The master of high blood pressure

The physiologist who created Brazil's leading team at InCor to conduct integrated research on blood pressure

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When Eduardo Moacyr Krieger, a native of the State of Rio Grande do Sul, received his medical degree in the city of Porto Alegre in 1953, one of his main objectives was to become a cardiologist and work at the Medical School. However, under the decisive influence of two prominent Argentineans (physiologist Bernardo Houssay, recipient of the Nobel Prize in Physiology or Medicine in 1947, and Eduardo Braun Menendéz, who discovered angiotensin in 1940), Krieger decided to change his career goals. As a result, Brazilians have a strong reason to be thankful to these two Argentinean mentors: the fields of cardiovascular physiology and, more specifically, the field of blood pressure research have benefitted the most from Krieger's work. Professor Krieger, now 84 years old, contributed enormously to the understanding of the mechanisms that control blood pressure. In addition, in the 1950s, he organized a prominent research group at the Medical School of the University of São Paulo (USP) in Ribeirão Preto. In 1985, he created Brazil's most highly respected integrated team for research on blood pressure, which was based at the Heart Institute (InCor) of USP's Hospital das Clínicas teaching hospital in São Paulo.

Krieger, who is one of nine children of a retailer of German descent who had settled in the town of Cerro Largo near the border of the State of Rio Grande do Sul and Argentina, was the only one of the nine to receive higher education. In addition to working as a professor and a researcher, he was actively involved in the politics of the academic community. One of his outstanding achievements was his 14-year term as chairman of the Brazilian Academy of Sciences (ABC). During this time, he worked tirelessly to improve the position of Brazil's scientific community and its scientific endeavors on the international stage.

Professor Krieger has two children, the well-known scientists José Eduardo Krieger and Marta Helena Krieger, and three grandchildren. He and his wife Lorena have been married for 55 years. He has also has been the vice-chairman of FAPESP since 2010. Currently, he is concluding one additional thematic project developed under his coordination and is preparing to take on a new challenge, that of organizing the discipline of translational medicine and the related department at InCor. Below are excerpts from the interview he granted to *Pesquisa FAPESP*.

Let's start by talking about the line of research that you have dedicated most of your attention to: the mechanisms that regulate blood pressure. How your interest in this area first aroused?
Actually, my interest was aroused when I began my scientific career. I had just graduated from the Medical School in Porto Alegre and met a group of Argentine physiologists led by Professor Bernardo Houssay, the 1947 Nobel laureate in Physiology or Medicine. His disciples included Eduardo Braun Menéndez, who had discovered angiotensin in 1940. Angiotensin is one of the substances that regulate blood pressure. At this time, I wanted to follow an academic career path. In 1954, this group came to Porto Alegre under a program organized by the Coordination for the Improvement of Higher Level Personnel (CAPES). The members of the group took turns coming to Porto Alegre, where they would stay for one month at a time. Bernardo Houssay himself spent some months in Porto Alegre. At that time, I was interested in cardiology, so I worked with Braun Me-

néndez. Then, I went to Buenos Aires, where I stayed for seven or eight months, working on the renin-angiotensin system.

At whose laboratory?

In Buenos Aires, I worked in Professor Bernardo Houssay's lab, who had had been out of the university community for nearly 10 years. Because the group had protested against the military dictatorship, it had been expelled from the Medical School in 1943. Houssay, a patriot, always said that science did not have a mother country but that a researcher always did. Although Houssay was a Nobel laureate, he refused to leave Argentina, where he worked under very poor conditions. His workspace consisted of a house that belonged to the very wealthy family of Braun Menéndez, where each room had been turned into a lab. The house was on Costa Rica Street in a distant neighborhood [Palermo]. The people from the medical school no longer knew Bernardo Houssay, but prominent researchers from all over the world would come to his lab every week. It was a fantastic environment. There was a small house next to the big one that was accessed via a gate in the garden, and this smaller house was the site of Louis Leloir's biochemistry lab. Leloir won the 1970 Nobel Prize for Biochemistry, and this was an environment populated by current and future Nobel Prize laureates. I joined it thinking that I would only go through an internship and then return to Brazil to specialize in cardiology, but this environment stirred my interest in basic research. As a result, I went to the United States to conclude my scientific training at the University of Georgia, in the southern US. Bernardo Houssay suggested that I go there because that was where the best cardiovascular physiologists were working at the time. I had gotten a grant from the Rockefeller Foundation, which had suggested that I go to a university on the East Coast or the West Coast. However, Houssay suggested that "the University of Georgia might not be the best university, but it has the top cardiovascular researcher."

And who was he?

William Hamilton. He and Raymond Ahlquist, who was also at the University of Georgia, had discovered the alpha and beta adrenoreceptors, and I learned

all about these receptors from the people who had discovered them. This was good; I stayed for a little over a year and took part in a fantastic cardiovascular physiology and pharmacology training program. While I was in the United States, I received an invitation to go to Ribeirão Preto. The university in Ribeirão Preto was getting organized and looking for prominent professionals from abroad; it wanted to hire someone who had been part of Bernardo Houssay's group. The university found Miguel Covian, who was from Argentina. He came to Ribeirão Preto and invited me to organize a cardiovascular group. I made my decision in the United States, and rather than returning to Porto Alegre, I moved to Ribeirão Preto. I knew nothing about the university except that it was part of USP and that it was a good reference center. I also knew that the university was heavily funded by the Rockefeller Foundation, which meant that the faculty could focus on scientific work. I arrived in Ribeirão Preto in 1957. The first group of undergraduates had entered the university in 1952 and graduated in 1957. Thus, I came into a prominent, captivating environment at USP's second medical school that was completely focused on research.

Basic research?

There was clinical research as well. Ribeirão Preto was a pioneer and exclusively dedicated to the field of clinical studies in Brazil. I started researching pressure regulation during hypothermia until equipment from the United States arrived. For these experiments, I studied reflexes to analyze how the nervous system and the regulation of pressure functioned at increasingly lower temperatures. I also had to stimulate the system using various forms of reflex, central or peripheral stimulation. This was very interesting, and during this research on reflexes, a field I was familiar with, I discovered that the nerve that controls and provides information on arterial pressure in rats, which receives information from what we refer to as baroreceptors or pressor receptors, was isolated from the cervical region. As this discovery of the isolated nerve was novel, I decided to conduct a systematic study of the pathway controlling the rat's pressor receptors. As a result, I was able to demonstrate total denervation of the system, a model that is still in use today. This component of my research has been cited most frequently, approximately 600 times. The study was published in 1964 in *Circulation Research*, a leading journal. Interestingly, this important research stemmed from a casual observation, one that I was not looking to make. However, after I had come across this nerve, I decided to conduct the systematic study, which resulted in several papers involving how traffic in these nerves takes place and what their blood pressure regulation characteristics are in rats.

Do you remember the day you discovered this?

I do. It was in the late 1950s or early 1960s. We didn´t yet have any students enrolled in postgraduate programs (postgraduate students came to the university from 1970 onwards), but a group from Buenos Aires would come to Ribeirão Preto during vacations, and each lab would show the group what it was working on. While doing some demonstrations for the group, I noticed that when I stimulated the central part of the vagus nerve, the pressure would sometimes go up but other times would go down. I found that rather strange, and one day I told the group during my demonstration that I would try to find out whether my hypothesis was correct, i.e., whether the curare I was giving the animal was causing response inversion. So, I administered the curare, stimulated the vagus nerve, and nothing happened. I decided to use a stronger magnifying glass and noticed that it was not only one nerve but actually two nerves that were involved. I also noticed that there was a small nerve – the sympathetic nerve – next to the larger nerve, which could be easily isolated when it was stimulated in the center. In most species, the smaller nerve is not separate from the larger nerve, but this was not the case in rats. So, I stimulated both nerves and found that one showed a drop in pressure while the other showed an increase in pressure. These results suggested that, in rats, one could isolate the sympathetic nerve from the vagus nerve and that the sympathetic nerve had aortic pressor receptor fibers. This was astonishing!

Your conclusion was: "I had just discovered something that nobody was aware of."

I conducted a systematic study and published several papers on traffic in these nerves; two or three of these papers described the possibilities of working with rat pressoreceptors. Then, I wrote a well-known paper on the denervation of the pressoreceptors. I got really excited because one of the most important aspects of my work was to discover how the nervous system adapts to hypertension, and the pressoreceptor is continuously a part of this process; at each heartbeat, the pressoreceptor is discharged because the pressure increases, distends the vessel and excites the receptors. Moreover, the pressoreceptors are the main source of information that enables the maintenance of blood pressure at normal levels. As pressure increases and the discharge increases, the inhibition of the sympathetic nerve causes the pressure to go down. Likewise, exciting the pressor receptors stimulates the vagus nerve to reduce the heart rate and cardiac output, which results in normal blood pressure levels. It is widely known that chronic hypertension does not provoke bradycardia, which shows that this reflex has adapted. Thus, I decided to study how this nerve functions under high blood pressure conditions. It had been shown that when acute hypertension occurs, these nerves adapt after a given period of time, which is why a person with high blood pressure does not experience a reduction in heart rate. However, this situation can occur if the pressure goes up suddenly, due to the reflex. In other words, the reflex adapts itself chronically.

You referred to bradycardia.

Yes, a slow resting heart rate – one of the leading indicators of how the pressoreceptor is functioning. When you increase the stimulus, this produces bradycardia and vasodilation because it changes the sympathetic nerve. This is the main reflex and is adapted in hypertension, which was common knowledge. However, the challenge was finding out how this occurs. Studies had been conducted with dogs in which adaptation began four or five days after the arterial blood pressure had increased. In the case of the rat – a model in which pressure can be better controlled – one of my early studies focused on the adaptation sequence of pressor receptors in hypertension. I triggered sudden

hypertension by compressing the aorta coarctation. I maintained the pressure at a high level and showed that a slight adaptation, approximately 30%, had occurred after six hours, whereas after 48 hours, most of the animals had adapted. What is adaptation? Adaptation is the movement of the stimulation threshold and the functioning range of the pressor receptors. I showed that full adaptation takes 48 hours, although in some animals, it may take more or less time. On average, nine out of every ten animals had become fully adapted within 48 hours. I conducted many studies on this topic to show how, when pressure returns to normal, the adaptation becomes normal as well. I also built kidney hypertension models, which is something I had done a long time ago with Braun Menéndez, by placing a clip on the renal artery to keep the rat's arterial pressure chronically high and the pressoreceptor adapted. I would also suddenly revert the hypertension by removing the clip and check how much time this would take, and I observed that six hours were necessary for the reversion. By doing so, I was trying to understand how the main reflex control mechanism works during increases and decreases in blood pressure. For example, does the mechanism adapt itself and how? Later, I found that the mechanism adapts itself and its functioning range increases in response to hypertension levels, although the sensitivity changes. Specifically, the mechanism becomes less sensitive, and I was the first to publish this finding in the literature. We were able to test the sensitivity of the mechanism by acutely varying the pressure and observing how the discharge of the pressor receptor located on the artery wall behaves. As this pressoreceptor sends information to the central nervous system, it was possible to compare the discharge curve of a normal animal to that of an animal with high blood pressure, and the latter curve was shown to be a sloping one.

Was that the article from 1970?

No. The 1970 article demonstrated the sequence of the adaptation. Later, I published many papers showing this reversion, and I published other papers showing that hypotension, which is very rare in clinical terms, also goes through this adaptation in approximately 48 hours and that the reversion is quite fast. Sensitivity is another issue, and this topic has regained clinical importance. For example, a patient with hypertension for any reason, where the main regulation mechanism is adapted yet shows decreased sensitivity, has a less efficient pressure control mechanism. Blood pressure changes from one moment to the next; when an individual is sleeping, sitting, getting up, or running, the pressure goes up or down according to the physiological circumstances. If the regulating system is less efficient, the fluctuations are sharper, and this happens because individuals with high blood pressure have a less sensitive pressoreceptor and their blood pressure levels can therefore fluctuate significantly. So what does this mean? It has already been proven that the level and variability of blood pressure can seriously damage the vessels. In the last few years, practitioners reinitiated an effort that hadn't worked very well in the past; specifically, they have stimulated the pressoreceptor to change the sympathetic nerve and reduce the arterial blood pressure. Technological improvements have made it possible to implant electrodes in the patient's carotid, and it seems that these electrodes do not damage the vessel significantly and can stimulate the site. Several papers have already been published showing that stimulating the baroreceptor in resistant hypertension is a possible therapeutic measure.

Houssay always said that science did not have a native country but the scientist does; this is why he never wanted to leave Argentina

What is the role of the kidney in regulating arterial blood pressure?

There is no doubt that primary hypertension is due to several factors, such as the imbalance between pressor and depressor mechanisms. The sympathetic nerve, which controls the calibration of the vessels and cardiac output, was the first pressor mechanism studied by researchers. This research was followed by studies on the renin-angiotensin system. Renin was discovered in the late nineteenth century, but angiotensin, the factor that increases blood pressure, was discovered by Braun Menéndez and by [Irvine] Page from the United States. These discoveries focused attention on the mechanism of the renin-angiotensin-aldosterone system. Angiotensin stimulates the adrenal gland to produce aldosterone, which provokes salt retention, and these mechanisms are well known. Depressor mechanisms involve the kinins, such as bradykinin, which was discovered in 1948 by Maurício Oscar da Rocha e Silva from São Paulo's Biological Institute. Enormous progress was made when Robert F. Furchgott, also a Nobel laureate, discovered twenty years ago that the endothelium, rather than merely protecting the vessels and preventing coagulation, is also a factory of hypertension and hypotension components. It was further discovered that nitric oxide (NO) acts on hypotension and exerts a tonic action. Each system previously believed to have a pressor or a depressor action was in fact shown to have both pressor and antipressor elements. Therefore, the pressure regulation mechanisms became very complex. So what causes high blood pressure? Based on existing data, we first know that the arterial blood pressure control system is very closely linked to genetics, as the synthesis of the pressor and depressor mechanisms is performed according to specific genes. Therefore, the genetic load may facilitate

the production of pressor substances or may produce less hypotension-inducing substances. As a result of an individual's genetic load, there is either the tendency to have high blood pressure or not. However, it is not enough to have a genetic predisposition; the environment also continuously affects the regulation of arterial blood pressure.

When you say the environment...
This includes salt, lack of exercise, obesity, stress, and, more recently, inflammation. All of these elements have an impact, in one way or another, on the regulation system. Therefore, if an individual has a very good regulation system, nothing will cause an impact on blood pressure; however, if an individual has a very poor regulation system, he or she will have high blood pressure regardless of salt intake or exercise. This combined effect of the genetic load and the environment represents the current dogma for primary arterial hypertension. It is currently very difficult to analyze the genetic component, but in the future, we aim to address each individual's genetic load. When this becomes possible, individuals will likely receive marriage counseling in relation to their hypertension genetic status.

You had already been working in the field of physiology, regulation mechanisms, etc. when many advances were made in the field of genetics in recent years. To what extent did these advances help your experiments?
For 28 years in Ribeirão Preto, my numerous postgraduate students and myself worked on lines of research that were mostly linked to the nervous system and to the regulatory mechanisms of arterial blood pressure. I subsequently came to São Paulo and continued working on this line of research.

When did you come to São Paulo?
I retired from Ribeirão Preto in 1985 and came to São Paulo at the age of 56 because I had been invited to research hypertension at InCor in an integrated manner. This is when the clinical part of my research began. I continued doing my experimental research because this was what I knew how to do and I had obtained international recognition for my efforts, but I also wanted to do clinical research. In Ribeirão Preto, I had worked in the Physiology Department with lab animals, but, in São Paulo, I had the opportunity to develop a line of research with patients. I studied pressure regulation during sleep and exercise and wanted to understand the influence of reflexes on arterial blood pressure by investigating the pressoreceptor and the chemoreceptor, the cardiopulmonary system. We developed a technique to register the sympathetic nerve, and therefore the functioning of the nervous system, using a needle placed in the peroneal nerve. We were able to observe the basal activity of the sympathetic nerve and how it behaves under different circumstances. In short, we set up an extensive line of research and also studied the role of pressoreceptors in the sleep mechanism, based on the sleep research of one of our collaborators, Geraldo Lorenzo, from InCor. One of the important research topics concerning hypertension at InCor is pressure regulation during sleep. Apnea is closely linked to arterial blood pressure, and the oxygen level increases along with the carbon level during apnea, which stimulates the chemoreceptors located in the carotid that are sensitive to the tension from gases. When a person stops breathing, the gases change, the chemoreceptors are stimulated and the pressure goes way up. After a while, the effects of these spurts have permanent consequences.

A person with a poor regulatory system can refrain from eating salt and exercise and will still have high blood pressure

Does sleep apnea alter the blood pressure?
It is very common for apnea to be associated with hypertension. However, an individual's blood pressure tends to fall when the apnea is addressed.

To continue, this interaction...
This is where the clinical part comes in. We have worked with clinicians, cardiologists, and pneumologists, as well as the physical education professionals who are part of the group headed by Carlos Eduardo Negrão, who was a member of our group and had worked on experiments with lab animals and then with human beings. Negrão is now pursuing an independent line of research. In regard to nursing, I started working on projects involving nurses who had had issues with patients' compliance with treatment. This was followed by work on molecular biology, which was included in a very interesting way. My son graduated from Ribeirão Preto in 1984 and then went to the United States to join the doctoral program on classic Guytonian physiology. Guyton was one of the world's foremost physiologists. My son concluded his doctoral program in early 1990, when molecular biology was beginning to play a major role in hypertension studies. He concluded his doctorate and went to Harvard and then to Stanford to study the molecular biology of hypertension. He joined our group after he returned to Brazil. Our first research work together was to mate rats with high blood pressure to normal rats. After the rats mated twice, their grandchildren displayed different blood pressure conditions. The goal of these experiments was to study these grandchildren; if they demonstrated high blood pressure, it means that they had inherited a predisposition from the grandfather with high blood pressu-

re. In addition, we studied the rats' genomes to detect differences in relation to the rats with normal blood pressure.

So this is when you identified some chromosome regions...
That was our first collaborative effort. We found five regions linked to hypertension. The projects that I submitted to FAPESP in the last ten years have always been integrated, with thematic projects comprising both experimental and clinical aspects. This is the type of work that I have done in recent years. Now, I am moving into another field, and I have organized a team of professionals from the fields of physiology, clinical medicine, molecular biology, physical education, nursing, psychology and nutrition who are all focused on studying hypertension.

So this research group is at the forefront of research work on hypertension.
Undoubtedly. Our group is quite distinct. One of the first members to leave the group went to Milan to study the monitoring of arterial blood pressure. Another member went to Paris to study the elastic properties of vessels and how they change under hypertension. Another member went to Charleston to study metabolism in relation to hypertension. Then, one more left to study neurogenetics, and the last member left to study sleep apnea at Johns Hopkins. This group from InCor is at the forefront because it integrates knowledge from world-renowned institutions.

And you, as the founder of the group, must feel very proud of this.
Yes, I am. In Brazil, I trained 32 or 33 PhDs, 10 of whom have become full professors. We have really good people working in our group. There is also a physiology group in the city of Belo Horizonte that is one of the world's foremost groups in this field. This group is studying angiotensin 1-7, which is different because it's the "good" angiotensin. Headed by Robson Augusto dos Santos, this group patented compounds with the potential to become drugs, which are being developed in partnership with Brazilian labs. Maria José Campagnole dos Santos is another full professor, Maria José and Robson worked with me in Ribeirão Preto, and then there's Kleber Franchini, in Campinas, who was my doctoral student. Franchini developed a molecule and is now trying to do something innovative with the Brazilian pharmaceutical industry. The group in Ribeirão Preto has two or three full professors, and Lisete Michelini, who leads cardiovascular physiology at USP's Biomedical Sciences Institute, worked with me in Ribeirão Preto.

You have written more than 200 scientific articles. Which was the article that contributed the most to knowledge on hypertension?

We found five chromosome regions linked to hypertension in our first research study on molecular biology

I would say it's the series of articles in which I explained how pressoreceptors function, regarding the adaptation sequence of these receptors in hypertension and hypotension and their sensitivity. Lisete Michelini and I studied their adaptation mechanism and showed that this adaptation sequence is the same as that which occurs during the dilation of the aorta in the case of hypertension. We associated this adaptation with the changes that take place in the vessels. By the way, I had an outstanding colleague at the Physiology Department in Ribeirão Preto, José Venâncio de Pereira Leite, who was extremely knowledgeable about science and was also very cultured. We would tell him about our problems, and he would try to solve them. As a result, I told him that I wanted to observe the behavior of the location where the pressoreceptors are found in acute hypertension. The literature refers to the Strain Gauge [a device used to measure the stress of an object], which was a Silastic elastomer with mercury on one of the tips of the Wheatstone bridge [an electrical circuit used to measure electrical resistance]. The Silastic was typically placed in the heart, or elsewhere, and has been widely used in medicine. However, this was impossible to do with the rat's small aorta because the mercury would be damaged. However, José Venâncio found a way, and he prepared a saturated copper nitrate solution that worked beautifully. We placed the Silastic in this liquid, which is a conductor and has some stability, for two or three days, which gave us enough time to carry out the experiments. Venâncio developed this solution together with Lisete, who was enrolled in the postgraduate program at the time. We were able to do several major studies showing how the aorta's caliber functions in hypertension. We also compared the adaptation time to the time it took the vessel to change, and we observed that the vessel adapts itself. During the first six hours, the vessel resists the increase in pressure, but subsequently, the pressoreceptors undergo a slight adjustment. The full adaptation takes 48 hours and varies from one rat to another and takes place when the aorta distends. The aorta reaches a new threshold and starts working normally, so to speak. That was how it worked previously, when the receptor was there; now it works with a dilated caliber, and the receptor is stimulated in a similar but not identical manner because the sizes are different and the sensitivity is reduced.

When the aorta is enlarged because it has adapted itself to the process, doesn't the blood flow more slowly? Doesn't the circulatory system slow down?
No, because hypertension occurs at the level of the arterioles, which is where the resistance increases. The aorta suffers the consequences of having to increase

the pressure to overcome this resistance. The aorta adapts itself because of its elasticity, and it stores a portion of the systolic volume. The heart beats, and, if the artery were stiff, the blood would flow directly to the capillaries and no blood would flow during diastole, which would result in fainting. The artery system is very interesting because the arterioles are highly resistant; they resemble tightly shut water faucets. So when the heart expels the blood, it has a higher possibility of distending the large arteries to accumulate the blood rather than to let it flow. As a result, the arteries accumulate blood. When the heart stops expelling the blood and goes into diastole, which lasts twice as long as systole, the large arteries release the blood that they had accumulated. In the capillary vessels, where the exchange occurs, the flow is continuous as a result of this fantastic but very dangerous mechanism, as any changes in the arterioles can induce hypertension. This is a fantastic mechanism that nature created, and the system would be very precarious if this mechanism didn't exist. A high-resistance elastic chamber is necessary for oxygen to reach brain cells that constantly require new blood.

You are about to resign from your position as coordinator of the group at InCor. What are you planning to do?

I have two tasks to conclude. One is a thematic project that should take another year or so. Specifically, we are trying to obtain biomarkers to assess patients' therapeutic evolution and to see whether a patient responds or not to a given treatment. The other project, which is conducted under the Ministry of Health and the CNPq, is related to resistant hypertension. Specifically, 26 research centers and universities are participating in this project, which is designed to enumerate the percentage of the Brazilian population that is resistant to hypertension treatment.

Is there any hypothesis?

Yes. In developed countries, 20 to 30% of patients continue to have high blood pressure even when they receive optimal treatment. However, there are no extensive studies on this in Brazil. We will evaluate patients who first undergo standard treatment with controlled, optimum doses, and then we will monitor the pressure to discover the percentage of resistant individuals. Then, we will randomize the resistant patients to determine the best medication for them, potentially one that will act on the central nervous system or the renin-angiotensin-aldosterone system. This is translational medicine, which involves two aspects. The first aspect translates research results into clinical applications, whereas the second aspect transforms clinical findings into public health measures. This project will be concluded in a little over a year, and we have already recruited one thousand of the two thousand patients we need to conduct the project.

My most important research studies describe the action of pressoreceptors on hypertension

The concept of translational medicine was developed approximately 10 years ago...

The theme is new, but the idea of translational research is not that new, as it goes back to the 1940s. Silicon Valley was established in partnership with Stanford University during the war because of the need for military technology, which illustrates the speed at which knowledge moves from universities to the private sector. This was the beginning of a virtuous cycle, which resulted from the fast pace at which knowledge was translated into application. However, medicine took a long time to accomplish this translation, and translational medicine became part of the medical field only 12 years ago. First, the Institute of Medicine of the US National Academy of Sciences began to discuss why clinical investigation did not advance at the same pace as basic, first-rate biomedical research. The NIH [National Institutes of Health] was concerned about this issue, and the matter moved forward when Elias Zerhouni became the president of the NIH. He prepared the so-called road map of the NIH that included three major areas: strategic topics that needed to be studied; multidisciplinary teams; and the re-engineering of clinical investigation or translational medicine. Zerhouni felt that an effort had to be made for clinical investigation to benefit public health. A program was created to fund translational medicine centers at universities, and this program began in 2007 and 2008 with the participation of 10 or 12 universities; currently, 40 or 50 universities have benefitted from this program. The NIH intends to fund the management of university research projects, with the goal of establishing a center of integration at the university, especially in the field of health, to foster basic knowledge through interaction with other fields of study (physics, chemistry, information technology, etc.). In addition, the NIH hopes that clinical trials can be quickly translated into clinical practice and public health. I recently visited the University of Pennsylvania, which has an amazing translational medicine center.

So you decided to organize something similar in Brazil?

Yes, I have thought about this. InCor was created to be a translational center; it was based on the concept that clinical knowledge must be translated from the bench to the bedside. In addition, I decided that the time had come to introduce a field of study called 'translational cardiology'. My objective was to help researchers conduct projects and

introduce innovations, one of the elements that permeate this field of medicine. A symposium on innovation was held at InCor, at which I spoke about the "Lei do Bem," the federal and state laws that address innovation. I stressed the importance of setting up technological innovation departments at research and university centers. I am also helping the director to make the Medical School's activities more international.

Tell us about your experience at the Brazilian Academy of Sciences.
I was part of the Academy for fourteen years. I became its chairman in 1993, and, in 1997 or 1998, the Academy was invited to join a federation of academies, namely, the Inter-Academy Panel/ IAP, which has nearly one hundred members. We had a meeting in Tokyo in 2000 at which the IAP's by-laws were approved. I was elected chairman to represent developing countries, and my term lasted from 2000 to 2003. I also represented the ABC at the Interacademy Council, which is comprised of thirteen academies. These two organizations enabled the ABC to gain international exposure. I became acquainted with scientific politics, how the academies help each other, and the global issues that academies and researchers should be concerned about. It is important to emphasize that my term as president of the ABC coincided with the opportunity to participate in the national political world. José Israel Vargas had been appointed Minister of Science and Technology when he was vice president of the ABC, and he promoted the academy, which gained nationwide exposure. The SBPC was the dominant entity, but we were able to balance the game, and currently both entities are considered equally important, as they understand and help each other.

You helped to create the Brazilian Journal of Medical and Biological Research.
I was the chairman of the Brazilian Society of Physiology, and we had discussed with professionals from the field of biochemistry that the time had come for the basic fields of biomedicine to create a national journal in English, as this field had grown considerably and many papers had already been written. We were contacted by the physiologist Alberto Carvalho da Silva and by the people from the CNPq concerning the hematologist Michel Jean, who had created the indexed *Revista Brasileira de Pesquisas Metrobiológicas*. They wanted us to become involved in the journal, but we wanted to promote a journal in English. The solution was to change the name, and Michel told me the following: "I'll pass the journal on to you to do whatever you see fit." The CNPq supported the idea, and so that's what we did. To make the journal feasible, we set up the Brazilian Association for Science Dissemination (ABDC), which comprised the same societies that would subsequently (four or five years later) become part of the Federation of Experimental Biology Societies/Fesbe. We created an association that would act as the owner and publisher of the journal. I became chairman of the association and the editor of the journal, together with Sérgio Henrique Ferreira. I was also a member of FAPESP's magazine committee. I worked with librarian Rosali Duarte, who came from the *Revista de Genética*. We realized that we had requests for journals, but we didn't know what this meant. So, we prepared the first paper to be published in Brazil concerning the qualification of journals. Thus, one of our papers contained the first classification of journals, but we had to do that to decide what the next step would be.

InCor was based on the idea that knowledge must be translated from the bench to the bedside

What was your most important achievement among all the accomplishments that you achieved in scientific politics?
My term as ABC chairman was my outstanding achievement, as this enabled Brazilian science to gain national and international recognition. Another achievement was the academy's recognition as an advisory entity to the federal government. I am still a member of the National Science and Technology Council, which reports to the President, and I always insist that the council must function more efficiently. The foundation of FESBE was important as well, as was the creation of the Brazilian Society of Hypertension. I have always been a member of different associations because I have always worked in labs; I am a professor, a scientist and an activist. When we established the IAP, Bruce Alberts, who had been the chairman of the American Academy for 12 years, wrote an article that I really enjoyed reading. His thesis was that academies should become more activist. A scientist's social obligation is to make sure that science results in benefits for society, and my current effort is to view medicine with a focus on prevention, as prevention entails education.

Does your relationship with translational medicine reflect this concern?
It is the focus. We are scheduling an international conference on medical education to be held at the medical school. We cannot train a physician who is knowledgeable about all fields of medicine but has no idea of primary care. Medical students must learn how to prevent and cure diseases. We do not have enough financial resources to provide technologically sophisticated treatment, so we have to put disease prevention in the spotlight because this is much cheaper and has greater repercussions. This will enable people to enjoy good health for longer periods of time. ■