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Historical Review

An Interview of Dr. Ernesto Carafoli with Charles Weissmann

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The first question is more or less mandatory, and could be disposed of by simply asking what motivated you to choose science as a life activity. However, to me your case is more intriguing: in 1956 you became a Medical Doctor at the University of Zurich, which was a renowned School, where students were certainly exposed to the most fascinating aspects of medicine. Yet, after graduating you moved away from Medicine, and 5 years later earned a Ph.D. in Organic Chemistry, How did that happen? Was it because Medicine had disappointed you, or did you think that you could still remain within the realm of Medicine by going into Chemistry?

My early ambition was biochemical research, but in the nineteen fifties there was no direct path to become biochemist. So I studied medicine and did my "elective" semester in the Institute of Professor Franz Leuthardt, where I was assigned the task of ascertaining whether RNA could be converted to DNA by incubation with liver homogenate – I am pleased to report that I did not succeed. My first independent research was carried out in a laboratory established in my bedroom and dealt with vital staining of newt larvae with Acridine Orange [1]. After obtaining my MD, I wrote a thesis on the role of transaminases in the diagnosis of myocardial infarction and practiced a little medicine as a substitute in Gossau, a village near Zurich. The sobering experiences I garnered reinforced my decision not to pursue a medical career, and, because I realized that my education did not provide a sound basis for a research career, I decided to study organic chemistry. The goal of my thesis work was to determine chemically the absolute configuration of strychnine (which was already known from X-ray crystallography).

You moved to the Laboratory of Paul Karrer, who of course was one of the Organic Chemistry giants of the first half of last century. However, the clichè we have of him is that he was very much the "Herr Professor" type who was so domineering, especially in German-speaking Laboratories, in those early days. You were his last Graduate Student: how was life with him and in his Laboratory? Did you ever felt any nostalgia for real Medicine?

I chose as my thesis advisor Paul Karrer [2], whose seminal work on carotenoids, flavins and vitamins A, B2 and E had earned him a Nobel Prize in 1937. Karrer was the archetypal German professor (although of Swiss extraction), authoritarian and, in general rather unapproachable. He was extremely soft spoken, almost inaudible when lecturing, and was not known to have ever raised his voice. He expressed extreme anger by rapping his fingers on the table top, which inspired terror in his subordinates. Karrer was extremely disciplined, making the rounds of his labs twice a day and shutting down the Institute at 6 pm, when all personnel left, as a safety measure. He was about seventy when I became his last graduate student, and much of the essential guidance I received during my studies was from two superb organic chemists at the Institute, Andre Dreiding and Hans Schmid. After I returned to Switzerland from the US in 1968, I occasionally met Karrer for lunch, and he eventually let me read his memoirs, in which he described himself as "a very emotional individual" – who would have guessed?! Unfortunately Karrer's descendents refused to publish this interesting record of a great scientist.

Normally, one would go to Paul Karrer's Laboratory because he has in mind a career in Organic Chemistry, and it would thus have been easy to predict that you could have become one of the glamorous Organic Chemists that have mad Zurich one of the Meccas of that science. Yet, you drifted away from it, and decided to become instead a bio-scientist. Again, how was it?

As I approached the completion of my thesis in organic chemistry it was borne upon me how little impact my work would have on chemistry in particular and on the world in general, and I was at a loss as to how to pursue meaningful research in classical organic chemistry. My epiphany occurred in 1959, when I attended a lecture by Severo Ochoa, then Chairman of the Department of Biochemistry, NYU, and became aware of the significance of nucleic acids as genetic material (of which I had heard nothing during my medical studies!). Immediately following Ochoa's lecture I applied to him for a position as a postdoc, and, as student of Karrer's, was accepted forthwith (provided I brought my own support, which I did, thanks to Karrer) [3].

I understand your stay in Severo Ochoa's Laboratory was a turning point in your professional life, and of course we all know that Ochoa was a charismatic personality. So, this brings me to the following question. Most of us in science recognize a personality, a Mentor, who has shaped us as scientists. Did anybody have this type of influence with you?

Ochoa had a profound influence on my development as a research scientist. He was a charismatic leader, with an instinct for the scientific jugular, sensing where research should be heading and making optimal use of the talent that surrounded him. An important feature of his department was the afternoon coffee hour, when its members drifted in and out of the library, partaking of scientific discussions which often resulted in useful contributions

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to ongoing research. When, after returning to Zurich in 1967, I started my own Department I instituted the infamous Saturday morning meetings, at which we gathered every other week to discuss and critique ongoing work, sustained by free coffee and croissants. During my more than 5 decades of scientific activity our lab contributed to many areas of molecular genetics, virology and biotechnology [4].

You have initiated your scientific life when the working conditions and related possibilities, even in a place like Zurich, were primitive to say the least. I am sure you had to make your own ATP yourself, and the unbelievable methodological advances introduced, for instance, by the technologies of Molecular Biology were nowhere to be see. Let alone, of course Bioinformatics. In your Historical article you have focused on the discoveries of new Methods, which you have described without any particular hierarchy. Could you think of a technological development that takes primacy over all others in terms of importance? Given the area you have worked in, do you think that recombinant DNA technology could be such a development?

I have indeed alluded in my article to the times where the preparation of an experiment, which might include purification of enzymes, substrates and cofactors, took more time than its performance. I believe that the availability of commercial enzymes, substrates, kits and indeed analytical and preparative services contribute critically to accelerating the pace of research. I have referred to several seminal events – introduction of isotopes, X-ray crystallography of macromolecules, recombinant DNA technology that revolutionized biochemistry and molecular biology. Advances in data storage and processing, as well as information retrieval have a profound impact on the way we do – and disseminate – science.

You have been a pioneer in the importance of the interplay between "pure" science and industry. As you know, this has been, and continues to be, a controversial issue. You have been the co-founder of one of the most important Biotech Companies, and by general agreement the outcome of that enterprise has obviously been positive for life sciences. But there is a point which is possibly related, on which I would like to sound you out: now, as you know, the trend has become universal in life sciences to extract profit from discoveries. Scientists now attempt to patent everything they find, including the most unlikely things. How do you feel about this trend?

Patenting scientific inventions is an old tradition in organic chemistry, but was a new development in biology and met with antagonism [5]. I believe that patents on the commercial *use* of genes and their products for therapeutic or diagnostic purposes (but not genes themselves) are justified, however, their use in basic research should be unencumbered. Patenting makes it possible for inventors in academia and their institutions to benefit from their work. The proceeds from licensing are usually distributed among the inventor, the institution and the department at which the work was performed and can thus be utilized as source of funding for further research.

My last question is also essentially mandatory. Based on your unusually wide and long experience in life science research, if you were asked for advice by a young student who wants to go into bioscience research, what would you answer?

I would answer: "Do it if you love research and can live with failure".

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