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Discovery of the heat shock response

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This story begins in the early 1960s at the Genetics Institute in Pavia when Adriano Buzzati Traverso organized a course on the biological action of radiations with the aim of introducing 10 young people to modern genetics. I was one of those young people.

During the course in Pavia, we were introduced to courses in advanced mathematics, English (not my major field of interest), biochemistry, physics, enzyme kinetics, radioisotopes, cybernectics, statistics and finally my beloved genetics: formal, bacterial, phage, human, vegetal, population and biochemical genetics. The staff were terrific: Magni, Cavalli-Sforza, Calef, Bianchi, Boeri, Ageno, Fraccaro, Ciferri, as well as Lederberg, Bob Perry, von Borstel, Giles, Caianiello, Cin Ciung Li and others. But it was Buzzati who gave us most. To Buzzati, research was a polite relationship between man and Nature that had to be deepened, and man was constantly part of that Nature which interested him. No element was greater or more important to him.

At that time, I read a small, fascinating book, *Bioenergetics* by Albert Szent Gyorgyi (1959). Mitchell's proton pumps were still to come. In his book, Szent Gyorgyi postulated that electrons, flowing along the respiratory chain, could drive ATP synthesis by resonance. He postulated that this could be possible if excited electrons underwent spin reversal, which would lengthen the life of their excited state. This was possible, he claimed, if water-embedding proteins of the electron transport chain had a structure like that of an ice crystal. Indeed, UV-irradiated flavins in melted water are fluorescent while, when irradiated in ice, they become phosphorescent.

During the second year of the course organized by Buzzati, I decided to work on *Drosophila*. I chose *Drosophila* because I felt that this organism was somehow between bacteria and man, and also because there were no other facilities to work with plants I preferred. Buzzati, obviously, approved my choice, although it was by no means an easy choice to make. At that time, those who were working with *Drosophila* were considered a sort of 'sub-community' of scientists, well below those working with bacteriophage T4.

At any rate, I established myself, set up a method for autoradiography with tritium and started to study what type of nucleic acid was synthesized in puffs of the salivary glands of *Drosophila*. In 1960, there was still some confusion on this matter. Pelling (1959) in Beermann's group had just shown the presence of synthesis of RNA in *Chironomus*, but Pavan (1958) had shown DNA synthesis in *Rincoshara*. Messenger RNA was just about to be discovered. I remember the emotion aroused by the publication of the paper by Brenner, Jacob and Meselson (1961). We spent many nights in the laboratory discussing it and imagining the future.

I cannot remember whether it was John Pulitzer or Inge or Clara Ghini or Giordano who shifted the temperature of my incubator, but one day I noticed a different puffing pattern! I calculated the right conditions for the shift and observed new RNA synthesis. I was impressed by the rapidity with which new RNA was synthesized: just 2–3 minutes! Similar puffs were also present in malpighians and gut polytene chromosomes, while those present before were shut off. Then I remembered the Szent Gyorgyi book and wondered whether heat might destroy the ice structure of water around the proteins of the electron transport chain, which would cause uncoupling of oxidative phosphorylation. I immediately did the experiments and observed that uncouplers of ATPase, such as dinitrophenol and salycilate, as well as recovery from anoxia, induced the activation of the same new genes. It does not matter if this interpretation was true or false; it was a working link between imagination and reality, like love.

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Inge Rasmussen, working with triploids in *Drosophila*, Giovanni Magni on yeast and Adriano Buzzati himself, discussed the new findings with me and helped me write up the paper; none of them insisted on having their names on the paper. As is widely known, the paper was initially submitted to a highly reputable journal. The journal editors rejected it, since they considered the new finding irrelevant to the scientific community.

Obviously, I continued to think the system was of general importance. This was not only because whenever I tested it (using different tissues, different developmental times, different *Drosophila* species) I obtained similar positive results, but especially because of the similarity of effects in response to agents like anerobiosis and uncouplers. I worked for a long time on the hypothesis that the system was directly correlated with energy production. Hans Berendes and his group also worked a lot on the system and shared my basic idea.

The recent concepts about the function of the system are fascinating, yet the system looks so complex that it might still hold some other surprises in store for us.

Note from the Editor

In this issue we begin our 'Reflections' articles in which pioneers in the study of cell stress and molecular chaperones share their personal views and remembrances of their discoveries. It is appropriate that we inaugurate this series with Ferruccio Ritossa and his discovery of the heat shock response almost 35 years ago. Many of us first learned the details of this event at the first international meeting devoted to the heat shock response held at Cold Spring Harbor Laboratory in 1982. Ferruccio was recognized for his pioneering work at this meeting. The recombinant DNA revolution has been so pervasive that we tend to forget that, in 1962, practically the only way to study gene expression was in systems like Drosophila polytene chromosomes where gene activity could be seen under the light microscope as chromsomal puffing.

Ritossa was interested in resolving a controversy over what kind of nucleic acid is synthesized in the puffs. My recollection of Ferruccio's story was that one day he observed a novel pattern of puffs uncharacteristic of that particular stage of larval development. Realizing that something was amiss, he discovered that one of his coworkers had adjusted the incubator in which Ritossa kept tissues to a higher temperature, thus delivering an inadvertant but serendipitous heat shock to the tissues. Ritossa repeated the heat shock, this time with normal temperature controls, and succeeded in producing reproducible puffing patterns, a clear example of Luis Pasteur's observation that chance favors the prepared mind. This observation was one of the clearest demonstrations of environmentally induced changes in gene expression to date. However, many years would pass before this seminal work would be developed and its significance broadly appreciated. Those stories will be the subjects of future 'Reflections'.

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