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Yuri Ovchinnikov: WORLD CLASS SCIENTIST AND SCIENTIFIC AMBASSADOR

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People are divided into three groups: those who make things happen, those who watch things happen, and those who wondered what happened [1]. Yuri Ovchinnikov was one of those rare people in the first group – he made things happen. I think of Yuri in many ways, as a complex and interesting man with many abilities and outstanding qualities. But most of all, I think of him as: one, a scientist; two, a scientific administrator and scientific ambassador; and three, as a colleague and friend. Today, I will briefly review all of these areas of Yuri's contributions to our society and try to place in perspective this remarkable man.

Yuri Ovchinnikov – the scientist. The roots of Yuri's love of science must be buried deep in his upbringing and his early training. You may recall that his father was an engineer, and Yuri's intellect and abilities were recognized by his admittance as a student to Moscow State University where he was influenced by knowledge of the major advances that were made in the '50's by Linus Pauling (the alpha-helix), and Fred Sanger's determination of the first amino acid sequence of a protein (insulin). In 1959, the Institute for Chemistry of Natural Products was founded here, and the outstanding Russian scientist, M.M. Shemyakin, initiated the study of naturally-occurring peptides and depsipeptides. Indeed, as a student and recent graduate, Yuri studied the cation transport regulating action of two depsipeptides: valinomycin and enniatin. Yuri appreciated the possibility of examining the effects of chemical and chiral changes on the structure of these compounds. But first he decided to spend a post-doctoral year in the laboratory of Professor V. Prelog at the ETH in Zürich. Prelog had recently started his work on stereochemistry (which led to his Nobel Prize). Ovchinnikov recognized that stereochemistry played a large role in peptide structure, so his choice of Prelog as a post-doctoral mentor was a natural.

In the '60's, Yuri pursued his studies of valinomycin and, in 1969, published (with Ivanov and Shemyakin) the "bracelet" structure of this cyclic depsipeptide and its potassium complex [2]. I won't go into the details of the reasoning which led him to this structure, but it is clear that he used all the physical data available to him, including optical rotatory dispersion and infrared spectral determinations. His grasp of the subtleties of the interpretation of the physical-chemical data, as well as his ability to visualize

three-dimensional structures was evident in this ground-breaking 1969 communication.

The work on valinomycin led naturally to the consideration of other ion-transporting natural substances, including the channel-forming linear peptide antibiotic gramicidin A, whose structure was being worked on by a graduate student in my laboratory, William Veatch. Veatch found that the linear pentadecapeptide gramicidin molecule forms four different conformational species which could be isolated from an organic solvent system and characterized by circular dichroism, proton nuclear magnetic resonance, and infrared spectroscopy [3, 4]. The end-to-end-helical and the double helical structures that these molecules form is shown in the next slides. These structures - and one in particular - now appear to represent the ion-transporting forms of gramicidin A.



Yuri Ovchinnikov in a typical pose in his old Shemyakin Institute office

Information about the structures of gramicidin were obtained mostly from NMR spectroscopy, and in the latter part of this work, we were fortunate to have the intellectual and material collaboration of Yuri Ovchinnikov, who was able to provide a series of shortened analogs of gramicidin which greatly aided the NMR interpretation [5]. In fact, this collaboration between Yuri Ovchinnikov's laboratory and my laboratory marked the beginning of a most fruitful period of scientific, intellectual and international collaboration between Yuri Ovchinnikov and me. More about this later.

One of the things that characterized Yuri Ovchinnikov's scientific career was his ability to select and then focus on important problems at the right time. Following his early work on cyclic peptides and his later work on linear peptides, Yuri and his colleagues, Bystrov and Ivanov, began to probe other interesting areas of natural products which included the structure of several neurotoxins, with the work done principally by Vadim Ivanov and Victor Tsetlin [6]. The Institute started toxin studies in 1973 in order to clarify some of their structural peculiarities and to find novel toxins. As a result of the work, more than 30 new toxins were isolated and several of their structures were established. The investigation of neurotoxins, which are some of the most powerful naturally-occurring poisons, had an interesting political fall-out, which perhaps can be discussed in a more informal setting.

Another area worked on by Ovchinnikov and his collaborators was the structure of the DNA-dependent RNA polymerase from *E. coli*. That work was soon overshadowed by the major effort of Yuri and his collaborators in deciphering the primary structure and topography of bacteriorhodopsin and bovine rhodopsin. Ovchinnikov's work in this area and that of his principal collaborator, N.G. Abdulaev, have provided much basic data and many insights. I should note, parenthetically, that his entry into this important and highly competitive area brought to bear all the characteristics that made him an outstanding scientist. First, the search for facts in an unknown system; and secondly, the drive and clarity of thinking which characterized much of his work. As a result of Yuri's and his collaborator's work in this area, we now have a much more realistic picture of this important membrane protein, and we know much more about how it functions. In addition, several anomalies in the amino acid sequence have been cleared up, and the work of the Ovchinnikov group has led not only to its complete amino acid sequence, but also to a better understanding of its functionality. Probably it is best to quote from Yuri's own words to describe the strategy [7].

"In setting up the strategy for the structural analysis of bacteriorhodopsin one had to take into account the unusual properties of this protein. As is well known [5], bacteriorhodopsin repeatedly spans the purple membrane and is therefore embedded within the lipid phase. Hence the high affinity of this protein for lipids and its relative "hydrophobicity" characteristic for the majority of integral membrane proteins. We, therefore, had a reason to expect that the isolation of bacteriorhodopsin and its structural study can hardly be based on the standard arsenal of methods of protein chemistry. This circumstance as well as the microbial nature of bacteriorhodopsin first gave us an idea of using, for the structural study of the protein, a now popular procedure of express sequencing of the appropriate DNA fragment especially as we had available the methodology applicable to *Halobacterium halobium*.

However we accepted an alternative approach, namely, direct study of the protein, since in addition to the primary structure it also provides valuable information on the reactivity and other properties of the whole molecule and its fragments, on the location of the active center,

polypeptide folding, etc., all these data being directly relevant to the structure-function relationship of the protein. In other words we believe that "reading-out" of the protein sequence from the structure of the corresponding gene deprives us of important information, perhaps, even more important than the primary structure as such. Our structural work with bacteriorhodopsin provided a good example for the above statement, since it yielded valuable knowledge of its topography and the mode of action".

This work on the primary structure led to additional work on the functionality of the protein, using not only their own data but the X-ray data of Henderson and Unwin [8]. These investigations resulted in a model of the functionality of bacteriorhodopsin which appears to be consistent with the work of several other important groups working in this field. It's certainly worthy of note that in deriving this model, Yuri Ovchinnikov used immuno-chemical approaches, as well as physical and chemical methods to understand its structure. And perhaps the work I have cited on bacteriorhodopsin and its analog, bovine rhodopsin, were the crowning scientific achievements of this extraordinary man.

Yuri Ovchinnikov — scientific statesman. Now let us consider the second aspect of Yuri Ovchinnikov's life — his role as a scientific statesman and scientific ambassador. I remember that I first met Yuri at a Gordon Conference on peptides over 20 years ago. Yuri and I immediately took to each other, and he went from the Gordon Conference with me back to Boston, and we discussed science all the way. It led to our becoming close friends and scientific colleagues. Yuri really had a way with people. He knew people, and he knew how to interact well with them. Following that meeting, Yuri and I interacted in many different ways. He not only visited me in Cambridge and Boston, but I visited with him in Moscow, in Riga, and in Pushchino. I will never forget the time he came to Boston in about 1975, and he wanted to meet with the then-President of the National Academy of Sciences — Philip Handler. It was summer time, and Phil was at his usual summer retreat, Woods Hole. Yuri and I had dinner together on a warm summer evening with Bob Woodward, and one thing led to another, and before we knew it, Yuri, Bob and I were in a talk fest that lasted well into the morning. In spite of this, Yuri got up, and we left at 7:00 a.m. for Woods Hole. Yuri wanted to discuss with President Handler the state of USSR-USA scientific relations, and he accomplished that in a most urbane manner. One could never have guessed what had gone on the night before!

I also remember Yuri's role as scientific ambassador during the celebration of the 250th anniversary of the Soviet Academy of Sciences. He was the quintessence of a good host. He was with people and he made them feel at home. By that time, Yuri had not only been elected a Corresponding Member of the Soviet Academy, but in 1970, a Full Member, and in 1973, a Member of the Presidium, followed by his election in 1974 as Vice President for both Chemistry and Biology of your Academy.

Yuri had the ability to "reach out" to people, and this quality allowed him to serve as a leading representative of soviet science in the councils of the world's international scientific organiza-



Yuri Ovchinnikov speaking at the 65th birthday celebration of Elkan Blout at Harvard in July 1984

tions. Let me mention just a few of his good works in this area. In 1978, he was made a member of the board of the Badger Institute of the Swedish Royal Academy of Sciences; in 1977, a member of the Scientific Commission for Chemistry of the Salvé Foundation. From 1982 on, he was a member of the Standing Committee on Structure and Statutes of ICSU, the International Council of Scientific Union. From 1984–1986, he was chairman of the Federation of European Biochemical Societies, and, in addition, he was a foreign or honorary member of many Academies of Sciences. In addition, he was given the CIBA Foundation Gold Medal and the Lenin Prize, the State Prize, and three Orders of Lenin, as well as receiving honorary doctor degrees from the University of Paris, Uppsala University, and Grenada University in Spain.

Of course, I knew Yuri in respect to our work in our respective Academies of Sciences. I remember when he visited my home in Belmont in 1972 with the then-President of the Soviet Academy of Sciences, M. Keldysh. This was soon after the Polaroid color photography process had been introduced, and we had a great time taking pictures with the new color camera.

I also remember Yuri very well during the opening ceremonies of this Institute. That was really a great week, when we planted trees and when we visited with a bevy of world-renowned scientists, such as Linus Pauling and Dorothy Hodgkin.

I also remember with particular poignancy the time during the "Cold War", when Yuri, somehow or other, managed to attend a wonderful celebration at Harvard of my 65th birthday. He was vital, charming, and happy during those two days.

I also remember more stressful times, such as when a series of articles appeared in the *Wall Street Journal* claiming that Yuri Ov-

chinnikov's work on snake venoms had a military angle. I queried Yuri about this charge, and he told me that no such work was going on at the Shemyakin Institute. Since I had also been working on naturally-occurring toxins, I felt impelled to write a letter to the editor of that well-known scientific publication, the *Wall Street Journal*, which was published on May 8, 1984 [9]. I should say that this communication from me was printed in toto, and that following that letter, no further editorials appeared on the subject of Yuri Ovchinnikov and the development in the Shemyakin Institute of "undreamed-of biological weapons" under the direction of Yuri Ovchinnikov.

1984 was an important year in international science, because that was the year in which our National Academy ended its two year freeze on exchanges with the Soviet Union, and we resumed the annual meetings of Officers of the two Academies. During the Cold War, these meetings were tense and did not accomplish much, even with the help of such internationally-minded soviet scientists as Eugenie Velikhov, Raoul Sagdeyev, and Yuri Ovchinnikov. We did, however, manage to keep the scientific personal exchanges between the USA and Soviet Union going, and that, perhaps, was no mean accomplishment.

I can't help but reflect on how Yuri would have enjoyed the present state of affairs, namely, the ending of the Cold War and the freedom of science and other aspects of the Russian scene. It is a tribute to Yuri Ovchinnikov's clarity of thinking, his drive, and his effectiveness, that we now stand in this group of buildings that represent the pinnacle of soviet biochemical sciences. I have told people several times that you have the best P-3 facility that I have ever seen. In addition, you have super laboratories, a wonderful scientific heritage, and, I fervently hope, a brilliant scientific future.

Finally, a few words about Yuri Ovchinnikov as a friend. As I indicated, he had a very inquiring mind, and he interacted well with people. Following our first meeting in 1970, we became increasingly friendly. We visited each other in our laboratories; we visited with each other in our homes. When Yuri got an idea and wanted to do something, such as taking a walk or attending the movies, his favorite words were "let's go". And these two words indeed typified his life. During the nearly two decades I knew Yuri, I found that always and in all ways he was reliable both as a scientist and as a person. Yuri was not only a social person but also a very sensitive one. Let me quote from a memoir on Yuri I wrote for the American Philosophical Society [10].

"Friendship was as important to him as his work. He had a feeling for human relations and was not afraid to show strong feelings and emotions. I remember hearing part of a telephone conversation in which he was demanding that someone in Moscow give him the reason a certain scientist was not allowed to visit the States. He had real concern for his colleagues and associates at the Shemyakin Institute and strove to make them better and more independent scientists. He felt almost a "father's" responsibility to all who came under his jurisdiction. He was understanding of the racial and ethnic problems of the Soviet Union and did not support many of the then-current poli-

cies regarding emigration. A revealing article appeared last year in the NIH Record on Dr. David Goldfarb, a Fogarty Scholar. As some will remember, Dr. Goldfarb tried to emigrate from the Soviet Union in 1979 but was not allowed to do so. In the above cited NIH Record article, Goldfarb is quoted as saying, "The KGB said I had access to secrets and I could not leave". "The charge was not true, — he said, — and I am grateful that the Academy of Sciences' Vice President Yuri Ovchinnikov confirmed this assertion, a rare display of defiance for a Soviet official".

This support for science and scientists, be they minor Siberian scientists or major refusnik scientists was typical of Yuri Ovchinnikov. Because of his vigorous support of science and scientists, Ovchinnikov was mentioned as one of Moscow's new generation in a major *Newsweek* article in 1985 on Gorbachev. Many scientists feel that Yuri Ovchinnikov would have been a natural choice for the Presidency of your Academy, but that was not to be, because of his illness. Although Yuri was obviously seriously ill at the time of the most recent meeting of the Officers of the National Academy of Sciences and those of the Soviet Academy of Sciences in January 1988 in Moscow, he continued to remain active as a Vice President of your Academy until his death. Some feel he lived his life so fully, with such commitment and drive, that he burned himself out at an early age. There is no question, however, that Yuri Ovchinnikov had a rich, rewarding and full life that many who live to their 80's and 90's never achieve. He will long be remembered by scientists from around the world as a major spirit of 20th century biological and chemical science.

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