that x-rays that had just been announced by Röntgen in reality did not exist, and were probably a scientific fraud. Clearly, Lord Kelvin was more at ease with thermodynamics than with a crystal ball.

Incidentally, he became a bitter opponent of Darwin, claiming that Earth was far too young to allow for all the mutations required for Darwinian evolution. Of course, poor Darwin had neither the expertise in physics nor the prestige Kelvin enjoyed to fend off those brutal attacks. We know today that in his calculations, Kelvin underestimated the age of the Earth by nearly 4 billion years.

Another example. After the telephone was adopted in the US (and, by the way, Western Union –our main communication company- was so unimpressed by Alexander Graham Bell’s invention that it declined to buy the patent), a group of British experts who studied the question concluded (and I quote from their report) that “the telephone may be appropriate for our American cousins, but not here because we have an adequate supply of messenger boys”. Finally, even more recently, after the computer had been invented in the mid 40’s, most people and even the experts could hardly see any need for such clunky and cumbersome machines. To such an extent that in 1947, Thomas Watson who was then the Chairman of IBM, declared: “I think there is a world market for, maybe, five computers”. Have you looked around lately? That was barely what, fifty, sixty years ago?

On the other hand, there are certain predictions that can safely be made because they are for the near future: we have identified the problems to be solved and we know the approaches needed to solve them. So let me now turn to human biology, which is really my field. To begin with, medicine as you know it today will never be the same in the years to come. Most households will be directly linked to core medical facilities through the Internet not only for diagnostic purposes as already done today, but even for health management.

I believe we will be able to eradicate most tropical diseases propagated by mosquitoes, flies or waterborn parasites such as malaria or dengue fever, trypanosomiasis such as sleeping sickness, leishmaniasis, and so forth.

The role of genomics will become preponderant in the prognosis, diagnosis and treatment of diseases such as cancer. The cost of gene sequencing will be reduced to the extent that we will be able to determine the genetic make-up of most patients for individualized and personalized medicine. This will allow us to decide which treatment, which drug would be the most appropriate, predict which patient would be the most likely to suffer a recurrence, etc. Today, we administer the same drug uniformly to most patients for a given condition, not knowing whether it will be effective, ineffective or perhaps even harmful. Drugs will be selected, if not taylor-made, for particular patients.

I can safely predict that we will have cures for many forms of cancer because we begin to understand the complexity of the disease. We know now that cancer arises from a series of genetic changes that occur over a period of many years, and that these, in turn, trigger multiple oncogenic events that collectively contribute to the advanced stages of the disease. But we know many of these steps and have characterized most of the major pathways involved. To such an extent that, I'm convinced, sooner or later (and probably sooner than later), we will be able to put all this information together and bring many forms of cancers under control.

In spite of its ups and downs including some severe setbacks, gene therapy (already used to target various hematopoietic diseases such as sickle cell anemia, ß-thalassemia or X-linked Severe Combined Immunodeficiences (X-SCID)) will become a reality and of widespread use, and we will learn how to regenerate tissues and perhaps organs through the use of pluripotent stem cells. And this brings me to the second extremely important –and equally controversial- problem that I want to bring up, namely, stem cell research as a means to cure diseases.

You have all heard about stem cells and know the tremendous potential they have to cure various diseases because of their ability to develop and to differentiate into any types of tissues. Indeed, they can be coaxed to become a heart cell that beats, a liver cell that produces glucose or a pancreatic cell that produces insulin, a brain cell that might be used one day to cure Parkinson's or Alzheimer's disease or a nerve cell that might help us repair a spinal cord injury. But we don't know the commands that will tell those cells to go where they are supposed to go, to become what they are meant to become. We know that they involve very intricate set of signals coming in part from other type of helper cells which they need to grow; the addition or removal of amaze of hormones, neuromediators, growth factors, cytokines, etc., but we don't know what these signals are though we begin to understand how they are received by the cell and how they are processed. It is an enormously complicated problem that has to be investigated, but for that, we need all the help we can get. And foremost among these is the possibility of utilizing the very versatile and pluripotent embryonic stem cells for therapeutic purposes, of course, and only for that purpose. I am not speaking of cloning an organism or a human being. This is totally unacceptable, aside from being nonsensical and stupid. This should be absolutely forbidden.

Now, of course, I am well aware of the bitter controversies that have surrounded this issue, deeply rooted in highly personal, emotional, ethical and religious considerations and further immersed in complicated, volatile and often irrational politics. Frankly, I see absolutely no immorality whatsoever in utilizing embryonic stem cells for therapeutic purposes when those same cells that have outlived their original purpose are piling up in the deep freezers of fertility clinics throughout the world and are destined to be discarded sooner or later anyway. At last count, there are more than 300,000 such embryos, stored in liquid nitrogen, waiting to be discarded as hospital waste because there is nothing else that can be done with them. On the contrary, for me, the real immorality is to destroy senselessly those cells that are so enormously precious, to discard them when their therapeutic use could give measure of hope to the sick that he might be cured one day, or to the paralyzed that he might walk again. The gross immorality for me is to prevent health scientists from studying this enormously complex problem when all the wisdom, knowledge, experience and expertise they have accumulated could be placed at the service of humanity. It is as if I had in hand medicine that would cure a sick person begging for my help, and I refused to give it to him.

For me, this is what is disheartening about the misconceptions many people show toward biology today: some see it as the universal panacea, as the remedy to all our ills while others suspect it of harboring dark imperialistic if not monstrous designs. Biology deserves neither this excess of praise nor this indignity.

Now, let me at last conclude by saying a few words about Science itself and the nature of scientific research, particularly for the benefice of the young fellows that are here and might want to go into that direction. At the onset, when a research scientist selects his research project, he must rely heavily on his imagination and on his intuition. In a way, he must invent his field of investigation just like an artist creates his own work of art. Like a visionary, he must see things that don't yet exist, but might. His success will depend on the depth and originality of his vision. To paraphrase Ed Wilson, the Harvard entomologist, "To the inept hunter, the woods are always empty".

But this is where the analogy between the sciences and the arts ends, where they go their separate ways. Because in science, every result obtained must be rigorously checked and rechecked; every experiment must be repeated time and again before being finally accepted. In science, nothing is acquired for good, nothing is absolutely definitive. As Einstein once said: "No number of experiments can ever prove that I am right, but a single experiment, at any time, can prove that I am wrong". Some people consider this element of uncertainty, of doubt as one of the major weaknesses of science, as one of its failures... For me, it is one of its finest qualities, as its real grandeur. Science teaches us that there is no single, absolute truth and, particularly, that the possibility always exists that one might be wrong. If everybody could accept this premise, this idea that **they might be wrong**, it would be put an end to fanaticism, all forms of fanaticism: political, moral, ethnic or racial and particularly, an end to religious fanaticism.

Anyway, from this point on, then, science builds on science where every answer obtained suggests the next logical question, and every question asked suggests the next experiment so that what will not be done today by one scientist will almost inevitably be done tomorrow by another. For instance, if Newton, Darwin, Pasteur or Einstein had never existed, how long would it have taken for others to come up with the same discoveries? Not that very long. For instance, Einstein's ideas about relativity were already kicking around, and all the things he did would have eventually been done. Not by one single person as he did, of course not: This was Einstein's extraordinary genius, but by many, working independently and arriving ultimately at the same result.

What this means is that in science (and I consider this a rather humbling thought), very few people are really indispensable. This is in sharp contrast with what happens in the Arts. Because if Mozart had never existed, nobody, but nobody, would have ever written his G-minor symphony, or *Don Giovanni* or *Cosi fan Tutte*. Or Schubert his *Schöne Müllerin* or *Der Winterreise.* Not in a million years. Artists shine by their uniqueness, by their individuality. This is why works of arts, paintings, sculptures, the treasures of architecture are so enormously precious and should be protected at all cost and under any circumstance. Because once they are destroyed, they are gone forever.

But then, coming back to science, its beauty is that everything is possible. It places the world at the tip of your fingers. Because whenever you consider a new project, any new project, you know where you start from but never know where you will end up.

Well, this is all I wanted to tell you here. I am delighted to have had this opportunity to visit once again your beautiful country, which has such incredibly historical past and rich artistic dimension. Thank you for your warm welcome and thank you for listening.