

How to boost science

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When looking for a reference text, Professor Michel Pinkus Rabinovitch opens a folder on his computer among a plethora of other folders, each relating to a subject of study or interest. The subjects are varied, and all refer to some area of science. When he granted the following interview earlier this year, he was studying a small molecule that is supposedly toxic to tumors, and at the same time, he was researching the lives of several scientists in order to write articles on the history of science. Intellectual curiosity, innate in every self-respecting researcher, remains strong in a professor who was much sought after by students interested in research at the University of São Paulo School of Medicine (FMUSP) in the 1950s.

Initially interested in hematology, Rabinovitch graduated in 1949, received his doctorate two years later and became an assistant professor of histology and embryology in 1959. At the end of a 15-year career at USP, where he advised and trained a brilliant generation of young students*, the scientist left Brazil in 1964 due to threats from the military

regime and began a 33-year journey from one institution to another in the United States and France. He was a researcher and professor at the Rockefeller University and the New York University School of Medicine, where he trained the Brazilian researchers Bernardo Mantovani, Momtchilo Russo and Clara Barbieri Mestriner, and at the Pasteur Institute in Paris, where he advised Silvia Celina Alfieri, Liège Galvão Quintão and Patricia Veras. He studied cell biology, protozoa and bacteria and met researchers such as Hewson Swift, Daniel Mazia, Zanvil Cohn, Rollin Hotchkiss and Ralph Steinman, among others.

In 1997, Rabinovitch returned to Brazil permanently, working at the Federal University of São Paulo (Unifesp) in the city of São Paulo, where he once again trained researchers. Today, he still advises students in conjunction with other colleagues and participates in scientific meetings in parasitology and microbiology. At 87, Rabinovitch lives in an apartment that is within walking distance from the university and full to the brim with books. In this interview, he talked about his extensive, rich scientific journey in Brazil and abroad.

AGE: 87

SPECIALTY:

Parasitology and cell biology

EDUCATION:

University of São Paulo (undergraduate and doctorate)
University of Chicago (post-doctorate)

INSTITUTIONS:

University of São Paulo
Rockefeller University
New York University
CNRS/Pasteur Institute

CURRENT

INSTITUTION:

Federal University of São Paulo (Unifesp)



You are well known for having been the advisor of researchers such as Ricardo Brentani, Nelson Fausto, Thomas Maack and Sérgio Henrique Ferreira, among others. What led to your advising such qualified individuals?

Several factors. In the 1950s, there were some excellent basic research groups at the Biological Institute, the Butantan Institute and the USP School of Philosophy. I myself attended the Friday afternoon meetings at the Biological Institute, chaired by Henrique da Rocha Lima. At that time, the scientific environment in the basic disciplines at FMUSP was limited to a few isolated excellent researchers, including Floriano Paulo de Almeida, Carlos da Silva Lacaz and Wilson Teixeira Beraldo. In a pioneering initiative at the end of the 1940s, little remembered today, the Andrea and Virginia Matarazzo Cancer Laboratory, directed by Piero Manginelli, was created on the fourth floor of the FMUSP building. Manginelli introduced tissue culture and oncology to the medical school, following in the footsteps of Robert Archibald Lambert in the 1920s. The major changes mid-century in the basic sciences began with Luiz Carlos Junqueira, followed by Isaias Raw and Alberto Carvalho da Silva. Before that, there were few opportunities for training students in experimental science. Students interested in clinical research headed for the Hospital das Clínicas, already staffed with high-level clinical researchers such as Michel Abujamra, my guru and lifelong friend; Helio Lourenço de Oliveira; José Barros Magaldi; and Dirceu Pfuhl Neves. In this context, I was a non-authoritarian, informal guide, a newcomer with excellent experience in the United States who was 10-12 years older than the students and interested in music, reading and the role of science in society. Additionally, my personal life allowed me to spend time with students inside and outside the lab. I believe these factors contributed to that historic occurrence, which would be difficult to reproduce today.

Professor Brentani said in an interview that FMUSP students with a talent for research were told by professors to “seek out Rabino.”

Ricardo was attracted to research and sought me out, and we worked together a lot—and had a lot of fun, too.

Was the Department of Histology the best at the school?

In 1946 or 1947, the Department of Histology and Embryology was still focusing on microscopic anatomy, embryology and teratology; it was descriptive, traditional and pre-modern. We used microscopes, microtomes, dryers and dyes. I learned the techniques with the help of José dos Santos, a splendid technician. Medical students were taught the necessary tech-

tometers, a fraction collector, microscopy, microcinematography, a warehouse of dyes and products for histochemistry. In Junqueira's opinion, research involved not just microstructure but also histophysiology, histochemistry, radioautography, the study of living cells and chemical and biochemical approaches, initially developed by Hannah Rothschild and later by José Ferreira Fernandes and others. Generously supported by Capes and CNPq, the department trained many students and postdoctoral fellows from São Paulo and other states. Some became members of the department, such as José Ferreira Fernandes and Ivan Mota; others, such as Chapadeiro and Tafuri (both from the state of Minas Gerais) and José Carneiro S. Filho, had brilliant careers. Junqueira

also brought high-level foreign professors to FMUSP for short periods to give valuable short courses. Among them were Eleazar Sebastián Guzman-Barron, Johannes Holtfreter and George Gömöri. It was the first revolution in the basic sciences at FMUSP, followed shortly afterward by metamorphoses in biochemistry, physiology and parasitology led by Isaias Raw, Alberto Carvalho da Silva and Samuel Pessoa's colleagues, such as the Deane couple, Luiz Hildebrando Pereira da Silva and the Nussenzweig couple.

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Why did you choose to study medicine?

niques to allow them to understand physiology and pathology. The same happened in other departments. Professor José Oria realized that change was needed. He even gave me a volume on nucleic acids from a 1947 symposium at Cold Spring Harbor. In 1948, Junqueira passed the official examination for head of the department and took over and revolutionized it, now renamed the Department of Cell Biology. Even at the age of 28, he already had a doctorate and teaching experience. Due to a lucky break, lightning-fast occupation of a large, available space on the second floor allowed him to build a large, airy laboratory, richly equipped by the Rockefeller Foundation with a cold chamber, centrifuges, electrophoresis, scales, spectropho-

I lost my parents early. My mother died from acute leukemia, and my father died from a renal tumor. They were 46 and 47 years old. That's why I studied medicine. Before that, I was planning to study engineering, my father's profession. I became interested in hematology because of my mother's leukemia, and I chose Oria and then Michel Abujamra as mentors. One of my first articles was titled "Cytochemical aspects of the leukemic cell." I entered university in 1944 and graduated in 1949. My father went to university in Lausanne, Switzerland, where he met the Brazilian artist Antonio Gomide, who insisted that he move to Brazil. So, he came. He moved first to Rio Grande do Sul and then settled in São Paulo. There

are still buildings here built by a firm at which my father was a partner. He met my mother in São Paulo, after she arrived from Odessa, Ukraine, in 1910.

Your mother's family immigrated earlier?

The first to arrive in Brazil, at age 18, in 1888, was my great-uncle on my mother's side, Jacob Zlatopolsky, who came here alone. He worked in a printing shop in the Brás neighborhood, became the owner of the business and opened a stationery store at Rua São Bento, 21A, in downtown São Paulo. I still remember the smell of Faber German pencils, that cedar smell that dominated the room. In 1910, he sent for his family, who was living in Geneva. He ended up marrying a niece, Genia, who had no children and with whom my brothers and I lived after my parents died.

You started your research career while still an undergraduate?

My first article was in 1947, when I was in my fourth year of university. I cut class to work in the lab, knowing I would be a researcher. I have never delivered a baby in my life. My first article was published in French in *Revista Brasileira de Biologia* (Brazilian Biology Journal). It was on the sexual dimorphism of the submaxillary gland of the mouse, a model that was later extensively used by Junqueira and his colleagues. The topic had been suggested to Junqueira by the French radiobiologist A. Lacassagne, who discovered the sexual dimorphism of rat submaxillary glands during World War II; he visited us at FMUSP, probably in 1946.

When did you go to Chicago?

From September 1953 to September 1954, I received a grant from the Rockefeller Foundation to study at the University of Chicago. I started working in Isidore Gerch's electron microscopy laboratory. He was an excellent scientist. He was developing a method for electron microscopy of ultra-thin, frozen, dissected tissue. I realized that it was not for me, and with the consent of the Rockefeller Foundation, I went to

work in the Department of Medicine at the same university with Eleazar Sebastián Gusman-Barron, who at that time was advising Hannah Rothschild, one of Junqueira's colleagues.

The researchers also went abroad?

Yes. This was the case for Hannah; me; and later Ferreira Fernandes, Ivan Mota and others. Gusman-Barron proposed that I verify if the pancreatic ribonuclease molecule had a free sulfhydryl group, as Belgian researchers believed. Barron asked me to use inhibitors and measure enzyme activity. I did, and we published a paper together on the results. In Chicago, I also had the opportunity to meet the remarkable biologist and man Hewson Swift, from the Zoology Department.

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And from there you went to California?

I went to the University of California, Berkeley, at the invitation of Daniel Mazia. I was bored in Chicago and decided to take a course on cell physiology at the Marine Biological Laboratory in Woods Hole, near Boston, in the summer of 1954. James Watson and George Wald were among the professors. Coincidentally, Hewson Swift and Daniel Mazia were also there. Daniel was another biologist who trained generations of researchers. After the course on cell biology, we could remain for the rest of the summer if we wished. I stayed in a room they let me use. I set up an experiment that attempted to study the synthesis of rhodopsin in

toads' eyes. It came to nothing, but Mazia liked me and invited me to work in his laboratory at Berkeley. The Rockefeller Foundation authorized the move. It was only four months, but it was worth it.

Why was this period important?

Because I joined an extremely interesting project. Mazia had brought together three high-level scientists: Walter Plaut, who was a master of high-resolution radioautography techniques; David Prescott, an excellent cell biologist; and Lester Goldstein, specialized in the micromanipulation and microsurgery of cells under the microscope. They obtained the first solid proof that RNA leaves the nucleus and enters the cytoplasm. In order to do this, they marked the nucleus of an amoeba with radioactive phosphate. The marked nucleus was transferred to another amoeba, whose nucleus had been removed. The passage of the isotope into the cytoplasm was demonstrated through radioautography. Initially, they thought that the isotope was associated with the DNA. Because I had worked in Hewson's laboratory, I knew a very simple way to determine if the isotope was in the DNA or the RNA. I showed them that the phosphate was in the RNA and that it was the RNA that migrated into the cytoplasm.

You published with them?

I published an article with Plaut in 1956 about what happened when the marked nucleus was transplanted into a nucleated cell. We became friends. Afterward, Plaut moved to the University of Wisconsin, Madison. He came to Brazil twice and taught classes at USP. In Wisconsin, Plaut thought he had discovered DNA synthesis in the cytoplasm of amoeba and thought it might be mitochondrial DNA. Visiting the laboratory, I demonstrated that isotope incorporation was due to the presence of symbiotic bacteria in the amoeba that he used. Plaut was convinced and published two articles about this in the *Journal of Cell Biology*. In another study, we demonstrated that the symbionts multiply in an uncontrolled manner in the enucleated amoeba.

This work was done in the United States. Were you able to do something similar in Brazil?

Many years later, back in São Paulo, at Unifesp, I began to infect enucleated cells with various pathogens.

What was it like when you returned to Brazil after that first trip abroad?

I returned in 1955. That was when all of those talented students came to study with me. I told them I had worked with ribonuclease [a type of enzyme that catalyzes the breakdown of RNA] in Gusman-Barron's laboratory. Then, we asked ourselves: do we have ribonuclease in our blood? Yes. And in blood serum? Why don't we try to figure out where the ribonuclease in the serum comes from? Sergio Dohi, Thomas Maack, Brentani and Nelson Fausto worked on this line of research. Experiments involving the removal of the kidneys from different species of animals suggested that the kidney filters the ribonuclease. In cooperation with colleagues in nephrology, we demonstrated that serum ribonuclease activity is also elevated in patients with renal insufficiency. The kidney filters and breaks down the enzyme. In a classic experiment suggested by the nephrologist Israel Nussenzweig, from USP, the urine in the ureters of a dog was diverted into the venous system. In this case, the animal developed uremia, but the serum ribonuclease level did not increase.

Who invited you to go to the University of Brasilia, UnB, in 1964?

I was interested in the fantastic plans for UnB, and I volunteered. I wrote to Professor Maurício Oscar da Rocha e Silva, then in charge of Biology. I went to Brasilia twice to meet with Antonio Cordeiro and some others. On April 1, 1964, I was appointed to a professorship in Brasilia. However, I never went.

You were appointed but did not take the post?

If I had taken the post, I would not

have been able to leave Brazil, and I would have been imprisoned. I engaged in very little political activity, but many of my students were Trotskyists, and others were Communists, and I was accused of being their mentor. But I was never a member of the Communist Party. I do not like the power of a few or political parties; I'm an anarchist.

Suddenly, you found yourself unemployed, without a position at USP or UnB.

Yes, I was. I was not affected by Institutional Act No. 5 [a decree giving almost absolute power to the military dictatorship] because I left the country. On April 1, a Commission of Inquiry was established at USP and started investigating me. The school's repression repre-

When they killed Vladimir Herzog, I became so enraged that I turned in my Brazilian passport

sentative was Prof. Geraldo de Campos Freire, and I sought him out to ask him why I was being investigated. He replied that my conscience should know. They imprisoned Thomas Maack. During a meeting of the Brazilian Society for the Advancement of Science, in the city of Ribeirão Preto, police appeared to arrest Luiz Hildebrando [Pereira da Silva] and me. Hildebrando, like a good communist, went ahead, surrendered and went to jail. Mauricinho [Rocha e Silva, son of Maurício Oscar da Rocha e Silva] told me they were looking for me and took me to São Paulo in his Volkswagen Beetle. I never saw my Ford Willis jeep again. It was intended to carry men and baggage from São Paulo to Brasilia. I took refuge

in the house of my cousin, José Mindlin, where I was visited by friends, but not by the police.

How long did you remain hidden?

About 10 days. Walter Plaut, who knew what was happening, wrote me that he had a job for me in Madison. It was an option, but I preferred to go to the Rockefeller University because I was interested in Cohn and Hirsch's work on lysosomes [cellular organelles].

Why didn't you return when amnesty was granted?

Because by then I already had a wife and daughters. Moreover, when they killed Vladimir Herzog, I became so enraged that I turned my passport in to the Brazilian consulate in New York and was nationless. I thought they'd never end those atrocities. I had to request United States citizenship. Do you remember Friar Tito [Alencar de Lima], imprisoned and tortured by the military? I translated his article into English for publication in *Look* magazine in 1970. We did what we could to help. When I came back to Brazil, Fernando Henrique Cardoso was president and gave me back my Brazilian citizenship, and José Goldemberg, then President of USP, gave me a retirement package. And now I am an emeritus professor. Nice, eh?

Were you investigated?

Yes, but I was abroad. Prosecutors appealed three times, and I was acquitted every time. That was in the military police inquiry, which continued in my absence. My lawyer was Mário Simas, who helped a lot of people on the left. The irony is that I owe my career abroad to the military dictatorship. I spent 16 years in the United States and 15 in France and returned 17 years ago.

Why did you go to France?

In 1980–1981, I spent a sabbatical year at the Pasteur Institute Experimental Parasitology Unit in order to study Leishmania with Jean Pierre Dedet in the laboratory directed by Luiz Hildebrando. I returned to New York and started the projects on the parasitophorous vacuoles of infected

macrophages. In 1984, I received an offer to work at the Centre National de la Recherche Scientifique (CNRS) at the Pasteur Institute. I couldn't refuse.

Was your second wife American?

She was Swiss, named Odile Levrat, but lived in New York. I have two American daughters. The oldest, Miriam, lives in Paris and, with Serge, gave me my only granddaughter, Eleanor, now 4 years old, the small greatest love of my life. My youngest daughter, Caroline, lives in New York. She has a degree in cinema and would like to be a writer.

Why did you return to New York after Paris?

My first stay at Rockefeller generated longtime friends. One was Jim Hirsch, who was initially interested in tuberculosis and then in neutrophils, macrophages, chemotaxis and phagocytosis. Jim died in 1987. Zanvil Cohn was a lover of macrophages and their multiple functions. When Cohn found out I intended to retire from the Pasteur Institute in 1994, he wrote me and invited me to spend a year at Rockefeller. Unfortunately, Cohn left us suddenly. His successor, Ralph Steinman, made sure the invitation remained open. That's how I spent another year at Rockefeller before returning to Brazil. During that year, I worked in Gilla Kaplan's laboratory, co-infecting cells with phase II *Coxiella burnetii*, *Mycobacterium avium* and *Mycobacterium tuberculosis*. But Ralph also died. He was replaced with the Brazilian Michel Nussenzweig [Ruth and Victor's son], who was my student at the New York University School of Medicine.

In addition to these bacteria, you also studied Leishmania?

Yes. In the case of Leishmania, there are species that inhabit large vacuoles [vesicles] that are similar to phagolysosomes. Others occupy vacuoles with little free space. When I worked at the Pasteur Institute, I knew that the bacterium *Coxiella burnetii*, the agent of human and animal Q fever, also occupies large vacuoles with

lysosome [another type of vacuole] characteristics similar to those of *Leishmania*. I compared the fusion capacities of *Leishmania* and *Coxiella* vacuoles with small phagosomes containing inert particles. I wrote an article on this subject with Denise Mattei and Patrícia Veras, who was my postdoctoral researcher in Bahia. One day, I was taking a shower, and an idea came to me. In the lab, I had two pathogens that lived in lysosomes. What would happen if the same cell were infected by both? Would they remain in separate compartments, or would they share the same vacuoles? I tried it out right away. On the same day, we infected cells already infected with *Coxiella* with *L. amazonensis*, too. The next day, many leishmanias were found in *Coxiella* vacuoles. Even more in-

One need not be a great scientist to motivate students to do good scientific research

teresting, the leishmanias divided in the borrowed vacuoles and reversibly transformed themselves into flagellated promastigotes. However, the reverse experiment did not work. If you infect the cells with *Leishmania* first, wait a day and then infect them with *Coxiella*, the two organisms each remain in separate vacuoles. That was in 1995 and represented the creation of what I called the construction of chimeric vacuoles, which do not exist, except in our imagination. Patricia then repeated the experiment with *Trypanosoma cruzi*. In this case, the trypanosomas swam, circling the periphery of the *Coxiella* vacuoles, as if they were looking for a way out. We made some magnificent videos that impressed some biologists.

Later, I demonstrated that mycobacteria in small vacuoles may also penetrate the vacuoles occupied by *Coxiella* in this way. This model, however, has not yet been studied to the extent that it should be.

How did you decide to return to Brazil and choose Unifesp?

I had colleagues and friends at the Unifesp São Paulo School of Medicine who knew me well and invited me to join them. I do not regret it.

Do you have a formal position there?

I am retired from USP and am an emeritus professor at Unifesp. Unifesp does not pay me a salary, but they gave me a laboratory, and I have a small office there that I still use. I attend seminars, participate in meetings in two areas and advise students and others, when requested. From time to time, I am called upon to give some seminars on science history, sociology and policy, for example.

Let's close this interview with the same topic we started with: what is the best way to train scientists?

My experience and that of others has shown me that one need not be a great scientist to motivate students to do good scientific research. The best educators and trainers of scientists convey their enthusiasm for science and emphasize the importance of curiosity and the need to play with ideas. There is a difference

between starting scientific research and development as a professional scientist. I do not think I did great science. The most important thing is that I was part of a community that wanted to learn from each other.

Given your career, it seems that you also did good research.

Yes, I did some, but not at the beginning. The best reward, however, is to help train someone who is a better scientist than you are. ■

* Sergio R. Doni, Jacob Kipnis, Nelson Fausto, Ricardo Renzo Brentani, Thomas Maack, Azzo Widman, Bernardo Liberman, José Gonzales, Sergio Henrique Ferreira, J. F. Terzian, Mauricio Rocha e Silva (Filho) and Waltraut Helene Lay.