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Biochemical and Biophysical Research Communications 312 (2003) 267–269
BBRC
www.elsevier.com/locate/ybbrc

From the Sorbonne to the prairie, and beyond

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Received 3 November 2003

Marianne Grunberg Manago, my mother, obtained a Fullbright Fellowship to assume a post doc position in the US. In 1952, the International Conference on Biochemistry was held in Paris. For the first time, Marianne had the opportunity to see in person famous scientists whose work she had read. She was particularly impressed by the work of Irwin C. Gunsalus (Illinois), also known as Gunny, and of Severo Ochoa (New York), as well as by their personalities.

Marianne met Gunny for the first time in a Paris café near la Sorbonne. Gunny was mostly doing the talking and Marianne the listening, not being able to understand what he was saying. It is often a challenge to understand Gunny, even for some Americans, and my mother was so excited to meet such a famous scientist that she had forgotten all her English. However, Marianne had the intuition that she could get along well with Gunny. She had been warned that Gunny could be unpleasant with people that he considered to be imbeciles. Gunny was very pleasant with her during that meeting, and she concluded that he did not think that she was an imbecile. However, after that first meeting, she was not entirely sure whether he had invited her to his lab or not. A few weeks later, she received a letter from Gunny and was eager to find out if he wanted her to come to his lab in Urbana! She quickly realized that Gunny's handwriting was even more difficult to understand than his spoken English.

She was not 100% sure that Gunny wanted her to come to his lab, but, being and optimistic person, my mother and my father Armand, who was an artist, left for the US on the ship "l'ile de France" in coach class. It took several days and was not so pleasant in wintertime. They landed in New York and took a train to Chicago, where they arrived several days later in the middle of a snowstorm—with their light Parisian clothes on! My father was not so happy and wondered if my mother could have picked a lab that was closer and that had warmer weather. Fortunately, the warm welcome and the hospitality of Gunny when they finally arrived in Urbana immediately erased all their doubts and fears. My mother was moved by the fact that Gunny came in person to pick them up at the railway station in Urbana, something the French professors she was working for at that time would probably not have done. Gunny turned out to be a real gentleman and he and his wife, Carol, helped my parents find an apartment in a nice sunny house. There was a large room with good lighting so that my father could paint.

Communication in English was still a challenge for both my parents. Shortly after they arrived, Lowell Hager, who was responsible for organizing seminars in the lab, asked Marianne to make a presentation on hydrogenase. After the seminar, everyone in the lab congratulated her, but she quickly realized that no one had understood a single word of what she had presented. My father bought a TV so that he could learn English. At the beginning, he had a tough time. My mother advised him to always say yes when he did not understand what people were saying. As a good Parisian, my father liked to take his time to drink his coffee, which was not the efficient way people did it in Illinois at that time. The waitress asked him something and my father answered yes as advised by my mother. The waitress took away his coffee. She had probably asked him something like "Do you want me to take this away?" The next day, the waitress asked him something and he immediately answered "no." Again, the waitress took away his coffee. This time, she probably asked, "Do you want some more?" My father was almost in a state of despair.

Gunny knew the paintings of my father and all his life he has been a loyal customer. He even passed his taste for art onto his children, Kristin and Tina, who spent most of their lives surrounded by my father's paintings. The first time Gunny wanted to buy a painting from my

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doi:10.1016/j.bbrc.2003.11.005

father, he told him to "keep an eye on that picture!" Armand did not understand that Gunny actually wanted to buy it, and he later sold that painting to the director of NIH. Gunny was furious, and my father had to explain to him that he had not been entirely clear that he wanted to buy it. Later he bought another one, the first one in a long series.

The 9 months my mother spent in Gunny's lab turned out to be decisive for the rest of her scientific career. There, she assimilated the basic techniques in enzymology and learned how to purify enzymes. When she went to New York afterward, in Ochoa's lab, she already knew the procedures and was confident in her skills. She found a lab where the atmosphere was less relaxed than that in Illinois and where there were many internal tensions. Severo Ochoa had a strong personality. To test newcomers, Ochoa used to give them an assignment on enzymology. She purified and studied the action mechanism of an enzyme that was activating acetate and must have succeeded because she was allowed to work on the most interesting subject in the lab, the one that all the great laboratories at the time were trying to resolve: the problem of incorporating phosphate coupled with transportation of electrons to form the triphosphate nucleotide ATP, the magical molecule of F. Lipmann that provides the energy for the life of the cells for animals, plants, and microbes. The synthesis of nucleic acid appeared not to be resolved through enzymology and, as a consequence, it did not generate a high level of interest in the most competitive laboratories.

It was thus on the synthesis mechanism of this triphosphate nucleotide ATP coupled with oxidation that she started her initial work. The idea that was very common at the time, and which was quite naive, was that there existed an X compound that would accept phosphate and that would serve as an intermediary in the reaction. It was thought that a simple reaction that involved adenosine biphosphate, ADP, and a molecule of phosphate allowed the synthesis of ATP. It is now known that this is much more complex problem and it took over 30 years of studies to purify a little more than 10 compounds and enzymes. This problem is still not entirely solved.

Having been trained as a microbiologist, instead of working on animal cells, Marianne chose instead to use a bacteria as a tool. It required aerobic conditions to grow and she had hopes that the synthesis of ATP would be more active. On the other hand, she decided to work in the presence of radioactive phosphorus and to follow its incorporation in ATP. If there were an intermediary, the reaction being reversible, the nonradioactive phosphorus of ATP would be replaced by the radioactive one. She was able to show that the soluble extract indeed catalyzes an exchange between the two phosphates, the one from ATP and the mineral one. She managed to partially purify the enzyme that is responsible for this exchange. The ATP she was using was commercially produced. It had appeared on the market recently and Marianne was extremely happy about this because before she came to the US, she had to prepare it from rabbit muscles. In the course of her work, the Sigma firm put on the market a crystallized ATP, which was far more pure than the one she had been using. When she tried it for this test, she no longer observed radioactivity in ATP. The old preparation of ATP therefore contained another molecule that was involved in the reaction. She decided to purify it and discovered this molecule that was simply the derivative with two phosphates ADP. This one, because of certain side reactions that occurred under certain conditions, made up ATP. She would never have had the idea to try this derivative. She remembered announcing this result during lunch, and Severo answering, "It's impossible." She was offended, as she was sure of her experience and went back to the lab. A few minutes later, Severo came back, obviously embarrassed and apologized, but it was clear to Marianne that he was extremely disappointed she was no longer working on the synthesis system of ATP. At that time, no one knew of an enzyme that could catalyze incorporation of phosphorus into ADP, and since this was a new enzyme, she decided to continue to study it. After many experiments, she finally identified the optimal conditions for this enzyme to work. This was key because she finally obtained enough product to be convinced that the product of the reaction was not a simple nucleotide but that it had a higher molecular weight. However, she was far from realizing that it was a macromolecule. Without much hope, she added in the mixture from incubation some trichloroacetic acid that precipitates nucleic acids that have a high molecular weight. To her great joy, she saw a gelatinous precipitation that became a solid mass. Then, without even finding out what the spectrum was, she had the intuition that she had for the first time synthesized a polynucleotide. Its molecular weight turned out to be a million. She lived a moment that could not be forgotten because at this time it was impossible to even imagine that one could synthesize, in a test tube, a long molecule with the same properties as a nucleic acid. This enzyme, called polynucleotide phosphorylase, is not the one that synthesizes in vivo a ribonucleic acid, but its biological role is still not fully determined. However, this discovery had a conceptual impact that was extremely important because it gave biochemists the ability to search for enzymes that are responsible for the synthesis of nucleic acids.

At the beginning, Severo Ochoa was still disappointed the compound that had been synthesized had nothing to do with this famous compound of oxidative phosphorylations. However, during a seminar at the National Institutes of Health, when he mentioned at the end of his presentation the discovery of polynucleotide

phosphorylase, he saw Kalkar (a Danish scientist who was working on the synthesis of nucleotides and who had the habit of sleeping during seminars) suddenly jump on his chair and wake up suddenly. This was an obvious sign that the discovery was important. Severo thus came back from NIH very excited, no longer regretting this change of focus in his research topic. Afterward, everything went very quickly and Marianne was able to identify the structure of the compound and show that it was indeed very similar to that of ribonucleic acids.

None of this would have happened if she had not spent 9 months in Gunny's laboratory and learned enzymology as well as protein purification.

Twenty-five years later, in 1979, I came to Gunny's lab in Urbana for a summer job. I ended up staying 4 years and did my undergraduate studies there. As far as understanding Gunny, I went through the same experience as my mother, but fortunately computers were now available and I could communicate with Gunny using what has now become e-mail. I also experienced Gunny's hospitality as well as that of his wife, Dorothy, who was a musician and a very generous person like Gunny. I remember how Gunny lent me his car so I could get my driver's license, and how he fought the various bureaucrats at the university so I could be admitted coming from the French system (Gunny does not like bureaucrats). Best of all, he helped the chaotic adolescent I still was at that time (I was 19 when I arrived in Urbana) find what I wanted to do with my life. I also met my dear wife, Anne, in Urbana, and we have been happily married for over 18 years.

I first worked in his group as a technician to sterilize lab equipment and prepare media. Then, I prepared columns for protein purification and finally did purification myself. I worked on the cytochrome c_{551}. For some reason, the cytochrome would not ever come out of the column when it was supposed to and I often had to stay up late at night to start and stop collecting it when it was finally coming out of the column. I began to be quite interested in computers, first to play games and then to program them, and after a couple of years I decided that this was what I wanted to do. I switched my major from biochemistry to maths and computer science with a focus on artificial intelligence. I came to France to do my Ph.D. studying machine learning and I eventually founded a company, called Kaidara, which today gets half of its revenue in the US and half in Europe.

Gunny manages people by trusting them and empowering them to do things. He then has very high expectations, and you'd better give your best. It was very challenging for me at first, but I'm glad that I grabbed the opportunities that were presented to me. Gunny taught me to have passion for what I do, and this is something that helped me for the rest of my career as well as in my personal life! On behalf of the Manago family, thank you, Gunny!