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The passage of Szent-Györgyi to biophysics: a journey from the blur of the boundaries of disciplines through the instruments used for research with a stopover at the *paprika* centrifuge and arriving at the super lasers.

Ever since I became a Rector, I have had to get used to the fact that other people direct my everyday routine. In fact, by now, I have also had to get used to the fact that other people give the titles to my lectures. Originally, I thought that now I would start with excuses because I have never held a presentation with such a complex title. Then, I have decided not to be apologetic because I have heard it from a great colleague of mine that he had only came here because he had never seen such an interesting title. So, all I have to do is to make an attempt to fill this content page looking title with substance. To begin with, and to some extent provide an explanation, we should listen to the words of a truly authentic person from an early 1940s radio coverage.

"My uncle on my mother's side Mihály Lenhossék was also a professor, a very famous histologist who dealt with microscopic anatomy and he set the intellectual trend in my family. I had a little problem with my uncle, as he was once a very precocious child, he believed that excellence is always very precocious, but I started to develop very late, so the family looked at me in general as if I were a fool. And when I was fifteen years old and told my uncle that I want to pursue a scientific career, he protested in every possible ways, and told me that I could only become a beautician. Later on his view improved a little, and he agreed to my becoming a dentist. Then when I finished high school he allowed me to go to his laboratory to work. Then I worked in anatomy for three years, but it did not satisfy me. I wanted to see life and what it was, so I went to physiology than worked with bacteriology – those bacteria are very small. Then I realized that the whole world was like that bacterium: for me it was overcomplicated; then I started to work with molecules, and in this way I started to become a chemist. Then I realized that for me even a molecule is overcomplicated. So then I started to work with electrons, which are very small parts of the molecule, and it is a huge separate discipline: quantum mechanics or wave mechanics which studies electrons. And I was quite mature when I started to work with these disciplines, so I went from science to science and I've felt that life is the totality of this all."

These are the words of Albert Szent-Györgyi. His thoughts provide the spine and outline of this lecture. I would also add that he is on a similar view with several world-renowned researchers. One of the sovereignties of our profession *Arthur Schawlow*, an American researcher who belonged to the greatest spectroscopists of the late 20th century, and who in 1987 received the Nobel Prize partly for the discovery of lasers, had the following witty saying: "*my problem with diatomic molecules is that in those there is one atom more than there should be*." For a physicist a rabbit is an incredibly complex universe, while the diatomic molecule is on the edge so that we may just dare to work with it. From what we have just heard, this line of thought had formulated in Albert Szent-Györgyi long before that. In the following, first I want to talk broadly about the thoughts that led Albert Szent-Györgyi towards simplicity. Then we look at what lasers have to do with the sub-molecular world that Albert Szent-Györgyi has actually talked about as a goal that he wants to reach. As a closing session, I shall make an attempt to connect two timely subjects. In this year, quite reasonably, we have talked a lot about Albert Szent-Györgyi and the laser facility that is being built in Szeged. These two are seemingly fully separate issues. I hope that by the end of the presentation, I can convince you that one doesn't really have to force it to link these two matters together.

Already in 1941, four years after he received the Nobel Prize, (at this time Albert Szent-Györgyi still works here in Hungary), Albert Szent-Györgyi said that among the molecules it is the protein molecules, those very large and bulky things, of course, now we have to think on an atomic scale, that cannot in themselves explain the subtleties of the vital signs of life.[1] He said this when others had just wondered on the protein molecules since at that time molecular biology was very very immature and one major step in this direction, through the discovery of vitamins, was actually made by Szent-Györgyi. Szent-Györgyi also raises the idea that in certain circumstances proteins may act like conductors. A little naively, he imagined proteins as small wire particles in which the mobile electrons do something important and the basics of the vital signs of life should be researched in this area. In 1947, he wrote the following: "*The findings are all the more accumulating and suggest that the biological reactions are the disorders of the common electron systems which may not just allow us to understand these reactions, but also describe them with a quantum mechanical formula*.[2] I emphasize that this idea was so ahead of

[1] Szent-Györgyi, A. Nature (London), 148, 157–159, (1941)

[2] Szent-Györgyi Albert, *Az élő állapot* (The Living State) Kriterion kiadó, Bukarest (1973) page 67

its time that at the time, even if it was put politely, it seemed to be nonsense: not many people thought that it was a useful theory.

From 1947, Szent-Györgyi is in the United States and engaged by then primarily with muscle research. (He had already started muscle research in Szeged, in fact, he achieved his fundamental results here. In the early 1940s, the publications by the Department of Medical Chemistry at the University of Szeged were the internationally authoritative sources for muscle research. Papers[3] published by Szent-Györgyi, Straub and Banga are still cited.[4,5] It is important to see that Szent-Györgyi, even at the beginning of his research career, liked to cross the boundaries of disciplines. Although he was a biochemist, he had the strange habit of inviting physicists to his own laboratory. For example there worked, on the field of ultrasound generation, *Sándor Szalai* who later became the founder and legendary director of the Institute of Nuclear Research in Debrecen. So the fact that for his research Szent-Györgyi has relied on co-sciences is, in fact, noticeable from the beginning of his research career.

After his departure to the United States, Szent-Györgyi began to work for the Marine Biology Laboratory in Woods Hole where he was somewhat disappointed. This was possible partly because the people who had invited him did not really keep their promises. However, it is likely that another fact also played a role, namely, that previously in Hungary Szent-Györgyi had a kind of celebrity status. In addition to his Nobel Prize, this status was also owed to the fact that during the Second World War, Szent-Györgyi played a little bit of a James Bond role: he went to Istanbul to negotiate an Anglo-Saxon- oriented peace treaty, which on the one side made him a wanted man by the Gestapo, while, on the other hand, by offering his Nobel Prize in support of the Finnish war, Szent-Györgyi became a wanted man by the Soviets. (I think that it is a proof for the fact that someone is on the right track, when he is seen as an enemy by all extremists.) In spite of all this, after the war, the Soviets actually wanted him to get involved in Hungarian public life. At first, he was

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[3] a) Banga, I. & Szent-Györgyi, A. Studies from the Institute of Medical Chemistry University of Szeged, Vol. 1 (ed. Szent-Györgyi, A.) 5–15 (S. Karger AG, Basel, 1941–1942)
b) Szent-Györgyi, A. (ed.) Studies from the Institute of Medical Chemistry University of Szeged Vol. 1 17–26 (S. Karger AG, Basel, 1942)
c) Straub, F. B. in Studies from the Institute of Medical Chemistry University Szeged Vol. 2 (ed. Szent-Györgyi, A.) 3–15 (S. Karger AG, Basel, 1942)
d) Straub, F. B. in Studies from the Institute of Medical Chemistry University Szeged Vol. 3 (ed. Szent-Györgyi, A.) 23–37 (S. Karger AG, Basel, 1943)

[4] Celler, K. et al. J. of Bact. 195 pp. 1627–1636 (2013)

[5] Braun, P. et al. Proteomics 12, 1478–1498, (2012)

committed and enthusiastic, but later realized that the Soviet system is not going to do much good for the country. Then Szent-Györgyi started to make enquiries on how he may relocate to the United States. As I have mentioned, in Woods Hole things did not go into the right direction. So much so that Szent-Györgyi had practically ran out of research money. It was then time for a major role of a financier who had Hungarian origins: *Stephen Rath.* He was able to provide good financial conditions. This was a very successful period in Szent-Györgyi's life as in 1954 he received the Lasker Award and in 1956 he was elected to become a member of the American Academy of Sciences. By this time, in addition to muscle research, Szent-Györgyi had been very busy with the idea of what role particles, that are smaller than molecules, play in the fundamental vital signs of life.

At the beginning of the 1950s, Szent-Györgyi announced that the formation of cancer is somehow explained by the behaviour of electrons. That was when he became interested in free radicals. Free radicals are molecules with an unpaired electron. In terms of our topic for today, it is sufficient to know about these electrons that they are only peaceful when they are in pairs. If there is an atom or a molecule in which an electron does not have a pair, it will look for one. It has to find another electron, therefore, these free radicals are highly reactive. Free radicals also occur naturally in our bodies, but enter the body through different external influences as well. Free radicals may indeed cause many problems in the body thus some sort of protection is needed. Antioxidants serve for this purpose. Antioxidants are molecules that are able to neutralize free radicals. Such an antioxidant is vitamin C that had been discovered by Szent-Györgyi, hence, from the beginning, he had attached great importance to the interaction between free radicals and antioxidants. In his thinking, this also suggested that the matter related to the electrons should also be looked into.

Szent-Györgyi started to learn quantum mechanics after the age of 70. Around the age of 60, he was only just talking to people who could inform him a little more about quantum mechanics. Then, in 1960, Szent-Györgyi published a very important book with the title: *Introduction to a Submolecular Biology.* This work was in many ways very decisive, even though some of the things have since already been outdated by science. However, it is still certain that there are a lot of important ideas in it. I cite two parts from this book. The first idea: "*something very important a whole dimension is missing from our line of thinking, without which*, [*the problems* Sz. G.] *cannot be managed*", the other idea is the concept of *charge-transfer.* At that time, many people denied the existence of charge-transfer, as at first sight, protein molecules are typical insulators and in insulation charges do not usually move. Protein molecules are quite tricky things because a protein molecule behaves very differently depending on whether it is dry or wet. Protein molecules are already very complex structures, and in addition to that, comes the nightmare of experimental scientists, physicists and chemists: water. Water is actually a very good thing when you're thirsty, but in a lab it is terrible because it is always line of where it shouldn't be present. All substances that we meet either absorbs or excretes water, but at a time when they should not. There is always water in a vacuum system. It simply crawls in. I say to this all the time that there is perfect vacuum everywhere, for example, in this room only that it is filled with air. In addition to that, in the vacuum of lab equipment there is also water. Seriously again, whether something is wet or not wet changes the properties of a material very much. However, the original assumption of Szent-Györgyi that dry protein molecules act as insulators and become conductors with moisture is a more complex issue which is very difficult to determine experimentally. In addition to that, the more complicated mechanisms of conduction processes may also play a role.[6] These complications come, in no small way, from the fact that in a macroscopic protein sample, during a moisturizing process, water molecules may be present in three forms: as free water, as tied to the distinct sites of the chains formed by the binding protein molecules and inside the (protein) molecules. However, the really important idea is not the role of water, but the charge-transfer itself: the process that in an atomic sense charges may transfer to longer distances consequently there may be a molecular-sized "power line system".

By 1970, Szent-Györgyi ran out of money, in fact, he was in a very desperate situation. It seemed that his research would completely come to an end. Partly, this was due to the fact that Szent-Györgyi was unwilling to write conventional applications, and, by that time, those gallant times were over when an easy proposal worked such as the single line submitted by Warburg in 1921: "*Ich benötige 10 000 mark*" (I need 10000 marks).[7] Fortunately, in 1971, a major US daily newspaper made an interview with Szent-Györgyi, where he said that he actually had an idea on how to cure cancer. Szent-Györgyi was a good communicator and able to present his ideas in a convincing way and, at the same time, he also added that he has no money to carry out such research. As a result of the interview, he was called by *Salisbury*, a Washington-based lawyer, who asked Szent-Györgyi where money can be sent, if he

[6] Rosenberg, B. Nature, 193, 364–365, (1962)

[7] Koppenol, W.H., Bounds, P.L., Dang, C.V. Nature Rewievs Cancer 11, 325–337, (2011)

wants to donate 25 dollars to Szent-Györgyi's research? Szent-Györgyi told him to send the money to the Institute and Salisbury did just as he was told. This act was followed by Szent-Györgyi sending the lawyer a thank you letter. The fairly rich Washington-based lawyer was so amazed by this fact that he began to wonder how it was possible that he gives 25 dollars, such amounts are very often donated by the people in the US, and a Nobel Prize winner says thank you to him in a long letter. By looking into the matters, he found out that the situation was indeed very difficult. Therefore, he launched a professional fund-raising campaign and founded an organization called the National Foundation for Cancer Research where, until his death, Szent-Györgyi had been working. The Foundation financed the research of Szent-Györgyi and others. It can be stated that the research that took Szent-Györgyi from biology to physics was funded at that time solely by that organization. Salisbury himself also took part in the work as he was the president of this organization.

Since the mid 1970s, Szent-Györgyi has established contact with *János Ladik*. János Ladik is an excellent quantum chemist. It has almost run out of my mouth to say physicists. (This is a good example for the fact that the blur between scientific fields is nothing new. The Schrödinger equations were invented by physicists and they are the ones who solve it, but if someone wants to calculate the structure of a molecule the Schrödinger equation is needed and this is usually already called quantum chemistry. Moreover, this varies in line with the traditions of university campuses. In Szeged, when I was a student, the subject was called molecular physics, while at the University of Technology it had the title of quantum chemistry because the person responsible for the subject named it in such a way. János Ladik was an excellent quantum chemist who started early to refine the thoughts raised by Szent-Györgyi. The original suggestion that molecules conduct electrons as if they were tiny pieces of wires is a rather naive one. Of course, on proper foundations based on physics, the problem may be investigated and a theory may be worked out. For example, on the slide illustration a letter is shown that was written by Albert Szent-Györgyi to János Ladik in which he requests János Ladik to write a few pages of summary for a semi-scientific book on the so-called band model of electric conductivity on which theory they used to work together. Here is another letter. I like this one very much because it starts with the following: "*I shall begin with a question that may seem a dumb question*". With all due respect, I must say that Szent-Györgyi was right in his suspicion. The question also demonstrates that the learning of quantum mechanics did not go smoothly because surely Szent-Györgyi had misunderstood the uncertainty principle which he refers to here. However, Szent-Györgyi was also aware of this aspect. In 1960, he wrote the following: *"Previously, each time I have begun a new line, I have always had the hope that I could learn all aspects of the field. With quantum mechanics, this is not the case …"*.[8] However, what is truly remarkable and honourable is the fact that someone actually sets out, at the age of 70, to learn a completely new and not easy discipline from the beginning just because he thinks that it is needed for the solution of his proposed problem. Even if in the details Szent-Györgyi had to face failures, he did deduce a very important thing here. In 2003 a conference was organized in Szeged by Professor Csizmadia and his colleagues. In the conference booklet of the conference the organizers quote a saying by Szent-Györgyi, certainly not by accident, that sums up the-above mentioned facts. Essentially, Szent-Györgyi says the following (right in his previously mentioned book on submolecular biology): "*The distance between those abstruse quantum mechanical calculations and the patient bed may not be as great as believed*". I believe that, in a sense, this is an essential criterion for modern sciences. Very often we work with very abstract and esoteric calculations, but more and more often these are getting close enough for practical applications. The distance between new scientific evidence and the tools for everyday life is very much shortened.

Let's look to see where Szent-Györgyi's suggestion is now. A recently published summary article[9] concludes that yes, there is such a phenomenon, although different in detail from Szent-Györgyi's initial idea, but founded on essentially the same basic idea. There is indeed charge-transfer in the DNA. The DNA helix is linked by base pairs and according to measures these electrons may travel up to 100 base pairs which means that the sections in the DNA can communicate with each other via electron signals. Furthermore, this form of communication is very sensitive to whether there are defects in the base pairs. It appears, therefore, that the DNA does indeed behave as a conductor and if the molecules are a little defected, they do not conduct well. In addition to that, the phenomenon is also sensitive to those proteins that attach themselves to the DNA and cause it to somehow twist. Via the electron transfer process, the DNA somehow performs scans within itself and this basic process may have a very large role in the DNA's self-repair mechanism i.e. in the correction of genetic defects which is one of the wonders of life (and for the understanding of which, a lot of research is still necessary). In the light of these results, it indeed seems that Szent-Györgyi did think of a very basic function

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[8] Szent-Györgyi Albert, *Az élő állapot* (The Living State) Kriterion kiadó, Bukarest (1973) page 6

[9] Sontz, P.A. et al. Accounts of Chem. Res. 45, 1792–1800, (2012)

Let's return to the experiments. With experiments there is a critical parameter: fast temporal resolution. Here we talk about phenomena that happen fast, but we can only understand these phenomena if we follow them in time. (If someone asks me why we need fast temporal resolution, my favourite example is pole vault. If we assume that our brain works like a camera and takes a picture every 1 second then pole vault would probably be the most boring sport because we would usually see two things: a jumper with a big stick is getting ready for something and then lies on his back on the sponge. The fact that it is a complicated process and quite interesting things happen during the process, for example, the pole bends then straightens and pushes the jumper over the bar remains unnoticed because these details are blurred on one picture. This can only be seen if there is fast temporal resolution, for example, if we can take photos using fast shutter lens and create still images of each section.) This is needed in the case of electric molecular processes. How can this be done? This is mainly done by lasers. Back in 1984, together with *Géza Groma* and *György Váró*, we carried out a test which was about the charge motion within a long protein molecule (rhodopsin). This in its time was the world's fastest experimentally detected bioelectric signal.[10] I could say now that we started to research what Szent-Györgyi had suspected and that would sound good in this presentation, but it would have nothing to do with the truth, as at that time it did not even cross our minds to think about Szent-Györgyi. (In retrospect, I regret this since Szent-Györgyi was still alive and we could have sent our results to him.) The true story of the project is perhaps more interesting from the point of view that its production process characterized Hungary in the late 1970s.

The Biological Research Centre (BRC) was an internationally renowned workshop for rhodopsin research. Among other tests, the electrical behaviour of molecules was extensively studied.[11] During the course of the tests, it came up that a partner should be found who could perform much faster measurements. Back then nobody knew our laser team in Szeged, especially not in Hungary. Professor Keszthelyi, who was at that time the director general at BRC, and came from Budapest, went, of course, to the laser team at the Central Research Institute for Physics (CRIP) and told them that he needs help to measure fast temporal signals. At the KFKI, professor Keszthelyi was told: "Lajos why don't you go over to the other side of the Tisza where we go to do measurements because there they have the type of dye laser such tests can be done with."

[10] Groma, G. Szabó, G. Váró, Gy. Nature, 308, 557, (1984)

[11] Keszthelyi, L. Ormos, P. FEBS Lett. 109, 189–193, (1980)

Professor Keszthelyi learned that we exist by going first to Budapest. I would add that Géza Groma was one year my senior at the University of Szeged, and lived in the next door room at the student's hall, but somehow, until then, it had not turned out that they have a problem that we may be able to solve. I make a notice here saying that although the measurement was at that time a world record, we were convinced that the phenomenon itself is much faster than how we detect it. Later it turned out that this proposition was indeed true.

With the development of lasers, temporal resolution improved further. In the second half of the 1980s, femtosecond lasers appeared. We have also worked on this subject. In part, we have developed such lasers and partly tried to exploit the new possibilities that were provided by the femtosecond laser. There was an issue actually which was a kind of dream from the discovery of lasers: selective photochemistry. Through an example, the basic idea is the following: take a molecule which has one atom at the end and connected to the atom through typical binding energy. This bond is to absorb the light with those wavelengths that are characteristic to the bond and which are different from what the rest of the molecule may be able to absorb. Let's tune the laser here and shoot a big one into the molecule and we can be sure to break the bond we have chosen. With this process, the molecules could be cut to our liking. When this was tried, it turned out that this is absolutely not the case. Within the molecule, energy spreads under ten femtoseconds, and the molecule always breaks and the same place, in fact, where it is the weakest. It's like as if we wanted to cut a chain at a specified location without scissors and we can only pull the chain, which, of course, breaks where it is the weakest.

For over 15 years, this very nice idea resulted only in failure because if energy really spreads, and the molecule breaks where it usually breaks, then that is no different from what can be achieved through heating, only that it is slightly cheaper to powerfully heat a material than playing around with laser. Nevertheless, there is a solution even though it is not that simple. It is called the optimal control of quantum systems. Now we take femtosecond lasers into consideration and with these lasers energy is delivered in such a way that the spread of energy within the molecule is taken into account. Thus, the molecule is not considered to be a ball, but a real quantum system i.e. with its microscopic properties taken into account (I usually say that we teach the atoms to dance). For his work in the field of femtochemistry: chemistry made with femtosecond impulses, *Ahmed Zewail* received a Nobel Prize in 1999. I would like to elaborate on this topic because, on the one hand, it is technically very close to what we are talking about, and secondly, it illustrates the changes experimental science has gone through in little more than half a century.

The title promised a discussion on the *paprika* centrifuge, but I do not want to talk about that. I want to discuss however how the complexity of the experimental systems has changed. It is true that in the 1930s, during Szent-Györgyi's first experiment a good technician could produce all experimental devices, only that, if the person was a chemist, they may needed a good glass-technician as well. Two or three good professionals could produce all experimental devices and technically operate a world-class laboratory.

Now let's look at the device that we had used for a quantum control experiment in Jena.[12] This experiment was one of the most complex experiments I have ever devised, but which is by no means unusually complex by today's standards. A work day was the following: we went to work in the morning, we set the laser in roughly three to four hours and we could start working after lunch. (I counted once that the laser system had 46 mirrors out of which if only one was set a little bit incorrectly then the system did not work at all, or even worse, it did work, but imperfectly and this led to miscalculations.) To begin working meant that we got at the device in the first place with which the experiment itself was performed: the molecules were made to dance. For this I say, that by today's standards, this was a moderately complex experiment. I also add that the investment costs were around 4 million marks (in 1997–98) and the system was built for nearly two years. This is how a paprika centrifuge looks today.

Of course, temporal resolution continued to improve. In the early 2000s, a new technique appeared that further shortened the time scale. In 2001, the Hungarian *Ferenc Krausz* and his colleagues succeeded in producing attosecond impulses.[13] (The current world record is 80.) What is actually an attosecond? That is 10^{-18} second. In proportion: an attosecond is to 1 second what 1 second is to the age of the universe. If, at the end of the 1940s, Szent-Györgyi could have dreamed something to Szeged, then recounting his dream, he probably would have said the following: in my sleep I had seen an attosecond laser center in Szeged, which system can be used to observe those electrons which I think provide the basics for the vital signs of life. (Surely, Szent-Györgyi would not have used the term attosecond laser because at that time not even the word laser was known.)

In the last and short chapter let's look, through an example, at what atto-science really is. Based on the calculations by *Cederbaum* and his colleagues,[14] we know that following an ionization process, the gap, that is the result of the lack of an electron, moves along a long oligopeptide molecule (Gly-Gly-NH-NH_3) in 5–6

[12] Glaß, A., Rozgonyi, T., Feurer, T., R. Sauerbrey, R., Szabó, G. Appl. Phys. B 71, 267–276 (2000)

[13] Hentschel, M. et. al. Nature, 414, 509, (2001)

[14] Kuleff, A.I. Lünnemann, S. Cederbaum, L.S. Chem. Phys. 414, 100, (2013)

femtoseconds. Moreover, this movement is sensitive to which molecular structure modification we are dealing with. (Szent-Györgyi was talking about something like this when he was working on the basics of the vital signs of life.) At this moment, however, only theoretical calculations are available. A revolution in the development of calculating methods and computers, which revolution occurred in the preceding one and two decades, was required to perform the above-mentioned calculations, but for the experimental examination of the phenomenon further considerable progress in attosecond technology is necessary.

Finally let's ask a question worthy of Szent-Györgyi: why are protein molecules, such as the DNA itself, stable even when the sun shines on them? There are a lot of ultraviolet photons in the sunlight. If protein molecules had studied from the introductory quantum mechanics textbooks, they would know that as a result of ultraviolet light, it would be their duty to immediately fall apart because an ultraviolet photon loads so much energy into the molecule that the chemical bond inside them should break. As mentioned earlier, within some ten femtoseconds energy seeks out the weakest bond and breaks it. So that this wouldn't happen, and experience shows that this doesn't happen or happens far less than it is expected, something must occur in less than some ten femtoseconds. What could that be? Remember what Szent-Györgyi had said: "*something very important a whole dimension is missing from our line of thinking…*". There is an answer to the above-mentioned question which answer seems to have been discovered by evolution as well. The answer is conic section. This term is rather abstract. The word section indicates that in case of polyatomic molecules, it may happen that the surfaces of the excited and ground state potential energy intersect. In this intersection, the electron cannot decide where it belongs and this dilemma results in the fact that the electron instantaneously disposes of its excess of energy and falls into a ground state. This is a very important process which certainly plays a crucial role in the fact that molecules stay in one piece. Of course, it also applies to this case that the behaviour of conic intersections is clearly outlined by theoretical calculations, but direct experimental data are not yet available. So if you asked me what that task, worthy of the intellectual heritage of Szent-Györgyi, may be on which the Szeged laser centre should begin working? My answer is that the direct experimental study of the conic sections is surely such a task.

Acknowledgement

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