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Fundamental Questions: An Interview with Professor Albert Eschenmoser

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Abstract: Albert Eschenmoser, Professor at The Scripps Research Institute (TSRI), La Jolla, California, USA, and Professor Emeritus at the Swiss Federal Institute of Technology (ETH), Zürich, Switzerland, was presented with the Benjamin Franklin Medal in Chemistry, 2008. The occasion gave the author the opportunity to speak with Albert Eschenmoser about his fascination with chemistry, the unusual progress of his career, and his groundbreaking approach to the study of the origins of life.
Key words: Albert Eschenmoser, Interview, Chemistry, Origins of Life

Resumen: Albert Eschenmoser, Profesor del Instituto de Investigación Scripps (TSRI) en La Jolla, California, EUA, y Profesor Emérito del Instituto Tecnológico Federal de Suiza en Zürich, Suiza (ETH), recibió la Medalla Benjamín Franklin en Química del 2008. Este evento propició la oportunidad al autor (de *News&Views,* TSRI) de entrevistar a Albert Eschenmoser sobre su fascinación por la química, el inusual avance de su carrera, y su investigación fundamental al estudio del origen de la vida.
Palabras clave: Albert Eschenmoser, entrevista, química, origen de la vida

Professor Eschenmoser was born in Switzerland, took his Ph.D. at the Swiss Federal Institute of Technology (ETH) with Ruzicka in 1951 and served as Professor of Organic Chemistry at the ETH. His interests in terpenoid biogenesis [2] turned towards synthesizing molecules. His first major success was to synthesize colchicines [3], but Eschenmoser truly made a name for himself when in 1972, with Robert Woodward, he synthesized Vitamin B12 [4]. Now a Professor Emeritus at ETH and Professor at The Scripps Research Institute, Eschenmoser has spent much of his later career on what he calls "chemical etiology"— the systematic attempt to determine why nature chose certain molecular structures for gene carrying, out of all the possible structures. This should, he believes, also help guide a theory on the origin of life on earth. Towards this end, he has investigated ribose synthesis and synthesized alternative backbone structures for DNA and RNA. In studying these, he discovered that nature's structures are not the only possible ones, opening up the question of how DNA and RNA ended up with these structures-the optimal ones for replication, thus enabling life [5].

The 2008 Benjamin Franklin Medal in Chemistry is presented to Albert Eschenmoser for seminal investigations into the origin of nucleic acid structure, which through systematic chemical synthesis have begun to answer the fundamentally important question of why DNA and RNA have the structures they do [6,7].

Mika Ono Benedyk: What is it about chemistry that you find the most fascinating?

Albert Eschenmoser: Chemistry is at the center of natural science, with physics at its right, and biology at its left. What has much to do with my personal fascination for chemistry is its close connection to biology. At the bottom of what is living in this world are chemical compounds and chemical reactions. You look at the world somewhat differently as a chemist, because you see on and behind the surfaces of molecules, structures, reactions, processes—how they can go well, how they can go wrong, how they relate to diseases.

Mika Ono Benedyk: How did chemistry originally catch your interest?

Albert Eschenmoser: Growing up in Switzerland, I attended a university preparatory school, where I had an extremely popular chemistry teacher. I liked him and, above all, he liked what he taught. Teachers at this level of education often have a strong influence on the field that science students are going to choose later.

Mika Ono Benedyk: How did you decide to focus on a subject area within the field of chemistry?

Albert Eschenmoser: My PhD Professor at ETH was Leopold Ruzicka, a famous organic chemist of Yugoslavian origin who had received the Nobel Prize in 1939 for his work on terpene natural products. At the time I was doing my PhD, he had become interested in collecting Dutch paintings and was therefore frequently traveling abroad. I never saw him in the laboratory during the time I did my PhD work. I was lucky, in a way, because I could do what I myself decided to do. Working on problems in terpene chemistry, I happened to be lucky indeed, because the results of my work came to be of much interest to Ruzicka.

Mika Ono Benedyk: What happened next in your career?

Albert Eschenmoser: After passing my PhD examination in 1951, I stayed on at Ruzicka's Institute, where he immediately gave me the opportunity to take my own graduate students and to build up my own research group. After four years, I became a *privatdozent*, a position more or less equivalent to Assistant Professor. After another four years, I was offered a professor-

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ship in America, and that made the authorities at ETH begin to wonder whether they should promote this young man to Professor, so he doesn't leave. And that happened, so I stayed on.

Mika Ono Benedyk: How did you end up in America after all?

Albert Eschenmoser: I think it was in 1989, in the mountains in Switzerland at Manfred Eigen's "Winter Seminar," that I met Richard Lerner (President of The Scripps Research Institute) who was giving a lecture on catalytic antibodies. I was also giving a lecture, on our work on alternative nucleic acids. That meeting was the beginning of developments that led to my becoming a part-time member of the Skaggs Institute for Chemical Biology at Scripps in 1996.

Mika Ono Benedyk: You are famous for your earlier work synthesizing vitamin B12, and also for more recent work on the origins of life. How did you find yourself changing research topics?

Albert Eschenmoser: In principle and over all, I did not really change. My first research paper in chemistry was on a natural product, a sesquiterpene, and my last paper, on nucleic acids, in a way was also. The change you mean by your question was from the synthesis of complex natural products to studying the properties of alternative nucleic acids. That happened when I was at the age of 61. Changing the type of questions within a field is healthy and important. In my case, it kept me from becoming disinterested in research with advancing age.

Mika Ono Benedyk: How did your vitamin work cross over to the origin-of-life work?

Albert Eschenmoser: Actually, there is a very close connection. The synthesis of vitamin B12 was a collaborative effort with Robert Burns Woodward's group at Harvard. The project took 12 years, from beginning to the end. It was a huge problem, because vitamin B12 was, at that time, by far the most complex organic molecule synthesized by chemical methods. Vitamin B12 is also a very old molecule, etiologically speaking. It is a vitamin to us because only microorganisms can produce it. Microbiologists tell us that very primitive microorganisms can be excellent producers of B12. After the work on its chemical synthesis, we continued research on vitamin B12 by doing chemistry of possible relevance to the molecule's biosynthesis. That chemistry taught us that the complex structure of vitamin B12 becomes a remarkably simple type of structure if one approaches it chemically from the "right," namely the natural, direction. This experience led us to ask: "What does it mean that this molecule is of intrinsic generational simplicity, while its structure looks so complicated? Where was this molecule coming from?" We started doing experiments that were inspired by these questions, and slowly but gradually they gave us answers. From being engaged in such chemistry and in such questions on the origin of a natural product structure such as vitamin B12, it was a small step to asking about the origin of the molecules most fundamental to life, the nucleic acids.

Mika Ono Benedyk: Could you tell me about nucleic acids?

Albert Eschenmoser: In biological evolution, living organisms acquire properties that allow them to survive in a changing environment. They reproduce these acquired properties in their progeny. The information required for these properties to be transferred from generation to generation is written down in the backbones of DNA molecules by a specific linear sequence of the famous four "letters," adenine (A), cytosine (C), guanine (G) and thymine (T). Such sequences are replicated from generation to generation with the help of what is arguably the most important molecular interaction in biology: the legendary Watson-Crick base-pairing. The question that underlies our work is: Can we understand on the level of chemistry why Nature chose as the molecular basis of her genetic function RNA and DNA, and not some other molecular system?

Mika Ono Benedyk: How is your approach to the question of the origin of life different from what went before?

Albert Eschenmoser: The crux of the question of the origin of life lies in the fact that it refers to chemical processes that happened more than 3 billion years ago. The origin of life cannot be discovered, as other things in science, it can only be "re-invented." In contrast to what some people may think, you cannot be overly ambitious when you do research on the origin-of-life problem, because any contribution you may make is bound to be a modest one. There will be no final solution of the problem. The absolute most you could dream of is a chemical model of life's origin, a reconstruction. Yet, the relevance of the question—scientific, technological, as well as philosophical—is such that any effort is worthwhile and important.

What differentiated our approach to the origin-of-life problem was asking and pursuing questions that refer to the function and not the formation of molecules. This avoids the handicap of the intrinsic uncertainty that burdens research referring to events of the past.

The role that nucleic acids play today in contemporary life can only mean that they must be a very old type of molecule, that they must have been part of a very early type of life. There are scientists who believe that life emerged in a primordial world as the very consequence of the emergence of the nucleic acids we know today. Irrespective of whether or not this was the case, as chemists we may ask why Nature has specifically chosen these molecules as her genetic material. The chemist can imagine and argue that by the same type of chemistry that must have led to today's nucleic acids, alternative types of nucleic acids could also have been formed, nucleic acids of a structure similar but not identical to those we now know. Here lies the opportunity: the chemist can synthesize by modern chemical methods alternatives that he imagines might

also have been possible solutions to Nature's problem of creating a genetic system, and ask, "could such alternative materials have been capable to function?"

Fortunately, addressing this question is easier than it would seem, because it leads immediately to a further question, which is: "What is the most important chemical property that makes the nucleic acid system capable of fulfilling the genetic function?" The answer is unambiguous: the capability of Watson-Crick base-pairing. This, in turn, defines a question that we can answer experimentally, namely, whether the alternative nucleic acids we may synthesize as chemists are capable of undergoing Watson-Crick base-pairing. If the answer is "yes," then the idea Nature could have used that alternative material remains a possibility. If, however, the answer is "no," then we know that such an alternative could not have been an evolutionary competitor to the nucleic acids we know today.

In this way, we can create by chemical synthesis a landscape of alternative nucleic acid structures that Nature might have had at her disposal when it came to the point when a genetic system had to be chosen. Experiments show that the capability of Watson-Crick base-pairing is widespread among nucleic acid alternatives. So we are left with the question: "Why did Nature choose RNA and DNA and not one of those alternative systems?"

Mika Ono Benedyk: How many contenders for genetic molecules are there?

Albert Eschenmoser: We don't know. That is what we would like to know. Only further work will tell. We continue to do such work in our group which I run at Scripps together with Ram Krishnamurthy.

Mika Ono Benedyk: What do you see as the impact of your approach on the field?

Albert Eschenmoser: This is not a simple question. At the time before this work was done, the general opinion in life science was that today's genetic material is functionally and structurally unique. I remember in 1989, when I gave the first lecture on a model of a nucleic acid alternative and pointed out that the system undergoes Watson-Crick base-pairing more strongly than the natural one, it came as an absolute surprise. After the lecture, a biochemist came to me, and said, "this is impossible," arguing that Nature's biochemical functions were always best and that, in Watson-Crick base-pairing, pairing most strongly had to be the best. That turned out to be incorrect. One of the consequences of our work was to move scientists away from the idea that Nature used the criterion of maximizing base pairing strength in choosing DNA and RNA.

Another consequence of the work relates to the question of whether it is conceivable that nucleic acids could have assembled themselves prebiotically. There are scientists who believe that they did. There are others who disagree and favor the scenario of life having started via primordial "metabolic" cycles. I believe that the nucleic acids we know today are structurally too complex for having assembled prebiotically, and that one should follow up the idea that they were preceded by simpler replicators. What we can and should do experimentally is to map the landscape of all chemically conceivable molecular systems deemed to have had a potential for self-assembly and self-replication under primordial conditions. In attempting to pursue such a goal, it becomes clear that this kind of work cannot be separated from a search for the chemistry that may have been the chemistry of a primordial metabolism. Eventually, such work may lead to a model of how chemistry and biology met in their most intimate way, in the origin of life.

Mika Ono Benedyk: At what point does chemistry become life?

Albert Eschenmoser: That depends on how we define life. It is quite instructive to observe how the scientific community has tried to define life over the past 100 years. It is notoriously difficult, because life covers a realm extending from organized chemical processes up to the noosphere. Such a phenomenon cannot be easily condensed into a definition. But for the purpose of our discussion, we may rely on the pragmatic definition NASA is said to be using: "Life is a self-sustaining chemical system that is capable of Darwinian evolution."

To learn the difference between "nothing-but chemical" and "living" chemical matter really constitutes one of the goals of the interdisciplinary research on the problem of life's origin.

Mika Ono Benedyk: Do you see this as a mystery?

Albert Eschenmoser: Yes, it's a mystery, and it's wonderful to be confronted, as a scientist, with a mystery. In a way, it is also an obligation of natural science to be concerned about the problem, because the question behind it is so fundamental.

Profesor Albert Eschenmoser.

The relevance of the question (of life's origin) - scientific, technological, as well as philosophical - is such that any effort is worthwhile and important, says Professor Albert Eschenmoser

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