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## “I think that the small peptides are the best for healthy ageing...”, an interview with Vladimir Khavinson

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**Abstract** Since its inception in 2000, *Biogerontology* has published interviews with some of the most renowned and intellectually influential biogerontologists, including Len Hayflick, Robin Holliday, Denham Harman, Vincent Cristofalo, Claudio Franceschi, Leslie Robert, Ken Kitani, Geroge Martin, Zhores Medvedev and John Maynard Smith. These interviews have explored the minds of these scientists in all aspects of their lives combining the private and the professional. Together, this series is a remarkable document providing an insight into the history of ideas in modern biogerontology. Here we present Vladimir Khavinson talking about his life and work in Russia during and after the Soviet times, his ideas on stress and health, his discoveries of the healthy ageing promoting small peptides, and other anti-ageing interventions.

**Keywords** Anti-ageing · Stress · Longevity · Thymalin

>I have known Dr. Vladimir Khavinson (VK) for more than a decade now, and we have met numerous times, mostly during international conferences held in different countries. I have always been fascinated by Khavinson's energy, enthusiasm and power of persuasion. He has

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been very active in the management and organisational aspects of ageing research and politics at the European and the global levels. In April 2011, he was elected the President of the European Region of the International Association of Gerontology and Geriatrics (IAGG-ER). I (SR) got the opportunity to know a little bit more about his life story, achievements and expectations, after the executive council meeting of the IAGG-ER, held in Athens, Greece, in January 2012. At the roof-top restaurant of the hotel with the Acropolis in the background, we talked for more than an hour or so on a chilly January morning (*see picture*).



*SR: Now that we are here for the executive meeting of the IAGG-ER, let us start from here itself; what is this organisation?*

*VK: This is a very important organisation; it is the brain for gerontology in Europe with its three sections—biological, social and clinical—all aimed*

to promote the highest levels of achievements in gerontological research and training in Europe. European Regional IAGG is one of the 5 regional branches under the IAGG global umbrella together with those from Asia and Pacific, Africa, South America and North America; and the European region is the biggest one with 37 member national gerontological societies from 34 countries.

*SR: How do you see yourself, as a gerontologist or as a biogerontologist, and what is the difference?*

VK: I am a biogerontologist, and biogerontology is the fundament of gerontology as a whole, because clinical gerontologists must shoulder on the basic knowledge obtained by biogerontologists. The same can be said about social gerontology in a way.

*SR: When did you enter the field of biogerontology and why?*

VK: My career started in the Soviet Union. I graduated from the Military Medical Academy in Leningrad, now St. Petersburg, in 1971 and served as a military doctor since then. In 1976 I got back to the Military Medical Academy as a scientist and in 1982 organised a special laboratory on bioregulation there, and I was the chief of this lab. The aim of this lab was to develop drugs to increase resistance of the military people to hazardous factors, especially to atomic weapons, because that was the time of the international cold war, and then later on the incident in Chernobyl made it even more important.

*SR: Was this a job given to you by the authorities to develop such drugs for the military or was your personal interest too?*

VK: It was my personal interest too. After I had read some articles by Hans Selye about stress, which was my first interest from student days already in 1968–69, I became even more fascinated. Stress has been a very popular topic....

### **From sun-signs to stress and peptides**

*SR: Sorry to interrupt you, but I am also curious to know a little bit about your age and other such things...*

VK: I was born in 1946 in Germany. My father was a military officer, and was posted not far from Berlin

after the Second World War when the Soviet troops were in Germany. I was born on the 27th of November, I am a Sagittarius.

*SR: Is this sun-sign association an important factor?*

KV: Very important..!

*SR: Does your being a Sagittarius has something to do with your interest in science?*

KV: Yes, very much.

*SR: In which way?*

VK: I think people born to this sign have more energy, I don't know why, but I feel I am much more energetic than others. It is very important for me not only to listen and study, but to act; I like action. By the way, I began my scientific work already from my second course at the Academy. But before that, I was a cadet student in the Suvorov Military School in Minsk for 6 years and I graduated from it with a golden medal. Frankly speaking, it was very difficult to join that school because it was the best school in the Soviet Union. Excellent education, good food, sports and discipline were school priorities. Thanks to my gold medal I managed to join the Military Medical Academy, actually a unique institution in the Soviet Union or even may be in Europe, which accepted students from many countries, including those from Asia and Africa. The history of the Academy dates back to 300 years ago. It was started by the Russian Tsar Peter the Great. All our prominent scientists in physiology and medicine such as N.I. Pirogov, I.P. Pavlov and others studied and worked at the Academy. It is a part of the history of medicine, not only Russian, but also European. I am only a small link in this chain. For example, when I was a second year student at the department of physiology, where famous I.P. Pavlov used to lecture, I felt myself like a grand-student of I.P. Pavlov, and it was very exciting.

*SR: I can feel that excitement; but coming back to your interest in stress....*

VK: The theory of stress is strongly important for me and served a crucial turn in my investigations. The stage of stress is very significant. During the first stage, the thymus, the pineal gland and the immune system become suppressed within 24–48 h, and this point of stress is called the stage of alarm. The second period is the stage of resistance, in which the pineal gland

comes to respond. But in case there is no proper response from the pineal gland, whatever the reason may be, genetic or some other factor, then the disease occurs. I wanted to follow this up and used to discuss these issues with my friend and co-student Vyacheslav Morozov. It is very important not to be alone, and to discuss your ideas with others. I discussed everything with Morozov. So we started thinking how to improve the second stage—the stage of resistance, and because thymus and pineal gland were the main parts involved, we decided to obtain the substance from the thymus and inject it into the organism in the second stage of stress to enhance body resistance.

*SR: You started doing that when you were still a student or had finished studies?*

VK: We were still students of the fourth course of the Military Medical Academy. We contacted a meat factory, got some thymus from calf and started obtaining peptides. Why peptides? You remember Andrew Schally, he worked with the releasing factors, which were peptides produced in hypothalamus and regulating hypophysis...

*We got interrupted. A group of 5 or 6 Chinese tourists, staying at the same hotel, came to the same roof-top restaurant and started taking pictures and talking among themselves. This was a bit of a distraction but we continued after a while...*

VK: So our main idea was to affect the regulation of hypothalamus, pineal gland and thymus, by using peptides. We tried to get these peptides from the corresponding organs, and we did not know at that time that A.V. Schally, and his colleagues, also worked on this, and he was awarded the Nobel Prize for this discovery in 1977.

*SR: So you isolated these peptides from thymus. But how did you know how to purify these things—you guys were not chemists!!*

VK: No we did not purify, we were using the total extract, and in the electrophoresis we saw many peptides. And then the second source for peptide extraction was the pineal gland. It was in 1986, at a symposium in Leningrad, when academician R. Milin from Yugoslavia showed a lot of interest in our work and asked many questions. He was also doing similar

work on the pineal gland. That opened our eyes and then we started working on the pineal gland.

*SR: OK, so now you had peptides from three parts: thymus, hypothalamus and pineal gland; what did you do next?*

VK: It was very difficult to work with hypothalamus because there was no standard experimental model for that. But working with thymus was easy since the model of the immune system and that of antibodies production was well established. So, we started our work at the Institute of Experimental Medicine (IEM) in Leningrad. By the way, Alfred Nobel allotted funds to this institute for its development. This institute was organised by Prince Alexander Oldenburgsky. There was an argument as to which of the two institutions - IEM or Karolinska Institute in Sweden—should be granted responsibility to award Nobel Prizes in Physiology or Medicine, and finally that honour was given to the Karolinska Institute.

*SR: How did you start working at IEM, did you get a job there or what?*

VK: At that time the immunological school was headed by the academician V. I. Ioffe, and we went to him, because it was impossible to do good immunology research elsewhere. He gave us space in his school and we began our investigations in the effects of extracts from thymus and performed experiments.

### **Cancer, cross-species and lifespan extension**

*SR: On what systems did you perform the experiments for testing peptides?*

VK: Firstly on mice, and we started with young mice exposed to radiation, but later on we decided that old mice were a very good model. In my view the best pathology model is ageing: you take young and old animals, see their differences, and do your treatment and see if you can make the old mice healthier.

*SR: That will be a kind of rejuvenation experiment...*

VK: Yes, absolutely, and I think this model of old animals is the best physiological model to restore any function—immune function, brain function and so on. Old animals suffer immune deficiency, especially in the function of T-lymphocytes; not in quantity but in

quality. Our extract from thymus stimulated the activity of T-lymphocytes, and the restoration of the immune function in old animals was very striking.

*SR: But what about this cross-species issues, you were using extracts from calf thymus and were testing it on mice and rats, and were expecting to use it on humans—are there any problems in mixing these species?*

VK: That is a very important issue. After we had seen that the thymus extracts showed very strong effects, we started collaboration with V. N. Anisimov in 1970. Now Professor Anisimov is the Chief of the Department of Carcinogenesis and Ageing at the N. N. Petrov Research Institute of Oncology, is also the President of the Gerontological Society of the Russian Academy of Sciences and is a member of the Russian Academy of Sciences. At that time he was not working on cancer, but on the endocrine system. He worked at the laboratory of the famous scientist V. M. Dilman. We went to meet Professor Dilman, and told him that we had extracts from thymus and pineal gland, and we wanted to investigate their effects on tumours. V. Anisimov showed lots of interest in doing these experiments. He was very young, about 25 years old, he is 1 year older than me. By the way, he was born on 7 December—another Sagittarius!!

*SR: Welcome back to the story of sun-signs...!!!*

VK: The important thing is that Anisimov took pineal gland extracts and tested them in transplanted tumour-bearing mice. I remember even today; there were 10 control mice and 10 experimental mice and he injected the latter with the pineal gland extract. We had prepared the extract in the drug factory in a ready to use form.

*SR: Which factory was that?*

VK: It was a drug factory located at the premises of the meat factory in Leningrad. This factory took raw materials from the cattle, and we designed new technology to get peptides from thymus and from pineal gland. By the way, the very first drug developed on the basis of thymus extract, thymalin, is now at the pharmaceutical market in Russia, and millions of people enjoy using it with no side effects.

*SR: So what happened with the experiments Anisimov did?*

VK: Two or 3 weeks passed and Vladimir Anisimov called; he was very excited and told me that he got super results. The extract from the pineal gland had suppressed tumours by 82 %, and Professor Dilman was extremely surprised. He immediately wrote a paper for the magazine of oncology.

*SR: A Russian journal?*

VK: Yes, it was the Russian journal “VOPROSY ONKOLOGII”; this paper was published in 1973; 82 % suppression was remarkable.

*SR: Were you a co-author on that first paper?*

VK: Of course, Dilman, Anisimov, Morozov and Khavinson. We also tested other extracts and substances. The most effective was the pineal gland extract, melatonin was number 2 showing 50 % of tumour suppression, and the third place in effectiveness belonged to the extract from thymus. Today it is 42 years that we have worked with Anisimov and we have published many papers together. All our activities in gerontology have been developed together. The reason for this was that after this investigation, we started experiments on the effects of these extracts on lifespan. And we started preparing documentation for the Pharmacology Committee of the USSR Health Ministry to get authorization for clinical trials, and one of the requirements was to indicate LD 50, i.e. to find out lethal toxic dose. So Anisimov started experiments to find out the toxic effects of the extracts from pineal gland and thymus, but there were no toxic effects. Extracts from pineal gland extended the lifespan of mice by 20–30 %, and a considerable suppression of all tumours was registered. Thymalin produced a bit weaker effect on lifespan but the same strong effect as regards tumour suppression. Twenty-five experiments were done on lifespan—I think it's the only place in the world where so many experiments on lifespan have been made!!

*SR: But all this was done only with the model system of rats and mice?*

VK: Yes, and these experiments were then very carefully planned in accord with international requirements—special conditions, special water and all that. It was possible because the Institute Director where Anisimov worked, academician N. P. Napalkov, had a long term experience in collaboration with the WHO and IARC and had worked there for over 10 years, so

he managed to organise the laboratory at his institute to investigate the effects of carcinogens on animals and people, and this laboratory met international standards. We performed all our experiments in this laboratory. Anisimov was the chief of the laboratory after Dilman left. Whereas other laboratories in Russia were not very good at that time, this laboratory was the best.

*SR: And you were still together with your friend Morozov from the Academy?*

VK: Yes, we were together.

*SR: OK, these were all a kind of anti-cancer effects. Where did the ageing aspect come in?*

VK: Well, we investigated ageing of the immune system as a very good model. I used to work in the surgery department of the Military Medical Academy, and they were checking these patients after the Chernobyl catastrophe. We witnessed strong depression of the immune system in the patients. After we began the injections of Thymalin to these people during the resistance stage of stress response, we noted many good effects, and our idea about stimulating resistance appeared confirmed as correct. At the same time, I compared stress with ageing, because ageing is a continuous chronic stress, and we see the same effects as the severe short stress. So when we injected Thymalin to old animals or to old people, we observed a restoration of the immune system, in terms of the activity of T-cells.

### **Cold war, Soviet Union and the human trials**

*SR: This is interesting that you were able to inject people; was it so easy to do that with human beings?*

VK: Yes, at that time in the Soviet Union, it was easy. There was no ethical committee, no big restrictions. We prepared all our documentation in 1975 and sent it out to the Pharmacology Committee of the USSR Health Ministry and very quickly we got permission for clinical trials, and we began it in 20 clinics all over the Soviet Union.

*SR: Were these military clinics or general public clinics?*

VK: General public clinics. The reason for this was that this testing drew attention of lots of scientists as

good research projects, and more than 60 laboratories throughout the Soviet Union got involved. Most importantly, preparing these drugs was free of charge.

*SR: Why was it free of charge?*

VK: Because the factory was state owned, and also the people from the factory, for example the director and the manager, were co-authors on my patent in 1978 granted in the Soviet Union. Later on we got the patent for Thymalin from the USA. I got several awards and I quickly became colonel in rank.

*SR: Did you ever do active military service also?*

VK: Of course, but as an investigator; there were 16 laboratories and my laboratory was one of the biggest with 30 officers in it. We investigated 10 drugs, from hypothalamus, from thymus, from pineal gland, from prostatic gland, from retina, from brain cortex and so on.

*SR: Why retina?*

VK: Because at that time both the Soviet Union and the USA were preparing the laser weapons to destroy retina. We decided to obtain peptides from retina. We collected 200,000 eyes from cattle at the meat factory, and I personally designed a method for getting retina from the cattle. Approximately 50 mg retina comes out of an eye, and it was almost impossible to get it from pigs. We collected 2–3 Kg of retina from the cattle, and obtained peptides from that raw material, then we tested the peptides on animals and got very good results especially with respect to quick restoration of the retina after laser damage, not complete restoration but partial, but still it is the only drug that can do that.

*SR: Does it also work as a preventor?*

VK: Yes, it even protects against some damage, but we were testing it mostly for its therapeutic effects. For this drug I got an award from the USSR Ministry of Defence.

*SR: Why did you prepare this drug in Russia and not in Europe or USA?*

VK: To make this drug in the USA, approximately 200 million dollars will be needed, and nobody would do it.

*SR: Do you mean to say that those were the good achievements of the Soviet times, and that these kinds of good things came out of that system?*

VK: When the Soviet Union crashed, we organised the Institute of Bioregulation and Gerontology in 1992, last December it celebrated its 20th birthday, and my laboratory became part of this institute. At that time many other laboratories were destroyed, but I was able to transfer all my people, my patents and my lab to this institute. And then we started to work on gerontology problems.

*SR: So what was the research done at this new institute?*

VK: We started to study peptide extracts. For example, we managed to isolate a dipeptide Thymogen from Thymalin, which had more than 50 peptides in it. Later on, we isolated peptides in collaboration with the Institute of bioorganic chemistry in Moscow and its director academician V. T. Ivanov. Then we turned to peptide synthesizing. Later on, we started getting synthetic peptides, because it was much cheaper and easier. We approached the Pharmacology Committee of the USSR Health Ministry and got their permission for clinical trials, and within 4 years we could even market this drug. Thymogen was one of the first synthetic dipeptide drugs in the world, and now it is possible to buy it everywhere. It was manufactured as a spray for intranasal use and as an injection solution. We have got 5 patents for it in the USA. We organised a company with people in Seattle and this company launched clinical trials. They raised 50 million dollars from various investors, including Microsoft, and have been continuing for 10 years, but it remained unfinished.

*SR: Why, did it not give good results or was there some other reason?*

VK: No, the results were good. They were testing the drug for treating Caposci sarcoma as a complication of AIDS. I had told them that it would not be a remedy for AIDS. Although the treatment could improve immune function and helped combatting the disease at an early stage it could not cure AIDS, and so the trial was stopped at Phase-2, and by that time the funds were over.

### Peptide drugs for health

*SR: What about the present state of these drugs; you have about 20 peptide drugs which are being used and marketed in Russia...?*

VK: To date I have created 6 drugs which are being distributed at the Russian pharmaceutical market, and in Ukraine and other CIS countries. These drugs are Thymalin from thymus for stimulating immune function, Epithalamin from pineal gland for restoring melatonin level in old people, Samprost from prostatic gland to restore the function of prostate, Cortexin from brain cortex for the restoration of brain function, Retinalamin from retina for the restoration of retinal function, and Thymogen which is a short peptide designed on the basis of Thymalin for immune system correction.

*SR: Are these drugs to be obtained by doctor's prescription or anybody can buy them over the counter in a drug store?*

VK: Anybody can buy them without doctor's prescription, first of all because they are safe and produce no side effects. Moreover the system of pharmaceutical turnover is not that tight.

*SR: So, can even healthy people use these drugs as preventors?*

VK: The drugs are largely recommended for therapeutic purposes, although in some cases they can be used for prevention. However, we designed and produced about 60 food supplements of the same origin and specific to different organs. They are produced in sub-therapeutic doses and employed as geroprotectors for enhancing human vital resource.

*SR: Are any of these drugs available in the European and USA markets?*

VK: The drugs are not available elsewhere and it seems hardly possible in the nearest future. As far as it concerns food supplements the process of registration is either in progress or in the process of negotiation with the companies in the USA, Europe, India and South America. We have 19 extracts and plenty of synthetic peptides, which can be used as food supplements.

*SR: So, just to recount and clarify—all these extracts and peptides are targeted for some age-related disease and problem, but we have no idea if these drugs can be taken by healthy people as age prevention measures, is that right?*

VK: Well, with age organism's functions slightly deteriorate even if it does not suffer any serious

problems. And here peptides become very useful to switch on the mechanism for enhancing the fading vital resource of the organism. So healthy people may take them as geroprotectors to maintain health and vitality as long as possible. Elderly people who definitely experience some health problems should use them in a complex treatment.

*SR: Do you also have any data on the mechanistic aspects of these drugs?*

VK: Oh yes, we have very important results. For example, in 2003 we showed the influence of the pineal peptide on increasing the telomerase activity and the length of telomeres in the fibroblast system undergoing ageing. I presented the data at one of the Cold Spring Harbour conferences, and they were published in the same conference book where Carol Greider's data are published (she later became a Nobel Prize laureate). Then we also showed the effects of these peptides on the regulation of gene activity in the brain, heart and other tissues of mice, and in a tissue-specific manner. I think these small peptides are signalling molecules acting directly. I think that this peptide signalling is a very important mechanism in evolution, because when two amino acids or three amino acids joined, the first information molecule appeared. These peptides are the same in all organisms, and in our food, and when we eat plants or animal protein, these peptides become available in the stomach after proteins are cut into small pieces, and then they penetrate the cells and regulate DNA.

*SR: Are there then any special foods which have more or less amounts of these peptides?*

VK: This needs to be tested, but we have tested more than 100 proteins and have seen that some proteins have more of these small peptides than others. In my view small peptides are very important information molecules, which interact with DNA, and now lots of people are making models about how peptides interact with DNA. We are now sending this paper to a journal in Russia, but will then be printed in English.

### **Publication priorities and politics**

*SR: Why do you publish your work mostly in Russian language, doesn't that keep it from becoming known and acknowledged in the wider world?*

VK: I publish in Russia first of all because it gets published in 1 month and then its English translation can become available in another 2 months or so.

*SR: Why haven't you published in those high profile journals such as Nature, Science, PNAS and others?*

VK: I think I will do that in future. I had sent some papers to Nature, but they rejected even without refereeing.

*SR: Why is that so; do you think it is some kind of discrimination?*

VK: Yes, I do think so. It is very difficult to get a paper from Russia published in those journals. And also for me it is a matter of claiming priority. I cannot wait for the long time those journals take. And I think that very soon there will be a Nobel Prize given to peptide-gene interaction.

*SR: Do you think your research on the health beneficial effects of peptides matches up with the criteria for a Nobel Prize?*

VK: Well, the work is very important but we need to show these mechanistic interactions and tissue specific mechanisms and all that. I am working in collaboration with lots of people within Russia and internationally, and perhaps we can work out the mechanisms.

*SR: So, during this almost 40 years of research in this area, have you created the next generation of scientists who think in the same way and who can take this field of research further or are you a one man show?*

VK: I think it is very important to attract and train students, not only from medicine, but also from biophysics, biochemistry, mathematics, system biology and bioinformatics who can make models, and who can design experiments. Several of my students work as independent scientists in many countries.

*SR: What is the state of ageing research in Russia—is there some important work going on?*

VK: There is some work on the genetics of ageing and extension of lifespan but not much. I think the peptide idea is one of the best. There are some private organisations trying to promote ageing research, but it is a very insignificant effort.

## Life, longevity and beyond

*SR: Are you satisfied with the international recognition of your work, do you think you got the recognition you deserved or not?*

VK: Well, recognition is important, but I think the results are more important. I have produced very good results and that is enough for me.

*SR: How long you think you are going to live?*

VK: My father died at 92, my mother is still alive at 92, I have developed a special complex from the pineal gland, from thymus, from brain, from vessels and from heart which I take as injections, not as food supplements, for 10 days every year. I think I am physically and mentally not more than 45 years old even though chronologically I am 66 years old at present.

*SR: Has anything become reduced with age?*

VK: Yes, energy, I think my energy level is not as high as it used to be. Whether peptide therapy can improve different functions needs to be double checked.

*SR: How long would you like to live if you have full and free choice?*

VK: Over 90 if I am fully active.

*SR: How do you want us to remember you?*

VK: I am a scientist and the organiser of science, and I want to be independent from anybody, so I need money to become independent. I am very happy about

scientific results, about new knowledge, new results, new experiments make me very happy.

*SR: Where do you get knowledge—from books?*

VK: Yes, from books, from arts, from people, from experiments. I like Shakespeare, but the number one book for me is that of Faust, I have read it again and again, especially the end of Faust, the last 10 lines, what is the sense of life, I know many of his writings by heart. One philosopher, B. Spinoza, said that everybody should read 60 books but main task is to find those 60 books – and I think I know about 40.

*SR: What is the message from Faust that you learnt?*

VK: That everybody must be very glad by what one has done for others and not for oneself—our purpose should be to make people more happy, more healthy.

*SR: Have you done enough?*

KV: My drugs have been used by over 15 million people, this gives me great satisfaction.

*SR: It has made you famous, but has it made you rich also?*

KV: It gave me some independence. I can now do whatever I want to do. But the best is yet to come.

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