Biochemical and Biophysical Research Communications 430 (2013) 868–870

Contents lists available at SciVerse ScienceDirect

Biochemical and Biophysical Research Communications

journal homepage: www.elsevier.com/locate/ybbrc

An interview by Dr. Ernesto Carafoli with Dr. Edmond H. Fischer

1. Can you remember how it was that you became interested in science? Was it any science, or something that had to do from the very beginning with chemistry and biology?

I got interested in science pretty early, perhaps at age 14 or 15, in the mid 1930s, I had read a couple of books such as Paul de Kruif's Microbe Hunters describing people like Robert Koch, Semmelweiss (the Hungarian physician who well before Louis Pasteur recognized the infectious nature of puerperal fever and promoted asepsis during child birth that killed so many women in those days) and, very particularly, Louis Pasteur for whom I had an immense admiration. He and his collaborators were those who had discovered the plague and leprosy bacilli, had shown that plague was transmitted by fleas, typhus by lice and malaria by mosquitoes, produced the first vaccine against anthrax and, with great difficulties and a real coup de force, against rabies. Rabies was such a widespread disease that this immediately contributed to his world-wide fame. Pasteur's group had done extensive work on tuberculosis and because my father had tuberculosis, I wanted to become a bacteriologist, dreaming, of course, to find a cure for it. Unfortunately, my father who was a heavy smoker, died of TB well before I could even enter the field.

2. And then, once you had decided that you wanted to become a biochemist, was your decision shaped by the intellectually pleasing rigor one finds in chemistry, or by the less rigorous, but perhaps more challenging, way of thinking in life science?

For my 16th birthday, I had asked my parents for a microscope. They lived in Shanghai, China, where I was born. So they asked my oldest brother (he was 7 years older than me) who was studying engineering at the Swiss Federal Institute of Technology in Zürich to buy one for me. I expected to receive the usual ordinary play instrument, but no. From the School's thrift shop, he got for me a superb Leitz microscope, a real professional instrument with 4 lenses including one of the most powerful immersion lenses available at that time. So, armed with this incredible machine, and together with my very best friend who also attended the Collège Calvin built in 1559 and who loved to tinker with machines, we thought we could solve all the problems of the world. For what would correspond to $ 4 a month we succeeded in renting a room in an attic, which we converted into a "laboratory". Ours even had a window, which was a luxury. So we started piddling around with the mike and had a lot of fun doing so.

People have often asked me what attracted me toward science. Yeah, well, truth is I never really asked myself that question. I never thought about it in those terms. I went into science because I just liked it, I thought it was exciting, but I never tried to rationalize why. I'm sure I was attracted toward science because of all the things it had taught us about us as human beings (Alexis Carrel had just come out with his book "L'homme, cet inconnu"–"Man, the unknown" and I was enthralled by it). What science had taught us about the world that surrounds us. All the knowledge it had given us over the centuries. And for this reason, I'm interested in just about any aspect, any field of science. Not that I'm knowledgeable in them, not by a very long shot, but I'm just curious about what's happening around us, about what's going on in science.

But what interests me the most is not so much the things we know about science but the things we don't know. What has yet to be discovered, the big mysteries that confront us. I am more interested in the future of science than about its past, about what has yet to be discovered. About some of the big problems, the big mysteries that remain to be solved.

As to what has always attracted me toward scientific research, what really fascinates me about it is the systematic way one has to proceed, the kind of logic that one has to apply to solve a given problem. In science, every result obtained suggests two or three new questions, and every question asked suggests the next experiment. One must follow those leads just like a detective follows different leads to solve a murder mystery, trying to select the most likely one to succeed, never knowing when the next breakthrough will occur. Because in science, one cannot order at will, or "buy" a great discovery, at whatever cost, because there is no way of predicting when and from where it will come. For me, this is the real beauty of scientific research, what fascinates me most about it: the fact that if one knows where one starts from on a research problem, one never knows where one will end up.

3. Scientists normally recognize a figure who has been pivotal in shaping their way of approaching and developing science; in my case, for instance, such a figure was Al Lehninger. You have always attached great importance to your scientific association with Ed Krebs. However, that occurred when you already were a biochemical authority on your own; before that time, to whom do you feel you owe a special debt for having shaped you as a scientist?

I don't believe I ever had this kind of a mentor who actually shaped my career or life. I had a great admiration for, and learned a lot from, Kurt H. Meyer under whom I carried out my doctorate degree. Kurt Meyer was one of the foremost authorities on macromolecules. With Herman Mark of the Brooklyn Polytech. Inst, he had published the famous "Meyer-Mark", the most definitive treatise on High Polymers. In it, they held that molecules such as starch or glycogen had molecular weights in the millions. This idea was summarily dismissed by many organic chemists (including Paul Karrer, the reputed Swiss Nobel Laureate in Chemistry) who declared that this was thermodynamically impossible. In fact Paul Karrer, in one of his early textbooks of Organic Chemistry, proposed an actual formula for

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http://dx.doi.org/10.1016/j.bbrc.2012.10.023

starch, assuming it was some kind of small oligosaccharide. But in a famous paper published in 1928, Kurt Meyer and Herman Mark finally convinced the chemists. Using X-ray crystallography, they showed that a synthetic polymer consisted indeed of a very long chain in which countless repeating subunits were linked to one another by covalent bonds.

Kurt Meyer was interested in the structure of starch and glycogen, and to dissect these macromolecules, he needed pure enzymes that would cleave them into small fragments that could be chemically characterized. So he proposed to me as a thesis project the purification of α-amylase, the abundant enzyme that randomly cleaves the α-1-4 glucosidic bonds of starch and glycogen.

There was another interesting reason for selecting this project. In the 1920s–early 1930s, Richard Willstätter (the German Chemist who had received the Nobel Prize in Chemistry in 1915 for his superb work on plant pigments including the structure of chlorophyll) and his collaborator Waldschmidt-Leitz had tried repeatedly to isolate α-amylase from pig pancreas. But all they obtained at the end was a fraction that contained no detectable protein, only some carbohydrate. I imagine they had no idea how potent enzymes were and the methods available in those days to test for proteins (mostly the Kjeldahl or Van Slike procedures) were far too rudimentary to detect the traces of proteins that must have been present. Anyway, Willstätter and Waldschmidt-leitz advanced the theory that enzymes might not necessarily be proteins but might have a structure similar to that of their substrates. And hence, an enzyme working on starch might have a polysaccharide-like structure. That was several years before Sumner had crystallized urease and shown that it was indeed a protein. Kurt Meyer thought that this was nonsense, so that a second reason for me to work on the purification of α-amylase from pig pancreas was to prove that they were wrong.

4. As we all know, your seminal contributions have been many. However, you are likely to go down in history for having been instrumental in the initiation of the enormously successful area of cell signaling. At that time, cell signaling barely existed. Did it immediately dawn on you that it would become one of the central areas of cell science? The question is not trivial; I was always struck by the fact that the landmark 1983 finding by Sidney Ringer on Calcium signaling in the heart—the first cell signaling experiment ever—was left essentially dormant for decades

As I said in the text, in never dawned on Ed or me that we were dealing with a fundamental process. In those days, 55 years ago, terms such as ''Signaling'' or ''Signal Transduction'', which are so commonly used today, would not have been understood. What we call Signaling today would have been referred to as ''Mechanism of Hormone Action''. A few metabolic or other pathways were known (glycolysis, the Krebs or urea cycle and other anabolic or catabolic pathways). They were viewed as simple linear arrays of enzymes acting successively on one another. Today we probably know most of the molecules involved, and increasingly about the complex environment in which they operate, with the participation of structural modules, chaperones, scaffolding proteins, substrate-binding, -targeting or -anchoring subunits, etc. And we know quite a bit about what happens when normal physiological processes are disrupted. We know that Signaling brings into play whole networks of channels, receptors and a maze of enzymes and pathways, all communicating with one another and interacting with sub-cellular elements such as the cytoskeleton, ER, Golgi, etc. And we must be able to understand the cross-talk that takes place among all these elements, the language they speak if we want to really understand how the cell functions. Only then, I believe, can we embark toward a rational approach to therapeutics.

5. Another thing that has always struck me is the fact that what is widely regarded as your second most important discovery—tyrosine phosphatases—happened at a time when you had already reached what is normally considered retirement age. Doesn't it mean that there should be no time limit for scientists who maintain the enthusiasm and the ability to think creatively irrespectively of their age? I am asking this because the tendency is now prevailing to invariably "make room" for the young, at the expense of older scientists who may still have a lot to say

We started with the tyrosine phosphatases only in the late eighties because tyrosine phosphorylation had been shown to occur by Tony Hunter just a few years earlier, and his group and others had gone nowhere in trying to isolate them. I think it would be silly to have age play any role in determining how long an investigator should work. That should be determined only by his imagination, creativity, stamina and desire to continue. There is no age limit to making a scientific discovery.

6. You have started your career in Switzerland, and then moved to the US. Can you compare the way science was made at that time in Europe and the US (admittedly, Switzerland may not be paradigmatic)? Not only funding, of course, but also the general atmosphere that surrounded science, the emphasis on novelty, the general aura of freedom in laboratories that were miles away from the Herr Professor European System?

In Switzerland, at least in forties and early fifties, biochemistry was essentially non-existent. We had far less research facilities, instruments, reagents, etc. than in the US and, particularly, far less money for research. As a consequence, we could not simply undertake a new project or engage in a different approach. Before starting anything new, we had many discussions to see if it were really worthwhile. And often, after considering all the pros and cons, we would drop the idea. Whereas in America, I have the impression that with abundant lab resources, one would simply initiate the new project and see later if it would pan out or not. Of course, in those days, we were in a different world. Enzymatic assays were carried out using 1 ml of enzyme solution which would be aspirated in one foot-long graduated glass pipettes and poured in glass test tubes containing 1 ml of substrate. Glassware was expensive so all was cleaned every night in chromic mixture. Enzyme purification was carried out mostly by ammonium sulfate and solvent precipitation. There was no affinity, exclusion or hydrophobic column chromatography (let alone HPLC); no SDS gels for determinations of purity or molecular weight: these had to be carried out in the ten feet long Tiselius free-boundary electrophoresis requiring nearly1 g of enzyme, or Svedberg's ultracentrifuge. There was no automatic anything and everything had to be done by hand. No Edman degradation or automated sequencers and none of the sophisticated instrumentation we have today such as the MALDIs, MS/MS, or NMR. Peptides were separated by chromatography or electrophoresis on thin strips of paper and stained with ninhydrin (everyone in the lab had blue fingers) and sequenced using Fred Sanger's FDNB reagent.

As to the Herr Professor system, yes, it was the norm everywhere (and still is in many countries). It was a breath of fresh air when I arrived in a lab and found the students calling their mentors by their first names. In fact, when I tell Europeans in Europe to simply call me Eddy, they absolutely cannot do it. I believe the NIH played an essential role in the advancement of biomedical research in this country when they awarded grants on the basis of their scientific value rather than on the position/importance of the applicant. They are those that completely shattered the European Geheimrat system.

7. And since I had asked you to compare science in Europe and the US in those old days, could I now ask you to extend the comparison to the present time? One has the impression that competition—for funding, for career positions, for being the first in the discovery is getting out of hand in the US more than in Europe; the first victim of this would of course be the fun which was such an important motivation for doing science. Do you share that impression?

Actually, I do not. Since funding/resources are more difficult to come by in Europe than in the US, I see at least as much competition for advancement and funds there than here. Of course, it depends very much on the country and the Institution. Much less in top institutions than in mediocre ones. I had the impression that in certain poor institutions (in France), it was more important that your colleague would fail rather than you to succeed.

8. A related point: in the old days the idea of making a profit out of science was essentially alien to those who practiced it. Now monetization has taken over in all possible ways, and more so in the US that in Europe. How do you judge this development?

When research scientists found out that people like Herb Boyer (the rich Boyer!), Bill Rutter, etc. made hundreds of millions of dollar by patenting their discoveries, it didn't take them long, to try to do the same. In this country mostly. If it is doable, they'll do it. And it had been encouraged by the universities who shared in the profits with their Technology Transfers. I believe that around all first-class research universities (Harvard, Stanford, UCSF/LA/SD etc., more than a hundred biotech companies have sprung up (about 50 in Seattle) In some countries, it has been discouraged or forbidden (like Italy).

What is new is that the individual research scientist himself profits from his discovery. In the old days, the chairman of the Department had agreements with the Industrial Companies that sponsored their work and paid them handsomely. In Zürich, Paul Karrer was supported by Ciba and Ruzicka by Hoffmann-La Roche. All their students were working on this or that particular reaction, a small part of an overall project that they mostly ignored. They were not allowed to speak with one-another about what they were doing. Of course, this takes away the romanticism and "purity" of basic research: research for the sake of research.

9. You have journeyed through biochemical science from the times of the pioneers, to the post-genomic era of today. Let me thus ask you to share with us the feelings of one who has seen the times when one had to make its own ATP, when there was no NMR, when protein crystallography was moving its first hesitant steps, when there was essentially no molecular biology and of course bioinformatics was far away in the future, and is now in the middle of the most fantastic instrumental and intellectual developments. My question to you is very simple: was it more fun to make science when you started, or do you think it is more fun today?

No, I think that scientific research will always be exciting and fun. It is true that, in retrospect, I had it enormously easy because for most of my professional life in this country, I did not have to worry about being funded. When I started, any good application was almost certain to be funded. Whereas today, I see the young researchers spending much of their time writing, and rewriting grant applications, which is horrendous. But the fun of research depends on the investigator only, on what he makes up of it.

10. One final, but mandatory question: suppose you were to advise a young student who is contemplating a career in biochemistry. What would you tell him/her, which direction would you suggest? Most importantly, how would you define for him/her as the most important problems that are still waiting for a solution in our area of science?

I would tell him or her first that in selecting a research project, he/she should focus on an important (as opposed to trivial) one. But one that isn't already investigated by too many groups or biotech companies, because he wouldn't have a chance. To avoid the "plate-bandes trop piétinées". Topics suggested by seminars, articles that excite them. Second, not to be discouraged when things don't work. Often, the most exciting discoveries come from experiments that failed, do not come out as expected. But then, if a research topic fails and fails and fails, to have the courage to drop it. At least, to place it temporarily on a back burner. It is very possible that a few years later, an article, seminar, comment etc. will open it up again, explain why it didn't work. But most importantly, chose a topic that really excites your imagination, that fascinates you. Because scientific research can be hard and you want something that will drive you forward under any condition.

One cannot select the most important problems that are still waiting for a solution in our area of science because it is impossible to predict which area will open up. Think of Mol Biol before it exploded in the late fifties, of DNA, RNA, catalytic RNA, iRNA which didn't exist; ubiquitylation, imaging, and all the fields that became available to investigators because of new technologies. Particularly the pervasive presence of the computer and bioinformatics that allow us to analyze and display data, store them and retrieve them at the touch of a button, today's investigator has at his disposal an incredible array of methodologies undreamed of just a few years ago. What were single topics before have become entire fields of investigation. We are in now in the era of "omics": genomes, proteomes, kinomes, primosomes, etc. It is really a new world and, I believe, a most exciting one.

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Available online 8 October 2012