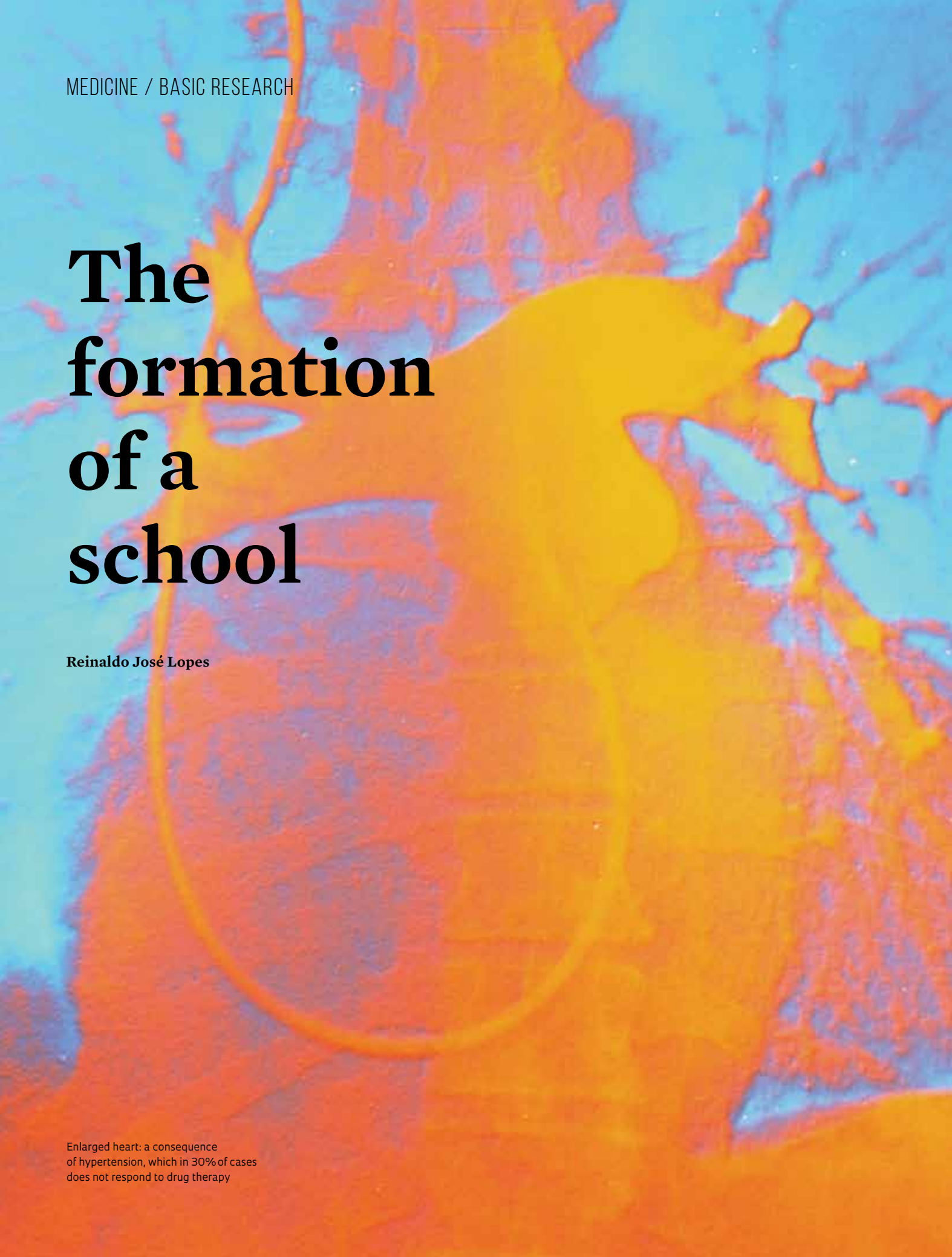
# The formation of a school

**Reinaldo José Lopes**



Enlarged heart: a consequence of hypertension, which in 30% of cases does not respond to drug therapy

**Beginning in modest circumstances, biomedical science groups are now in the forefront**

Dr. Eduardo Moacyr Krieger, 86, of the University of São Paulo School of Medicine (FMUSP), is enthusiastic about the preliminary results of a recent study in which he is participating: an analysis of about 2,000 patients with hypertension from all over the Brazil. The goal is to find out what proportion of them are resistant to the treatment for high blood pressure. In developed countries, up to 30% of patients fall into this category.

The good news: "The response of Brazilian patients to the treatment for hypertension has been really spectacular. The percentage of those with resistant hypertension is very low compared to the international average, provided that the patient receives all the necessary care. It is something comparable to the best results obtained in other countries. This will be very useful as a standard for the Unified Health System (SUS)," says Krieger, who cannot yet reveal the exact percentage because it is a multi-center study with 26 participating institutions.

Krieger's career and that of other scientists of his generation, many still active, is illustrative of the transformations and the considerable advances in biomedical research that have been made at Brazil's largest university. From modest beginnings, when USP researchers had to face challenges of infrastructure and public health or political persecution during the military regime, the university has been able to form groups that are carrying out ambitious projects of scientific and social impact, working in cutting edge areas such as cell therapy and personalized medicine.

### INSPIRED BY BUENOS AIRES

An interesting aspect of their origin is that many of the USP biomedical research groups received their inspiration and encouragement from Argentine researchers, who were already renowned as physiologists in the middle of the 20th century.

Among these figures was the first Argentine—and first Latin American—to receive a Nobel Prize for his achievements as a scientist: Bernardo Alberto Houssay (1887-1971), who won in 1947 for his work on the hormonal regulation of blood sugar levels. Under a program sponsored by the Brazilian Federal Agency for the Support and Evaluation of Graduate Education (Capes), the Argentine laureate and his colleagues visited Porto Alegre (Rio Grande do Sul State) in 1954. That's when Krieger, a newly minted doctor, met Eduardo Braun Menéndez one of the disciples of the Nobel laureate, and was invited to spend a few months in Buenos Aires working with the team.

The environment had to be improvised. Because of his opposition to the Argentine military regime, Houssay and his colleagues

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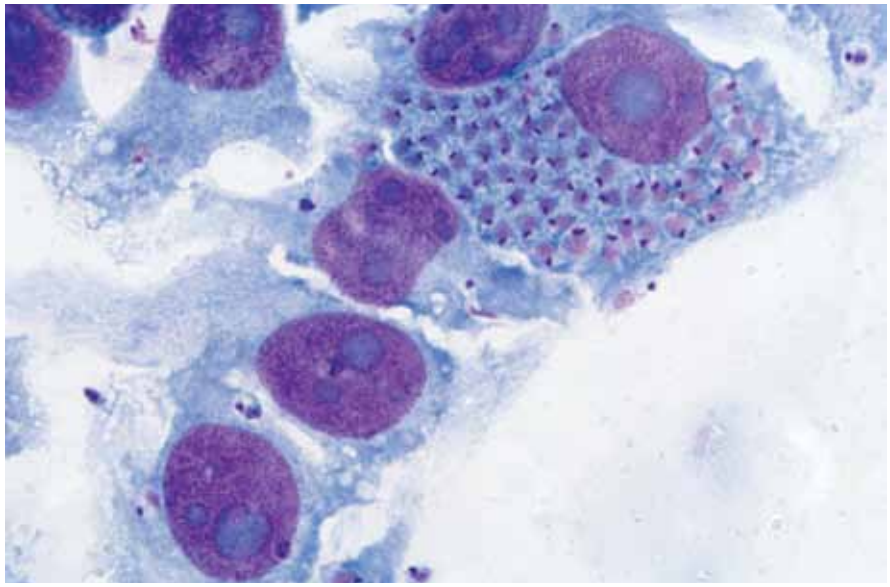


*Trypanosoma cruzi* under the microscope: its proliferative form (*smaller circles*) within a cell...

had been expelled from the University of Buenos Aires and forced to establish the Institute of Biology and Experimental Medicine in a house provided by Menéndez's wealthy family—a different laboratory in every room. But the intellectual fervor of that environment was so great, according to Krieger, that he fell in love with basic research and decided to deepen his understanding of the fundamentals of the cardiovascular system.

But the Argentine connection does not end there. Dr. Miguel Covian, another member of Dr. Houssay's group, was invited to join the Ribeirão Preto Medical School, established in 1951 by a São Paulo doctor, Zeferino Vaz, with a mission to become an institution dedicated to research. Since he knew Krieger from Buenos Aires, Covian called him to Ribeirão Preto, where the young doctor settled in 1957.

"I usually say that I became a physiologist only because I worked with a Nobel laureate in physiology," says Krieger. "This kind of leadership in research is fundamental to one's career because, after all, you learn science from those who know it, not from reading a book in the library. The training of a scientist is still very much like learning a craft: you start as an apprentice. And these great personalities are the ones who are enthusiastic and persuasive and who create a kind of genealogical chain of researchers." Coincidentally, with regard to the genealogy itself—not the metaphorical, involving teachers and students, but the literal, from father to son—the Argentine doctor also inspired Krieger's son, José Eduardo Krieger to follow in his footsteps. He now heads the Genetics and Molecular Cardiology Laboratory of the Heart Institute (InCor).

**DNA REVOLUTION**

Indeed, the atmosphere of that time both inside and outside the state capital involved some common ingredients. One of the most important was what you might call the first revolutionary phase of molecular biology, explains Dr. Erney Plessmann de Camargo, 79, a parasitologist at USP's Institute of Biomedical Sciences, who in the early 1970s, in a nod to university reform, brought together teachers and researchers from several of the university's basic science departments. Formerly scattered throughout various USP faculties, specialties such as histology, parasitology, immunology and physiology, in addition to others that today are the source of significant scientific production at the international level, migrated to the Institute on the main campus in the São Paulo neighborhood of Butantã.

**"Science is learned from those who know it, not from reading a book in the library," says Dr. Eduardo Krieger**

Camargo, who has done major work on the biology of Trypanosoma cruzi, the parasite that causes Chagas disease, cites several seminal discoveries that, during the 1950s and 1960s, seemed to finally be revealing the secrets of how life works from the standpoint of its molecular bases: the discovery of the famous double helix structure of DNA; the process of energy production in mitochondria, the "power plants" of cells; how proteins are produced in ribosomes. "The circumstances were very favorable for becoming interested in science, and we had great teachers to show that to us," he says.

According to Camargo, another reason he was attracted to parasitology was political: almost all the researchers involved in the field were politically left-leaning. "We were the red department of the School of Medicine," he jokes. Among his leftist colleagues were Luiz Hildebrando Pereira da Silva, who died in 2014 and was a little older than Camargo, and Professor Samuel Pessôa, a friend of military officer and communist leader Luis Carlos Prestes. The association between political engagement and the parasitology department, then located at the Medical School headquarters in the neighborhood of Pinheiros, was logical for many of these researchers, if one considers the link between poverty and serious diseases caused by parasites. "Professor Pessôa said he wanted to solve the problems of the Brazilian people," says Camargo.

If this view served to stimulate the scientific production of the group, it also placed its members in harm's way following the military coup of 1964. Several USP parasitologists were stripped of their political rights by the new regime, including Camargo. Both he and Pereira da Silva would later be arrested. Camargo would not return permanently to USP until the 1980s, welcomed at an event attended by about 200 people that served as the university's way of making amends to the formerly persecuted parasitologist.

To Camargo, although today's university environment at times seems less po-

**PHOTOS** LUCIANA LIMA / ICB-USP

liticized than the 1960s, the differences are not as great as one might think. "I do not believe that the intellectual and political structure of the scientific community has changed significantly since then. What changed greatly were the circumstances: the end of the specter of the Cold War, the end of the physical and cultural oppression when the military regime collapsed, and the continuing, though slow, humanization of capitalism. I'm fairly certain that if some kind of oppression were to return, the nonconformism of the scientific community would also return, and would again be called subversive," he argues.

Camargo is now engaged in trying to understand, in a broad sense, the evolutionary history of the trypanosomatids group, as it relates to causing Chagas disease. A wide variety of vertebrates, from fish to reptiles, are affected by these creatures, not only transmitted by insects known popularly as o barbeiro (the kissing bug), but also by ticks and leeches. Being able to study this fascinating evolutionary trajectory is, in part, a measure of the success of parasitology, he says.

"The parasitology of my early career had incredible sanitary and socio-political challenges linked to malaria, Chagas disease, schistosomiasis and diseases caused by other vermin. It was, quite correctly, a parasitology directed toward human diseases. Today, these problems are not on the same scale as at other times, nevertheless parasitology has become a very important branch of natural history, since parasites constitute the largest group of living things on the Earth."

## FROM BENCH TO BEDSIDE

At about the time Krieger was becoming established in Ribeirão Preto, the duo formed by Drs. Maurício Rocha e Silva (who died in 1983) and Sérgio Henrique Ferreira, now 80, did work that would become the basis for some of the first effective drugs for reducing hypertension. They analyzed, for example, how substances found in the venom of the Bothrops jararaca (pit viper) affects bradykinin, a molecule produced naturally by the body.

Later, Ferreira would explain the mechanism by which substances such as aspirin and morphine combat pain and inflammation. Today, younger colleagues of Ferreira at USP in Ribeirão Preto, like Fernando de Queiroz Cunha, are continuing this work in order to tackle diseases involving inflammatory mechanisms, such as sepsis (generalized infection), rheumatoid arthritis and psoriasis.

"You could say that Mauricio Rocha e Silva is my scientific 'grandfather' and Sergio Ferreira is my 'father,' " says Cunha, returning to the genealogy metaphor—Ferreira in this case was his doctoral advisor.

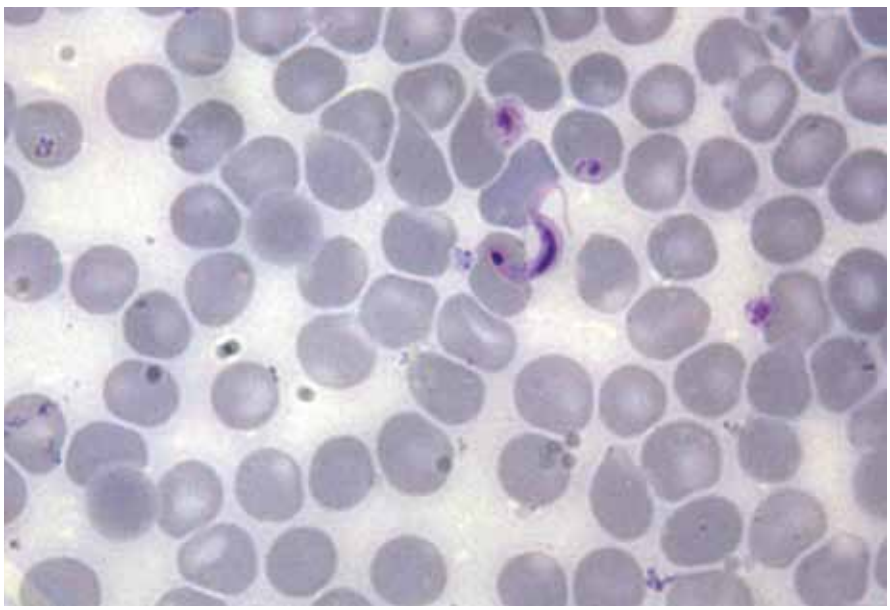
Although several USP biomedical research groups have for decades focused on the clinical applications of the findings of basic science, Cunha says the pace has picked up over the past five years, with an increasing emphasis on so-called translational research.

The advantage of the Ribeirão Preto campus in this regard, according to Cunha, is that it has a good hospital and is very active in basic research. In addition to pharmacology and immunology, groups such as the one headed by Dr. Marco Antonio Zago, current president of USP, have won distinction. Zago's group investigates hematological diseases and the use of stem cells to treat some forms of blood cancer.

"The issue," says Cunha, "is that the Brazilian pharmaceutical industry is only now beginning to realize the importance of radical innovation. The market share controlled by Brazilian companies is important and robust, but until recently has focused almost exclusively on generic or similar products." Thanks in part to research-sponsoring agencies, according to Cunha, cooperation between the university and the productive sector is beginning to take hold. "We cannot expect the university to bring a new product into the market," he says.

An example of an initiative that may become a reality in the future is an immunobiological test developed by Cunha and his colleagues for patients with rheumatoid arthritis. Most patients with this autoimmune disease respond well to the use of methotrexate, a major anti-arthritic drug. However approximately 30% of patients do not respond to it, but this becomes clear only three to six months after the start of treatment. The test developed by the Ribeirão team would indicate from the outset that methotrexate will not work for a specific patient. "This means that six months of treatment would not be wasted," he says. The team has already applied for a patent for the test and is negotiating its manufacture by Brazilian companies.

The group has also made progress on understanding sepsis, a generalized infection that can affect hospitalized patients following major surgery and is fatal in up to 50% of cases in Brazil. Sepsis is a complex phenomenon. Part of the risk it poses to health comes from the fact that, at some stage, signals of the immune system become confused and "tired," thereby preventing it from effectively attacking the bacteria that cause sepsis. The Ribeirão team has now identified a molecule that could serve as a target for new drugs that would restore that signaling. ■



... and its extracellular form, with flagellum, in blood from an infected mouse