2008 Sabin Gold Medal Award Acceptance Speech

2008 Sabin Gold Medal Recipient
Ruth Nussenzweig, M.D., Ph.d.

I feel deeply honored to receive this prize, and to be in the company of a very distinguished group of scientists. Thank you for giving me this distinction. I am also grateful for the kind words of introduction from the president of his society, Dr. Philip Russel with whom I have in common many years of attempting to develop an effective malaria vaccine, a goal that seemed remote when I started this project, but which appears to be close by now.

I thought that you might be interested in my early research career, that started in Brazil where my family ended up after a year in Belgium, always chased by the advances of Hitler in Europe. At that time Jews that had converted to Catholicism had much better chances of being admitted in several countries, including in Brazil. My mother obtained a baptismal certificate from a Polish priest who was a friend of my grand parents in Poland, and we were among the lucky ones to escape in 1939, just when the war had started. My grand parents, however, were not so lucky.

In Brazil, I felt soon welcome. Most Brazilians are generous, warm people and do not discriminate against foreigners. I entered high school although the exam questions were answered partly in French, since I had spent one year in school in Belgium waiting for my Brazilian entry visa. I then applied to Medical School against the wishes of my parents, who preferred that I became a nurse. Both my parents were physicians, and although they had graduated in Vienna, anti- Semitism was so widespread that they were not permitted to exercise their profession. My parents thought that nursing would be a safer profession for me, fearing that the Brazilian dictator GetulioVargas would join the Axis powers in the war. He nearly did.

I had read Sinclair Lewis' Dr. Arrowsmith translated into French, and was so deeply impressed that I decided to become a scientist. Since there were no graduate programs in Medical Sciences at the University of Sao Paulo, I applied and entered the Medical School that had a very good reputation. Several professors at the University were also European refugees. The School of Medicine was in fact the only one in Brazil that had the recognition of the Rockefeller Foundation.

Medical education took six years, and the first two were dedicated to basic medical sciences. The presence in the lectures was obligatory, but I preferred to study from books rather than class notes. The person who was in charge of controlling the presence in the classes was friendly and knew that I was instead doing research in the department of Parasitology.

And a very exciting research it was. In many regions of Brazil, Chagas' disease was highly prevalent, and during the chronic stage there are very few parasites in the blood and most patients are symptomless. Several were in fact blood donors, particularly in Public Hospitals. During the second year of Medical School, Victor and I joined a group in the Dept. of Parasitology that demonstrated for the first time the transmission of the disease by blood

transfusion. At that time Victor was deeply involved in politics, but it was easy to convince him that it was science that could provide lasting benefits to mankind.

We decided to search for a trypanocydal drug that could be added to the blood prior to transfusion, and was harmless to the recipient. We isolated a strain of Trypanosoma cruzi that killed 100% of mice after many passages, and mixed it with different drugs and injected the mixtures in mice. For months, we went through many drugs, and several hundreds of mice whose blood we examined every morning, to search for the flagellate under a monocular microscope. We were excited and confident that we would find Ehrlich' magic bullet described so well in Paul de Kruif's book Microbe Hunters.

After many trials, we found that Gentian Violet killed the trypanosomes at a dosage that had already been given to humans to treat infections with Strongyloides stercoralis.

We were happy to find that within a short time Gentian violet was added to the blood destined to transfusions initially at University hospital, and later in many endemic areas of Chagas disease, all over South America. More than 200,000 transfusions of blue blood were used without a single case of transmission of the disease, or any deleterious side effects of the drug. There are now sensitive immunoassays for Chagas' disease and they are used in many blood banks to remove positive samples. However, if I had to receive a blood transfusion in South America, I confess that I would still prefer a blue-looking bottle.

Our next project as medical students was to try to reproduce the findings of two Russian scientists who used extracts of T. cruzi to cure cancer in humans.

We failed, but learned the hard way that papers containing sensational observations about cancer treatment are sometimes incorrect. We found out much later from credible sources that the two Russians, Ruskin and Klueva, lost their jobs by direct orders from Stalin, but not because the facts in the paper were wrong, but because they had dared to publish their findings in an American Journal and thus divulge the Russian secret cure for cancer.

After graduation we decided that we should have post-doctoral training in Paris. We spent two years there with our two small children, Victor at the Institut Pasteur and I at the College de France. I was working on the metabolism of iodine, labeling intermediates with milicuries of 131 iodine nearly without any protection, injecting rabbits and looking for the radioactive products in the urine by paper chromatography.

I had my third child when we returned to Brazil in 1960. After a couple of frustrating years at the University of Sao Paulo, we decided to go abroad again. It was not an easy decision because now I had three children and the youngest was less than three years old. We applied and were accepted as post-doctoral fellows at NYU School of Medicine: Victor with Baruj Benacerraf, and I with Zoltan Ovary, both of them immunologists working in neighboring laboratories in the Department of Pathology.

We tried to go back to Brazil in 1964, but unfortunately the military took over as soon as we arrived, and it was difficult to work in the Medical School. We returned to New York a few months later to our previous positions.

Soon after I arrived, Dr. Harry Most, the chairman of the Department of Preventive Medicine at NYU, asked Dr. Ovary whether he could recommend an Immunologist to work in Immuno-Parasitology. This is how I moved to Harry Most's department, and started almost immediately studying the possibility of developing a vaccine against the pre-erythrocytic stages of malaria, initially in collaboration with Jerry Vanderberg. Just at the time of my arrival in Most's department, another Faculty, Dr. Meyer Yoeli, had managed to maintain, for the first time, the complete life cycle of the a rodent malaria parasite (P. berghei) in the laboratory. The name Plasmodium yoelii was given in his honor. As a consequence of his achievement it was possible to immunize mice with sporozoites and try to develop a vaccine.

There was nothing in the literature about malaria vaccines, except that in the 1940's protection against bird malaria had been obtained. When infected with sporozoites ducks died of malaria, but they could be immunized and protected by injection of parasites attenuated by exposure to ultra-violet light. The exo-erythrocytic stages of bird malarias develop in macrophages, rather that in hepatocytes, and there was no a priori reason to insure that an attenuated sporozoite rodent malaria vaccine would be equally effective. I decided to try. Because it is easier to quantify the levels of X-ray irradiation, this was the choice to obtain attenuated parasites. In collaboration with Jerry Vanderberg and Harry Most, we rapidly determined the optimal dose of radiation leading to complete protection against challenge with P. berghei sporozoites. Early on we had an excellent post-doctoral fellow, Dr. George Spitalny, and quickly established the best route of immunization and the stage and species specificity of protection. At the same time, Elizabeth Nardin, initially a masters degree student and then a PhD candidate, demonstrated that the immune responses to sporozoites in the rodent models also occurred in humans living in malaria endemic areas. All these findings put to rest the idea that a malaria vaccine was impossible because in endemic areas people have multiple infections, and "you cannot do better than nature".

For quite a few years I continued to work in various rodent and monkey models and trying to reply to the criticisms of skeptical colleagues. I remember vividly a couple of the criticisms, such as "protection is non-specific and mediated by contamination with mosquito salivary glands", or that the vaccine would not work "if one sporozoite escapes", Later on, it was shown that the principles established in our rodent malaria model were reproduced in humans immunized with irradiated mosquitoes infected with falciparum or vivax sporozoites. Vanderberg had previously shown that protective immunity could be produced by X-irradiated sporozoites of P. berghei.

The initial experiments in human volunteers (prisoners in fact) were performed by the groups of Clyde and Rieckman. Complete protection was obtained by repeated boosts with hundreds of infected mosquitoes. These important experiments, and the recent partial success of the RTS,S vaccine show that we are on the way to obtain an efficient malaria vaccine. All of my malaria vaccine research could not be done without the collaboration of numerous colleagues, students and post-doctoral fellows.

Again I thank the Sabin Foundation for this honor that I humbly accept.

Thanks very much.