CHEMICAL HERITAGE FOUNDATION

ALBERT ESCHENMOSER

Transcript of an Interview
Conducted by

Tonja A. Koeppel

at the

Swiss Federal Institute of Technology

on

7 October 1985

(With Subsequent Corrections and Additions)

Albert Eschenmoser

CHEMICAL HERITAGE FOUNDATION
Oral History Program
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ALBERT ESCHENMOSER

1925 Born in Erstfeld, Switzerland, 5 August

Education

1949 Dipl.sc.nat., Swiss Federal Institute of Technology (ETH), Zurich
1951 Dr.sc.nat., Organic Chemistry, Swiss Federal Institute of Technology (ETH), Zurich

Professional Experience

Swiss Federal Institute of Technology, Zurich
1956-1960 Instructor, Organic Chemistry
1960-1965 Associate Professor, Organic Chemistry
1965-1992 Professor, Organic Chemistry
1992- Professor Emeritus

The Scripps Research Institute, La Jolla, California
1996- Professor, Skaggs Institute for Chemical Biology

Honorary Degrees

1966 University of Fribourg
1970 University of Chicago
1979 University of Edinburgh
1989 University of Bologna
1990 Johann Wolfgang Goethe-Universität
1991 Université Louis Pasteur de Strasbourg
1993 Harvard University

Awards

1949 Kern Prize, ETH
1956 Werner Prize, Schweizerische Chemische Gesellschaft
1958 Ruzicka Prize, ETH
1966 Fritzsche Award, American Chemical Society
1973 Marcel Benoist Prize, Eidgenössiches Departement des Innern
1974 Robert A. Welch Award, Houston

1976	Kirkwood Medal, Yale University
1976	August Wilhelm von Hofmann Medal, Gesellschaft Deutscher Chemiker
1976	ACS Centennial Foreign Fellow, American Chemical Society
1977	Dannie Heineman Prize, Akademie der Wissenschaften
1978	Davy Medal, Royal Society
1980	Dr. Cliff S. Hamilton Award in Organic Chemistry, Lincoln, Nebraska
1981	Honorary Fellow, Royal Society of Chemistry
1981	Tetrahedron Prize for Creativity in Organic Chemistry, Pergamon Press
1982	George Kenner Award, University of Liverpool
1984	Arthur C. Cope Award, American Chemical Society
1986	Wolf Prize in Chemistry, Wolf Foundation
1988	M. M. Janot Medal, Gif-sur-Yvette
1991	Cothenius Medal, Deutsche Akademie der Naturforscher Leopoldina
1994	CIBA-Drew Award in Biomedical Research, Drew University
1995	H. H. Inhoffen Medall, Gesellschaft für Biotechnologische Forschung
1998	Nakanishi Prize, Chemical Society of Japan

ABSTRACT

Albert Eschenmoser begins the interview with a discussion of his early life and education. Born in Switzerland, he attended school in the canton of Uri. At the age of sixteen, he decided that he wanted to become a secondary school teacher, and attended an Oberrealschule in St. Gallen. He received his Maturität in 1944, and continued on to the Eidgenossische Technische Hochschule (ETH). Eschenmoser was encouraged to pursue chemistry, and—inspired by Leopold Ruzicka—concentrated on organic chemistry. His research focused on sesquiterpene chemistry. In 1949, he earned his diploma, and became a doctoral student under Ruzicka. His doctoral thesis addressed acid-catalyzed cyclization, and in 1951 he received his doctorate. Eschenmoser's research interests then turned to the synthesis of colchicine, which his group accomplished in 1959. Next came vitamin B_{12} and the corrin ligand system. ETH collaborated with Robert B. Woodward's Harvard research group on this project, and in 1972 they announced the success of the vitamin B_{12} synthesis. Eschenmoser concludes the interview with a discussion of research funding, his professional recognition, and the ramifications of the vitamin B_{12} synthesis.

INTERVIEWER

Tonja A. Koeppel received a master's degree in chemistry from the Swiss Federal Institute of Technology in 1944. Since then she has written about chemistry, conducted research, and taught college chemistry. In 1973 she earned a Ph.D. degree in the history and sociology of science from the University of Pennsylvania. She is especially interested in the development of organic chemistry in the nineteenth and early twentieth centuries.

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INTERVIEWER: **Tonja A. Koeppel**

PLACE: **Swiss Federal Institute of Technology**

DATE: **7 October 1985**

KOEPPEL: Professor Eschenmoser, you were born in 1925 in Erstfeld in Kanton Uri. Did you stay there? You were not originally from Uri.

ESCHENMOSER: Each Swiss citizen has a citizenship and is not necessarily born in the village of his citizenship. I am a citizen of Balgach in the Kanton of St. Gallen, but I was born in Erstfeld, Uri and essentially spent the first sixteen years there. I went to the primary school in Erstfeld and then I was sent by my parents to the Collegium in Altdorf to attend the Realschule for three years. After that, at the age of sixteen, I was sent by my teacher in Altdorf to St. Gallen.

KOEPPEL: Was this a scholarship? Why did your teacher send you to St. Gallen?

ESCHENMOSER: It is a very involved story. My father was a butcher. Our family did not have any academic tradition and at the age of twelve, when I was sent to the Realschule in Altdorf, I developed the desire to become a primary school teacher. At the end of the Realschule, one of my teachers in Altdorf proposed that I should become something more advanced—a secondary school teacher and not a primary school teacher. In order to become this, I would have to go to a Mittelschule, and he proposed to do that in St. Gallen. There I would attend the so-called Oberrealschule. There was no Oberrealschule in Kanton Uri at that time. And, being a citizen of the Kanton of St. Gallen, it was natural that I would go to the city of St. Gallen to go on with my studies.

KOEPPEL: So, Oberrealschule is really a college preparatory school with emphasis on mathematics and sciences?

ESCHENMOSER: Yes, that's right. Oberrealschule is the equivalent of a Gymnasium except that you don't have Latin and Greek and philosophy; you concentrate on science and mathematics.

KOEPPEL: You must have shown a great deal of potential. Were you mathematically talented?

ESCHENMOSER: No, I never had the feeling that I had some specific talent in that direction. I didn't know what chemistry was. I just liked to go to school. Maybe I liked to go to school because I couldn't think of any practical activity that I would like.

KOEPPEL: You must have had some desire to work in an academic field in some way.

ESCHENMOSER: At that time, I did not know what that was.

KOEPPEL: It was just intuition?

ESCHENMOSER: When you grow up in a small village, there are teachers, priests, and one or two doctors. In such a village, one doesn't know of any other dimensions of academic life. My desire at the age of about fifteen was to become a teacher, and it was only my teacher who convinced me not to become a primary teacher, but to perhaps consider becoming a secondary school teacher. That's why I went to St. Gallen to the Oberrealschule for three years, from 1941 until 1944. At the end of that period, I had developed the desire to become a teacher at a Gymnasium or an Oberrealschule. That meant I had to go to a university. I ended my Oberrealschule with the Maturität and instead of continuing my studies as the Lehramtsschule in St. Gallen, as originally planned, I went to the ETH [Eidgenossiche Technische Hochschule (Swiss Federal Institute of Technology)]. It was natural to do that because the ETH was well-known, and my chemistry teacher in St. Gallen had also studied chemistry at the ETH. That's how I achieved, step by step, my original goal to become a teacher—from the level of primary school teacher, to that of secondary school teacher, to the level of a teacher at a Mittelschule, and, finally, to that of a professor at a university. I think without that kind of stepwise escalation I probably would never have arrived at a university. This is one possible way of growing out of a milieu with no academic tradition and reaching an academic life.

KOEPPEL: Did your parents approve of what you did or did they have reservations about it?

ESCHENMOSER: I had a strong promoter in my mother. She was in favor of the idea that I become a teacher and she was strongly supporting my education. The fact that I liked to go to school, and that I didn't find it necessarily difficult, was enough for my parents to support me.

KOEPPEL: You must have been a good student. Otherwise, they probably would not have

approved of it. Did you like chemistry at this Oberrealschule? What subjects did you take there?

ESCHENMOSER: You cannot choose subjects in the Oberrealschule. The choice you have is the Oberrealschule, or the Gymnasium, or the commerce school. These were the three options at that time. In St. Gallen I was living in the house of my father's sister and I very early met my long-time friend, Ernst Vogel, (now retired director of Fluka Company) who was an extremely enthusiastic young man, studying chemistry at the Abteilung für Naturwissenschaften, at the ETH. My chemistry teacher, Charles Enz, had also studied at the Abteilung für Naturwissenschaften. He also was an enthusiastic chemist and moreover, a fabulous teacher. These two men are probably largely responsible for my becoming a chemist. Originally, I didn't really have any preference either for chemistry or biology or anything else.

KOEPPEL: You went to the natural sciences and not chemical engineering. But, this was also considered to be the preparatory school for Gymnasium teachers. You were thus able to reach both of your goals: to expand into chemistry and to possibly still go into teaching.

ESCHENMOSER: Yes. When I left St. Gallen in 1944 with my Maturität, I was convinced that I would still become a teacher. Therefore, I chose Abteilung für Naturwissenschaften, which was officially an Abteilung for preparing Gymnasium teachers. At that time, one had to begin by taking biology, chemistry, mathematics, physics, geology, and petrography. After two years you had to concentrate and decide whether to become a chemist or a biologist or an "earth scientist". It was very probably a consequence of the influences I mentioned before that I concentrated on chemistry, but again not necessarily because I specifically liked it.

KOEPPEL: You took inorganic chemistry first and you are definitely an organic chemist. Did that play a role in your selection? How was inorganic chemistry taught?

ESCHENMOSER: Inorganic chemistry was taught in a pleasant way. The inorganic chemistry professor was William Treadwell. Did you know him?

KOEPPEL: Yes, I remember him. He was very pleasant.

ESCHENMOSER: He did not necessarily minimize our interest for inorganic chemistry. But, inorganic chemistry was very classical at that time. In retrospect, I feel it was the relationship of organic chemistry to biology, to what is living around us, that may have been a factor of my gradually rising conviction that I should concentrate on organic chemistry. There is, however, no doubt that another strong factor was again a person, namely Leopold [S.] Ruzicka, who gave

the lectures in organic chemistry. To me, he was one of the most powerful lecturers at the ETH at that time. I remember how I was impressed by his first organic course. Each Saturday I went home to my parents who still lived in the Kanton Uri. I didn't have the money to spend the weekends in Zürich, and also I went home to eat well, once a week. After all, this was during the war. Each Sunday I typed my Ruzicka lecture because I decided I wanted to really know these lectures. Typing lectures heard during the week on the weekends is probably the best way of really learning them.

KOEPPEL: As far as I remember, he didn't really follow a textbook. The big [Paul] Karrer book was just a reference book for most students (1).

ESCHENMOSER: Sometimes he actually mentioned the Karrer book, but in an ironic way. He used to tell the story that a Japanese chemist told him that he was a greater chemist than Karrer. When Ruzicka asked him why, he replied, "Because you have never written a book." [laughter] Ruzicka's lectures were extremely intense and reflected his very strong personality.

KOEPPEL: He was very demanding too, wasn't he?

ESCHENMOSER: Yes.

KOEPPEL: He did not seem to be interested in mediocre students. Is that correct that he was always on the lookout for young talent?

ESCHENMOSER: Yes. Because he was known to have a very demanding personality and his institute was known to be a correspondingly demanding institution, students were cautious in choosing his institute.

KOEPPEL: You only saw him when you took examinations?

ESCHENMOSER: He was scheduled to examine me in the Vordiplom and in the Diplom, but he never came. He always asked [Vladimir] Prelog to do it for him.

KOEPPEL: I see.

ESCHENMOSER: I had a nice diploma examination with Prelog as the examiner.

KOEPPEL: You did not have the examination with Ruzicka?

ESCHENMOSER: I never saw Ruzicka in examinations before my Ph.D. I only saw him in lectures. But that was good enough. Should we speak of the ETH now, or would you like to know anything before we move to that?

KOEPPEL: No, I think that I would just like to clarify the dates. Do you remember when you entered and how many years you spent as a student?

ESCHENMOSER: Yes. I went to the school in Altdorf from 1938 to 1941. From 1941 to 1944 I was in St. Gallen. From 1944 to 1949 I was a student at the ETH.

KOEPPEL: That was up to your diploma, which was comparable to a master's degree. In 1944 you entered and in 1949 you finished this stage.

ESCHENMOSER: That's right.

KOEPPEL: You did your diploma thesis in 1949, and then became a doctoral candidate with Ruzicka.

ESCHENMOSER: Again, it was a slightly special situation. My teachers in organic chemistry were Ruzicka, Prelog, and Plazidus Plattner from Chur in Graubünden. I did the Diplomarbeit, the experimental part of the diploma examination, in the laboratory of Dr. Hans Schinz. He was originally a collaborator of Ruzicka, a chemist paid by the Firmenich Company in Geneva who worked on monoterpenoid and perfume chemistry. This was during the period when Ruzicka had retired from active chemical research and had become busy with collecting paintings.

KOEPPEL: How old was he?

ESCHENMOSER: In 1947, he was sixty years old.

KOEPPEL: So he slowed down relatively early, didn't he?

ESCHENMOSER: No, this is more complex. After the war, he had his great time in collecting paintings. He had money from his research patents and he decided to invest it in Dutch paintings. At that time, he was very often absent and the following situation developed. Dr. Schinz had no academic function but ran a laboratory as a consequence of his previous collaboration with Ruzicka. At the time, I did my Diplomarbeit in this laboratory, Schinz was personally not on good terms anymore with Ruzicka. There were some political difficulties; Ruzicka, being a kind of cosmopolitan character and originally a Yugoslav, had developed during the war different ideas about the world than Hans Schinz, being more of a Swiss conservative, had. But Ruzicka, generously enough, allowed Schinz to have Ph.D. students on his own. That's how I became a Ph.D. student of Dr. Hans Schinz, since it was he who had control over the Praktikum of the chemists at the Abteilung für Naturwissenschaften. Ernst Vogel, who I mentioned earlier, had been assistant in that Praktikum as one of Schinz's Ph.D. students while I was an undergraduate. Officially, however, it was Ruzicka who was my Ph.D. mentor.

KOEPPEL: But he was your advisor.

ESCHENMOSER: I never had a chemical discussion with Ruzicka about my thesis during this whole time. This again was a special situation. Ruzicka delegated his functions to Schinz.

KOEPPEL: Was he still the chairman, or was Prelog the chairman?

ESCHENMOSER: No. He was the chairman of the department until 1957.

KOEPPEL: You worked mainly on terpenes and azulenes?

ESCHENMOSER: The topic in my thesis dealt mainly with sesquiterpene chemistry. In part, it developed out of the research which was going on in Dr. Schinz's group. Hans Schinz worked on the isolation of new monoterpenes and the synthesis of irregular monoterpenes that were of perfumery interest. What turned out to be important for my own future research was that he was very knowledgeable about a reaction of central importance in terpene chemistry: the acid-catalyzed cyclization of terpenoid dienes. Certain acyclic terpenoids can be cyclized to give corresponding cyclic compounds by this reaction. His group had about ten Ph.D. students, some of them were working with this reaction. One of Schinz's Ph.D. students, with whom I made my Diplomarbeit, worked on a research topic in this field. My task was to synthesize a new monoterpene of which it was assumed that it would cyclize to a new cyclic monoterpene. But based on my own theory on the mechanism of the cyclization reaction, I predicted that it would not. And as a matter of fact, it did not. That gave me a special reputation as an "expert

on reaction mechanisms" and was my entry into the research field of acid-catalyzed polyene cyclization.

KOEPPEL: What was his name?

ESCHENMOSER: The Ph.D. student?

KOEPPEL: Yes.

ESCHENMOSER: His name was Alfred Lauchenauer; he is now a very successful independent consultant on chemical innovation. I just happened to meet him again a few weeks ago.

KOEPPEL: Then your doctoral thesis was in 1951?

ESCHENMOSER: Yes.

KOEPPEL: And it was also on the acid-catalyzed cyclization?

ESCHENMOSER: The first topic in my thesis was to prove a claim I had made at the time of my diploma work; the theory I had formulated in there allowed the prediction of whether in a given case the cyclization would or would not work. During this time I intensively studied the literature and collected published examples of such cyclizations. Among many others I came across a paper written by Ruzicka on the constitution of the sesquiterpene zingiberene (from ginger oil). This sesquiterpene was known to undergo such a cyclization. However, if Ruzicka's structure of the sesquiterpene was correct, the cyclization, according my theory, should not occur. Therefore, the structure would have to be wrong and of course, I was strongly attracted to the prospect of showing, as part of my Ph.D. thesis, that my teacher, whom I admired, was wrong.

KOEPPEL: What a challenge!

ESCHENMOSER: Yes, what a challenge. However, when I wanted to start my Ph.D. work, Dr. Schinz proposed a topic of his own. I must be grateful to him that he did not push his too much. I told him I disliked his topic (resolution of racemic iron into its enantiomers) and that I

wanted to work on another problem, namely, to disprove Ruzicka's formula for zingiberene. Schinz generously agreed since he was interested in it, too. I must, in retrospect, be very grateful to him that he agreed. Within a month, it was shown that Ruzicka's formula was wrong (2).

KOEPPEL: Indeed!

ESCHENMOSER: Such an experience is extremely important for the psychology of a young man. He will be lost to chemistry, probably forever. That happened to be my beginning. In the wake of this experience, I did a lot of thinking on the mechanism of the acid-catalyzed polyene cyclization reaction. For a young chemist, that period was an extremely interesting time, because a real revolution happened to be going on in organic natural product chemistry. It was the change from the classical to the modern mechanistic thinking. It also happened to be the time (from 1949 through 1951) when the [Robert B.] Woodward era started.

KOEPPEL: Did that radiate into Switzerland?

ESCHENMOSER: Yes, gradually. I think there are various points to be mentioned here. First of all, the ETH group was very fortunate to get into contact with American organic chemistry immediately after the war. That was a consequence of the close pre-war relationship of Ruzicka with important American chemists, such as Roger Adams. Ruzicka was a man of action; when the war was over, he immediately made the connections. It was also due to him that Woodward was invited to come to Europe for the first time. That was an extremely important invitation because it had great impact on the future of organic chemistry at ETH. Sure, Ruzicka was a classical chemist by any standard. But he was a powerful, open-minded one, and a great initiator. There was the open field of terpene chemistry waiting to be reinterpreted by the modern views that were already highly developed in America and England, but were essentially still missing in the basic organic chemistry lectures on the European continent.

KOEPPEL: What were these? Were they reaction mechanisms?

ESCHENMOSER: They called it the "electronic theory of organic chemistry." There were books appearing such as that of Michael Dewar (3). I remember how intensively I studied these books because it was clear that there was something new there that we had not been taught. As it happened, with these new views it was a real pleasure to reinterpret much of the published terpene chemistry. The second part of my thesis had a lot to do with the reinterpretation of the assignment of structural formulas in the terpene field.

KOEPPEL: Did you get into the biogenetic isoprene rule then? Ruzicka is very well-known for his isoprene rule.

ESCHENMOSER: Oh, yes. Now perhaps that's...

KOEPPEL: Am I jumping ahead?

ESCHENMOSER: No. It goes more or less in this direction. At the end of my thesis, which dealt with the cyclization of terpenoid polyenes, it had become clear to me that the structural formulae of cyclic terpenoids, especially sesquiterpenoids, could be derived from acyclic terpene precursors by such cyclization reactions. In my thesis, I proposed new formulas for a number of sesquiterpenes, correcting old ones by following that postulate. Shortly afterwards, I extended the postulate to the then known formulas of cyclic triterpenes by deriving them from squalene. These ideas became the essential mechanistic part of the biogenetic isoprene rule. Ruzicka gave a lecture in Stockholm in 1953 where he proposed these relationships for the first time in public.

I must now pause for a moment and describe how at that time Ruzicka's preoccupation returned from art collecting to chemistry. When he saw that a new development was going on towards reinterpreting terpene chemistry, one paralleled by important advances in biosynthesis—especially of steroids—he became highly interested in chemistry again. His main interest was focusing on the biogenetic relationship between terpenes and steroids. Having been the pioneer in the application of the formal isoprene rule in terpene chemistry, he recognized the opportunity for, and the importance of, a reformulation of the isoprene rule on the mechanistic level. At that time Konrad [E.] Bloch spent half a year in Ruzicka's laboratory, that is, in the laboratory of Dr. [Hans] Heusser, who was in charge of steroid research at the Ruzicka Institute. This too was very important for Ruzicka's return to chemistry, because Konrad Bloch was the major figure in the elucidation of cholesterol biosynthesis. At ETH he experimentally proved the origin of one of the carbons of cholesterol from acetic acid. To be sure, Ruzicka had been interested in aspects of steroid biosynthesis for a long time. I remember how he told us many times that he never believed that cholesterol was formed out of fatty acids, as a German chemist had proposed. The problem of cholesterol biosynthesis had always been in his mind. This longstanding interest had been one of the many factors came together in the early 1950s and brought him back to chemistry, leading to and culminating in the lecture he gave in Stockholm at the IUPAC [International Union of Pure and Applied Chemistry] meeting. There he surveyed the results from his laboratory on the structure elucidation of terpenoids and propounded what he called the biogenetic isoprene rule (4). That name was absolutely his invention.

Another factor that importantly contributed to what was going on at ETH was the problem of the structure of lanosterol. The experimental work on lanosterol was directed by Ruzicka's former assistant [Oskar] Jeger. Ruzicka was eagerly participating, especially when results came to be published. The ETH group determined the structure of lanosterol in

competition with the group of [Sir] Derek [H. R.] Barton in England. The triumph of the ETH group was to have found the correct formula for lanosterol and to have shown that it does not concur with the classical isoprene rule, but is reminiscent of the formula of cholesterol. That was in 1952 (5).

KOEPPEL: There was also the squalene hypothesis—that the whole synthesis went via squalene.

ESCHENMOSER: Yes, absolutely. And there was the Woodward-Bloch paper (6).

KOEPPEL: So, here comes Woodward.

ESCHENMOSER: Yes. That's one of the ways that Woodward came in.

KOEPPEL: Through the back door?

ESCHENMOSER: No, not necessarily the back door. Woodward had been invited by Ruzicka to come to Switzerland and lecture in the scheme of the Swiss-American association. That was in 1948.

KOEPPEL: Was the Woodward Institute established then?

ESCHENMOSER: No, that came much later. Woodward's first visit to Europe was in 1948. He came to the ETH and gave his famous lecture on santonin. Woodward was the young, brilliant star in natural-product chemistry from America.

KOEPPEL: Did you meet Woodward?

ESCHENMOSER: Not in 1948.

KOEPPEL: Ruzicka had a very good relationship with Woodward, and regarded him very highly.

ESCHENMOSER: Yes. He claimed that he recognized the talent and potential of Woodward. That was the time when Woodward was still an aggressive young man, and aggressive young men in their immediate neighborhood are… it's different to judge from far away.

KOEPPEL: Yes. He was quite controversial. Many chemists seemed to reject him.

ESCHENMOSER: Ruzicka, also an aggressive personality, apparently liked him immediately. A sort of fatherly friendship between he and Woodward developed that was very important for all of us. Later on, we will talk about the vitamin B_{12} collaboration, it has its roots in this relationship. It was Ruzicka who brought Woodward close to our institute very early; the relationship extended first to Prelog, and then essentially to all the others.

KOEPPEL: You were a post-doc at that time. What happened after your dissertation? Why did you stay here?

ESCHENMOSER: I was forced by Ruzicka to finish my thesis after essentially one and a half years.

KOEPPEL: That's very early. That was pushy.

ESCHENMOSER: He said, "You don't get any money unless you finish your thesis."

[END OF TAPE, SIDE 1]

KOEPPEL: Did Ruzicka accept the concepts of the electronic theory?

ESCHENMOSER: Without reservation, and at the time after the thesis, he and I had many discussions about this. I considered this as a great honor for me, and it was exciting to be able to discuss with him what he was so interested in. When he published the lecture he had given in Stockholm in 1953, he wrote a chapter which was specifically devoted to the biogenetic isoprene rule, and he put myself and Hans Heusser as co-authors of that specific chapter (4).

Perhaps a word on Hans Heusser. Why is he in that paper? Hans Heusser was a Privatdozent in our Institute and acted as the host of Konrad Bloch when he was at ETH. Stimulated by his guest biochemist, Heusser had started to think about the problem of formulating biosynthetic pathways from squalene to cholesterol via lanosterol and also from

squalene to other triterpenes. For my part, rather conceited as I had become, I was quite critical about the schemes he wrote, and started to think about the problem myself. I was mostly concerned about sesquiterpenes before that. It is clear that what Hans Heusser tried to do had a stimulating influence on my own activity. Therefore, maybe Ruzicka decided that he should be a co-author on the biogenetic isoprene rule chapter.

KOEPPEL: But you are partly credited with it, too. What was your role in it?

ESCHENMOSER: My contributions were all the detailed mechanistic schemes leading to the cyclic sesquiterpenes and triterpenes described in that chapter. They specifically showed for the first time how the triterpenes can consistently be generated by oxidative cyclization of squalene. The scheme which was published corresponds to the one I had thought out.

The next step was concerned with the stereochemical aspect of the biogenetic isoprene rule, which led to the 1955 *Helvetica* paper (7). In the meantime, I had started to work experimentally on the stereochemistry of polyene cyclizations, independently of work done in America by Gilbert Stork. The first paper of this work, in 1954 (8), had been published with Schinz, after I had convinced him that he should extend his studies to the stereochemistry of one of the cyclizations he had been studying. You see, these things are interwoven and difficult to separate. What then came 1955 was the well-known paper, "A stereochemical interpretation of the isoprene rule in the triterpene series" (7) in *Helvetica Chimica*. In there, the previously proposed mechanistic schemes were extended to include the sterochemical course of cyclization and rearrangement steps and it was possible to postulate a consistent network of relationships between squalene and all the triterpene structures know at that time. The paper was co-authored by Jeger, Ruzicka, and [Duilio] Arigoni. At that time Duilio Arigoni was a member of Jeger's group, and had already made brilliant contributions to structure elucidation in the triterpene field. He was also the one who importantly contributed to the content of the 1955 *Helvetica* paper.

KOEPPEL: Your next field of interest involves the synthesis of colchicine. Would you like to talk about this?

ESCHENMOSER: The experimental part of the investigation on the stereochemistry of polyene cyclization, on which the biogenetic theories were based, was published in 1957 (9). For me, that more or less closed the topic of the biogenetic isoprene rule, because I felt that it was now up to the biochemists to prove these schemes. In fact, much of this has been done since then, and the content of the 1955 paper still stands more or less unchallenged. My original hypothesis that the squalene cyclization is induced by OH+ (4) was later extended by the finding of [Elias James] Corey and [Eugene] van Tamelen that squalene epoxide is the intermediate (10).

Now, I want to come back to your question. At that time, we became interested in the synthesis of complex natural products. We had already taken part in a collaboration that involved ETH groups, the Reichstein group and the Ciba group on the synthesis of aldosterone. That operation didn't turn out to be very successful for us; however, it was successful for Oskar Jeger's group. In fact, our major focus was the challenging problem of a synthesis of colchicine. Why colchicine? First of all, because it was a classical, well-known alkaloid of medicinal importance since ancient times. Second, it was in the limelight of research in natural product synthesis because it had a highly unconventional structure, just recently recognized to be a tropolone derivative. Tropolones were new and unorthodox structures. It was almost a must for somebody who wanted to do research on the frontier of natural-product synthesis.

I want to add here why I had become interested in the total synthesis of complex natural products in the first place. I think this was essentially the influence of R. B. Woodward. His syntheses were so spectacular, and so captivating to the young generation that the desire to do such work yourself was quite natural. Colchicine was the topic to focus on in order to find out whether or not we could do such a thing.

KOEPPEL: So that essentially brought you into natural product synthesis?

ESCHENMOSER: I think so. As it happened, R. B. Woodward was also working on colchicine. This too probably had an influence. It's hard to reconstruct such influences in retrospect. I may say something relating to Woodward later on, which is significant in this context. We started, and within four years we succeeded to have the first total synthesis of colchicine (11). Psychologically that was an enormous stimulus for our young group. The Woodward group and about ten other groups were working on a synthesis of colchicine at that time.

KOEPPEL: You got it first, before the Woodward group?

ESCHENMOSER: We were lucky to win the race, but the following story belongs to this statement. It was 1959, towards the end of the race. We knew that the Woodward group was also far advanced. And we knew that they had been able to degrade colchicine (by Hoffmann degradation) to an intermediate that could be used as an advanced relay compound. In their synthesis they didn't need that. But our synthesis had been planned in such a way that the relay compound was important. When the time came that we needed the relay compound from natural colchicine, we were not able to make it, despite our efforts. I decided to write a letter to Woodward, telling him what we failed to accomplish the Hoffmann degradation of colchicine and asking whether he would send me the procedure, because we had been able to obtain by total synthesis what we believed to be the relay compound.

KOEPPEL: You wanted to compare it?

ESCHENMOSER: Yes. Woodward knew that if we were able to prepare that relay compound we would probably win the race. He immediately sent us the procedure.

KOEPPEL: He did?

ESCHENMOSER: Yes. At once we were able to repeat his procedure (using a much more highly concentrated sodium hydroxide solution than we had used before) to get the compound in a reasonably large amount and go ahead. When everyone says that we had been able to win the race, it is because of this. That's significant.

KOEPPEL: Were you the leader of this group, or was it a team effort of several people?

ESCHENMOSER: When Ruzicka pushed me out of my thesis work, I had the great fortune of getting my first Ph.D. student the moment I started working on my own. During my own thesis work, Jacob Schreiber had done his Diplomarbeit with me on the structure of caryophyllenic acid, and he decided to be my first Ph.D. student. He was the main actor in the colchicine story, which went on for four years. Colchicine was done with a group of three or four people, and I myself was not involved in the experimental work.

KOEPPEL: I see.

ESCHENMOSER: But I was directing that research project.

KOEPPEL: Yes. What was your position at that time?

ESCHENMOSER: I was a doctor.

KOEPPEL: You were not an assistant professor?

ESCHENMOSER: No. I became Privatdozent in 1956. This means that at the time of the colchicine synthesis I was a Privatdozent. Dr. Jacob Schreiber is still with me today, we have become good friends. He is going to officially retire next year. We agreed that he may stay on

and do some "post-retirement" work. Dr. Schreiber is a very creative and exceptionally gifted experimentalist.

KOEPPEL: Then you went into corrins?

ESCHENMOSER: Yes. The point was, after colchicine what should one do? We were now convinced that total synthesis of natural products was the thing for us to do. At that time, research in total synthesis was in the limelight of organic chemistry. It was the time of the climax of the Woodward era, when, in choosing the targets for total synthesis, one had to go from one level of structural complexity to the next higher one. You were not supposed to repeat yourself and stay with the next synthesis on the same level of complexity. The next synthesis had to be more complex than that done before. In 1956, the structure of vitamin B_{12} had been elucidated by x-ray crystallography in the laboratory of Dorothy Hodgkin at Oxford [University]. It was clear that organic chemists who wanted now to do research at the frontier of total synthesis would have to attack vitamin B_{12}. At the beginning, to many it sounded like a joke, because the new vitamin was really far more complex than anything that had been done before.

The most complex molecule that had been done before was chlorophyll, a biologically very important and chemically very interesting structure. The Woodward group had just accomplished it in 1960 (12). Chemical synthesis had to now go beyond chlorophyll. That it would have to be vitamin B_{12} was more or less natural. Probably there might also have been adequately complex targets among the alkaloids, but in comparison to vitamin B_{12} alkaloids were biologically not too interesting. The biological interest in a target compound has always played a major role in planning a total synthesis.

KOEPPEL: Was the relationship of Vitamin B_{12} to chlorophyll and hemoglobin a challenge for you?

ESCHENMOSER: Absolutely. It was a "superporphyrinoid" and it was so challenging because there was essentially nothing known about its chemistry. It had become clear up to that time that research in total synthesis could no longer justify itself by the classical function of proving a structure, and that it would be through x-ray analysis that the structural elucidation of complex natural products would be done in the future.

KOEPPEL: Yes, not by degradation.

ESCHENMOSER: Not by degradation anymore. This became an important aspect in choosing a target molecule for a total synthesis. From that point of view, vitamin B_{12} was ideal:

it was unknown chemically, biologically important, and structurally complex.

KOEPPEL: You said you were daring, but nevertheless confident, when you tackled it?

ESCHENMOSER: Yes, that is what I meant. Having accomplished colchicine in a race and having ended first probably gave me the courage to tackle it. Yes, I am quite convinced; otherwise I would have worried and, so to say, been realistic and would have stayed with smaller topics. There's a lot of psychology in such a situation.

KOEPPEL: What did you do first? How did this begin?

ESCHENMOSER: In the beginning, I did nothing but think about it. I remember, when I started research, I had the tendency of jumping to the laboratory and asking my students to start, as soon as I had thought of something. Then, I had already grown old enough to know that this was not the way things should be done.

KOEPPEL: You worked a lot with models. Is that what you're referring to?

ESCHENMOSER: No. I referred to the time before we started working on corrins. The corrin ligand system is the core of the vitamin B_{12} structure, and it was clear that we must first develop in a model system the methodology for constructing a corrin ring; no corrin derivative had ever been synthesized before. It had a chromophore which was different from that of a porphyrin. It had stereochemistry. It had cobalt. There was essentially no known corrin chemistry. It was about three-quarters of a year that I spent thinking about possible synthetic approaches. Once it had become clear that the corrin chromophore might be constructed by what we now call iminoester-enamine condensation, we started in the laboratory and systematically studied this type of condensation reaction and, eventually, developed the first corrin synthesis. That lasted four years.

KOEPPEL: When did you start?

ESCHENMOSER: It was December of 1959.

KOEPPEL: December of 1959. How do you know it so exactly?

ESCHENMOSER: I know it exactly because Rolf Scheffold, who is now a professor of organic chemistry in Berne, had written an article on Vitamin B_{12} chemistry on the occasion of my sixtieth birthday (13). There he wrote that in December of 1959, I had come to his desk, put on it a bottle containing a white substance, and asked him, "What are we going to do with this?" He pondered it. Then, I told him—not completely, but partially—as a joke, "We are going to make Vitamin B_{12}."

KOEPPEL: What was his reaction?

ESCHENMOSER: I do not remember what he said. Anyway, he became the first collaborator on the corrin project. Soon a group of about six students were part of it and in 1964 we were fortunate to have accomplished the synthesis of a corrin complex.

KOEPPEL: You dedicated this paper to Professor Hans Meerwein and mentioned that you were inspired by his work (14).

ESCHENMOSER: Meerwein was still alive. I think he was eighty-five at that time.

KOEPPEL: Yes, it was for his eighty-fifth birthday.

ESCHENMOSER: He had discovered the trialkyloxonium salts before the war, and published about them in Germany (15). However, these compounds were completely absent from textbooks and lectures in 1960. They had remained essentially unknown. Since our main effort in the corrin project was to develop the iminoester-enamine condensation process, we searched for methods of preparing iminoesters. So we found Meerwein's paper that showed that one can O-alkylate lactams or amides with trialkyloxonium salts to get iminoesters. That's how we got into contact with the Meerwein chemistry. This chemistry turned out to be absolutely essential for our corrin synthesis, since there are a number of steps in which trialkyloxonium salts were used. Our corrin paper just was a perfect opportunity to point out the importance of Meerwein chemistry for organic synthesis. Today, of course, all these things are well-known. But I remember, when I saw that Meerwein paper on trialkyloxonium salts for the first time, I hesitated to believe it because its content was absolutely outside of common textbook knowledge. That corresponded to the fact that essentially nobody had made use of it. Of course, it was also the war that had precluded Meerwein's paper to become generally known in time.

KOEPPEL: When you started on this, did you think it was going to be Mount Everest?

ESCHENMOSER: No. After all, we didn't start by attacking vitamin B_{12} directly. It was in 1961 that the news arrived from Harvard that Woodward had started on vitamin B_{12} directly.

KOEPPEL: I see. Harvard started before you.

ESCHENMOSER: While working towards the model corrin, in the summer of 1960 we also had started on the synthesis of the B-ring of vitamin B_{12} itself. Woodward knew that and followed our work on corrin synthesis with great interest.

KOEPPEL: You were the first ones to start the corrin synthesis, before Harvard. Then Harvard started independently?

ESCHENMOSER: Harvard started absolutely independently in the sense that it did not start working on a model corrin synthesis, but directly on a synthesis of the A-D portion of the vitamin B_{12} molecule. Woodward probably assumed that our approach to construct a corrin chromophore would succeed. I still remember that when it eventually did, Woodward sent me a congratulatory telegram. He was very much interested in our work, kept himself informed about what was going on, and I myself was stimulated by his interest.

KOEPPEL: So you actually had the corrin framework before Harvard?

ESCHENMOSER: No. Not the framework of the B_{12} molecule.

KOEPPEL: But, if he started on the A-D portion and you did the whole synthesis...?

ESCHENMOSER: Now, we must get clear ourselves. When you start with a model study in natural product synthesis, the target molecule of the model synthesis cannot be transformed into the natural product molecule.

KOEPPEL: By model you mean that you work out the individual reactions?

ESCHENMOSER: By model I mean a structurally simplified version of the natural product structure. But that simplified version must contain the crucial structural features of the natural product molecule. And the essential structural feature of the B_{12} molecule is the corrinoid

chromophore skeleton.

KOEPPEL: You got the skeleton?

ESCHENMOSER: Yes. The corrin we made was a molecule in which the peripheral side chains of the vitamin B_{12} molecule were replaced by methyl groups. In 1964, when this model synthesis was over, gradually the question came up whether the Harvard and ETH groups should join forces. As mentioned already, before we had been through with the model synthesis, we had started with a synthesis of ring B of vitamin B_{12} itself, aiming at a synthesis of the B-C side of the molecule. This is the side complementary to the A-D side, which the Harvard group was working on. It was not before 1965 that Woodward and I really decided that the two groups should work together in trying to accomplish a B_{12} synthesis.

KOEPPEL: Did you get B-C hooked up?

ESCHENMOSER: At that time, not yet.

KOEPPEL: You just had B and C individually?

ESCHENMOSER: We first had ring B, which is more complex. Then we developed a method for converting ring B into ring C, however, as it turned out, for analytical purposes only. At Harvard an efficient C-synthesis starting from camphor had been worked out, closely following the ring C synthesis from camphor that had been accomplished before by [Sir John Warcup] Conforth, who had been the first to start synthetic work on vitamin B_{12}.

KOEPPEL: Why did he give up?

ESCHENMOSER: That's a good question. I would say, because he did not first study a model. His plan for constructing the corrin ring was very different from our corrin synthesis. The plan was very beautiful, but also very demanding—too demanding, maybe. Perhaps another reason is that at that time he had his beautiful work on the biosynthesis of steroids underway. This also may have drawn him away from B_{12}.

KOEPPEL: Did you use your method of sulfide contraction?

ESCHENMOSER: The sulfide contraction method came in 1965, and was developed as the solution of the problem of joining rings B and C. Then the Harvard-ETH collaboration really set in. We had the B-C component, and the Harvard group... You know what happened in 1965—that's the year of the Woodward-Hoffman rules.

KOEPPEL: That came as a consequence of joining A and D?

ESCHENMOSER: Yes, in trying to join A and D. It was a plan that did turn out to be unsuccessful, but of course it was very important. It was a terrific plan to get this A-D part, not just by joining two rings, but by constructing the A-D component as a whole in a very Woodwardian way. The plan resulted in the grandly heuristic failure which gave birth to the Woodward-Hoffman rules.

KOEPPEL: He used photochemistry to join those two rings?

ESCHENMOSER: I can describe it to you if you wish. In the original design for the synthesis of the A-D component, it was planned to get the ring D attached to the ring A portion by a cyclization of a conjugated triene enolate derivative to a conjugated cyclohexadiene derivative, actually a kind of intramolecular version of a Diels-Alder reaction. Woodward believed that he could predict the stereochemistry of that reaction by using steric approach arguments. Here we have one of the most important factors in the development of the Woodward-Hoffman rules: in his time, Woodward was one of the very few chemists who believed that he would be able to predict the course of reactions. His self-confidence in thinking about reaction mechanisms made him assume that, if a prediction failed, there would have to be a very special reason, a reason unknown in organic chemistry, not just unknown to him. If a prediction happened to fail, an ordinary chemist might well accept it and say the prediction was a weak one. Not so with Woodward. When he predicted, he didn't really reckon with failure. When he failed, he took it seriously and searched for the unknown reasons. That attitude was at the origin of the discovery of the W-H rules.

At that time, it had become clear that the original plan for the A-D synthesis would not lead to the target molecule. It was not that important, because the rules and the whole chemistry of the rules became Woodward's preoccupation for a year or so. I remember that. And when the work on the A-D component went on, it did so by following a different plan, one which was somewhat less daring.

KOEPPEL: In other words, he joined the two rings A and D.

ESCHENMOSER: He did not really "join" rings A and D.

KOEPPEL: He constructed A-D.

ESCHENMOSER: He constructed a complex molecule which finally became, through various rearrangements and ring-openings in a characteristically Woodwardian manner, the A-D component.

KOEPPEL: Later, there was a hook-up of A-B-C-D and then A-D was cyclized.

ESCHENMOSER: That was much later.

KOEPPEL: And that provided the impetus for the Woodward-Hoffman rules.

ESCHENMOSER: No.

KOEPPEL: No? I'd like to clarify this because it's a little complex, to say the least.

ESCHENMOSER: Yes, I don't blame you. What we have discussed so far is the Harvard-ETH approach of B_{12} synthesis in which the A-D component is joined to a B-C component between the ring C and D, to be followed by a macroring closure to the corrin ring between rings A and B. The B-C synthesis was done at ETH. In pursuing that problem, the sulfide contraction method was developed. The synthesis of the A-D component was developed at Harvard. The first synthetic approach to this component did not lead to the target, but to the Woodward-Hoffman rules. The second approach (actually it was the third) then led to the A-D component. When these two pieces had become available, they were exchanged between Zürich and Harvard. This meant we got A-D material from there and we sent B-C material. Hooking together the A-D component with the B-C component was the first problem, investigated simultaneously in both laboratories. Again, the sulfide contraction provided the solution. The next problem, again studied in both laboratories, was closure of the macrocyclic corrin ring between rings A and B. Two solutions were found, one again by sulfide contraction, the other by thiominoester condensation. In the meantime, here in Zürich, an entirely new project was taken up and investigated experimentally while the work referred to above was going on. It arose as a consequence of the Woodward-Hoffman rules and the new reactivity concepts which went with these rules. This project was a new corrin synthesis, studied again first in a model system. A concept of closing the macrocyclic ring, not as done before, between rings A and B (that was the 1964 approach), but between rings A and D. Such a ring closure to a corrin was never considered before because it was obvious that this was not the way to do it—

considering the stereochemical problem connected with the A-D junction. How can you form that saturated ring junction when there is no double bond to start with in the ring D region? With the help of the Woodward-Hoffman rules one could conceive of such a process, one with essentially no precedent. Crucial was the new concept of sigmatropic rearrangements which was part of the Woodward-Hoffman rule theory.

KOEPPEL: So in a way, he developed it on the project and used the rules to...

ESCHENMOSER: That's what we did.

KOEPPEL: So you joined rings A and D.

ESCHENMOSER: It took two years of work to construct the model system. Then it was found that the hypothetical ring closure reaction worked beautifully indeed. This was the second corrin synthesis developed at ETH, the one with the photochemical A-D ring closure (16). You should remember, the Woodward-Hoffman rules were developed as a result of the work done at Harvard on the difficult problem of getting B_{12}'s A-D junction. Then, at the end, one of the consequences of these rules was the development of a very simple solution to this very same problem. In 1969, we started our work on the photochemical approach to cobyric acid, while the Harvard group continued with the original synthesis. The two syntheses were finished simultaneously.

KOEPPEL: It didn't work on the cobalt compound. Didn't you make the zinc compound first?

ESCHENMOSER: In retrospect, it appears absolutely essential that the photochemical variant had been extensively studied first in a model series. Without knowing from the model studies that the critical A-D ring closure works, it would have been impossible. I think in both projects of B_{12} synthesis, the two corrin model studies were essential. In the photochemical version it was recognized that one cannot use cobalt or nickel ion as a complexation center, a discovery that was very interesting from a theoretical point of view. One must use an inert metal ion which does not quench the photoexcitation of the chromophore system. We found that zinc works well and that, in the natural series, cadmium leads to an essentially stereospecific cyclization.

KOEPPEL: When you had the cobyric acid, who hooked up the other parts? Was it Harvard?

ESCHENMOSER: Oh, yes. We had not been concerned at all about hooking on the

nucleotide loop to cobyric acid, because that had already been done by a biochemist through partial synthesis in the natural series. But R. B. [Woodward], being a perfectionist, wanted to have truly "synthetic" vitamin B_{12} and not a relay synthesis of it. He, together with his last collaborator in the field, Dr. [M. A.] Wuonola, converted synthetic cobyric acid to Vitamin B_{12}. This was in 1976.

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KOEPPEL: Woodward announced the synthesis of vitamin B_{12} in 1972 at the Congress of Pure and Applied Chemistry in New Delhi. Was it a surprise?

ESCHENMOSER: No. It was the opposite of a surprise. The situation was the following. In 1971, both Woodward and I gave a lecture at the IUPAC Congress in Boston (17). Disappointingly to both of us, the synthesis was not finished. In Boston, it was the first time that I lectured on the photochemical pathway towards cobyric acid. That was in the summer of 1971, and the New Delhi symposium was in February of 1972. I actually had been asked by the organizers of the New Delhi conference to give a lecture, but I declined, thinking that it would be too early, and that we should not lecture at another IUPAC conference without the synthesis complete.

When Woodward agreed to lecture there (he did not publish the Boston lecture), we agreed that we should try everything in order to finish the synthesis before New Delhi. We organized ourselves. Harvard was concentrating on the last step—the ammonolysis of a hexamethylester-monoacid to give cobyric acid—working with partially synthetic material derived from vitamin B_{12}. At ETH we did the identification of that intermediate with material made by total synthesis, actually with material made by the photochemical version. And so, the task of providing all the proofs necessary for the formal B_{12} synthesis to be finished was accomplished complimentarily in the two laboratories. Before the lecture, Woodward and I had a long phone call between New Delhi and Zürich, and I told him the last results of the ETH group. So, there was no surprise whatsoever. Everything was highly organized, and I felt it was all right that Woodward should announce the accomplishment of the synthesis.

KOEPPEL: You then discussed it in Zürich at the meeting of the Swiss Chemical Society.

ESCHENMOSER: Yes, that was in April.

KOEPPEL: April 22nd?

ESCHENMOSER: I think in April, 1972 (18).

KOEPPEL: A lot of this work wouldn't have been possible without extensive teamwork and modern instrumental techniques. You mentioned that high speed liquid chromatography was developed just at the right time.

ESCHENMOSER: Yes, and the credit for applying that technique in the field of organic synthesis for the first time should go to Dr. Jacob Schreiber. Initially, he had not been involved in the B_{12} project. Over the years, he had developed a special interest in chromatography techniques and became the chromatography expert in our group. He was watching the literature on chromatography, decided just at the right time our group should have HPLC [high performance liquid chromatography], and started to build his own HPLC machine. This was extremely fortunate. When, in our B_{12} work, we were confronted with the complex mixtures of diastereomeric cobalt corrin complexes derived from the photochemical A-D cyclization reaction, we realized that we could not separate these mixtures by conventional chromatograph. Schreiber was here with an operating HPLC machine, ready to help us separate these mixtures. He was dramatically successful in doing that. His contribution was of the utmost importance to us and to B_{12} chemistry.

A similar kind of mixtures of diastereomeric cobalt complexes was observed to be formed also by the A-B cyclization variant, and there was a time when Woodward sent one of his post-doctoral collaborators to Zürich in order to do separations using Schreiber's HPLC machine, since no such machine was available at Harvard. Later on, the Harvard group got their own machine from the Waters Company. Incidentally, to say the truth, I always had difficulties with the fact that the contribution of Schreiber had never been mentioned by Waters in the propaganda for their new machine.

KOEPPEL: Oh, he developed the machine? He developed the process?

ESCHENMOSER: Well, Schreiber was the one who had used the HPLC technique for the first time in organic synthesis and this on the occasion of the vitamin B_{12} synthesis.

KOEPPEL: And Waters commercialized it?

ESCHENMOSER: The extraordinary importance of the HPLC technique for the synthesis of vitamin B_{12} made Waters build a machine for the Harvard group immediately. Of course, there is no reason to complain about that—quite the contrary. But then Waters went into business with the machines with the B_{12} product and Woodward's name as part of their commercials. At that time I felt Waters should perhaps also give some credit to Schreiber.

As I mentioned, not only did we exchange materials between Harvard and ETH, we exchanged methodologies, techniques, even people. The Harvard group was absolutely superior with respect to mass spectra. Their mass spectrometer was much more powerful than that at ETH. So we got all our critical mass spectra there. Nevertheless, there was still something else. In an address given at the Welch Foundation, I called the relationship between the two laboratories during the vitamin B_{12} time a "competitive collaboration" (19). The competitive aspect was important for both. It provided stimulation to both groups. No doubt there was a kind of "intragroup-patriotism" among the young who wanted to show that they could beat the others.

KOEPPEL: I noticed that at least I could not find any record of joint publication between you and Woodward. Was this to emphasize that the work was done independently on both sides?

ESCHENMOSER: No, that is the sad part of the vitamin B_{12} story. First of all, no doubt, both of us were truly exhausted at the end. I didn't know before what it means to be exhausted. After that, it became clear that R. B. had no intention of writing the publication. He postponed it. When I tried to urge him that we should do that work now, he perhaps not incorrectly said that maybe in the back of my mind I was also not ready to do that work.

KOEPPEL: That was shortly before his death, wasn't it?

ESCHENMOSER: That was after 1973. He died in 1979. He had six years.

KOEPPEL: He had six years. It had no bearing on his reluctance?

ESCHENMOSER: I think he felt it would be something that he didn't have the strength to deal with. I did not have the strength, either, to do it independently. I felt it was not correct to publish our own part independently. It had to be done jointly. That is sad. With Dr. [Engelbert] Zass, who is my assistant in these matters today, we have now essentially worked up the whole of the experimental reports of the Harvard group. I can understand what Woodward meant when he said, "This is going to be a momentous task." I think he was tired.

KOEPPEL: He was tired and he could not handle it anymore. I see.

ESCHENMOSER: Yes. However, I shouldn't blame him exclusively for this. There was also a specific exhaustion on my part.

KOEPPEL: Would you like to add something on the B_{12} work?

ESCHENMOSER: Yes. There is no doubt that this work has to be fully documented. We are almost through with the documentation of the Harvard reports. Everything that had been done at ETH—the B_{12} synthesis models and cobyric acid—is fully described in published theses (20). The Harvard part is just in post-doctoral reports.

KOEPPEL: And it's not published?

ESCHENMOSER: It's not published except in Woodward's lectures.

KOEPPEL: Will you do this for Harvard?

ESCHENMOSER: Yes. That will be done by us. Alone, I probably couldn't do it. The experimental part is momentous, but together with Engelbert Zass I hope to be able to fully document everything.

KOEPPEL: Do you know where it will be published?

ESCHENMOSER: We have a number of options.

KOEPPEL: I see. So after the vitamin B_{12} synthesis you seemed to get interested in the biosynthesis of B_{12}?

ESCHENMOSER: I will tell that story briefly. It was clear that the photochemical A-D cyclization was a very direct, surprisingly effective and simple solution of what at the origin of the B_{12} project had appeared as the most complex problem of a vitamin B_{12} synthesis. Therefore, the question arose whether Nature uses the same type of process in a modified form in the biosynthesis of vitamin B_{12}. Since we knew that the production of vitamin B_{12} does not require light, we started a project, again in the same model series which we had used in developing the photochemical corrin synthesis, to look for dark versions of the cyclization process, versions which would not require light. We soon found a reductive version, and things developed very encouragingly. Gradually we found more and more versions of the process, versions which were all mechanistically very closely related to the photochemical cyclization.

KOEPPEL: What is the energy source in the dark version?

ESCHENMOSER: Perhaps the most interesting is the one operating in the version developed by Bernard Kräutler, who is now Privatdozent at ETH. In his thesis he was assigned to replace light by an electrochemical redox process. The idea was to electrochemically take one electron out of the chromophore, then to give back an electron to form first an excited state of the chromophore which would convert to the triplet state which in turn would do the same chemistry as when formed by photoexcitation. The project was successful, although the reaction turned out to be mechanistically much more complex than we expected at the beginning. The discovery of a whole series of such A-D ring closures eventually changed our attitude toward the vitamin B_{12} structure and the problem of its synthesis. We were led to ask the question whether the notorious complexity of the B_{12} structure is in fact an apparent complexity only, whether it should be considered to represent an elementary type of molecular structure, the core of which might be older than its biosynthesis, as presumed to be the case for amino acids and other enzymatic cofactors.

KOEPPEL: Would you base this assumption on the fact that it is essentially composed of simple molecules like the pyrrole system, and that this could be hooked up somehow?

ESCHENMOSER: For porphyrins it is by no means a new idea that they might have had a pre-biotic existence.

That the molecular structure of vitamin B_{12} should be looked at in such a way seems rather peculiar at first sight. However, all the experiments that we were led to carry out as a consequence of this kind of thinking were encouraging, to say the least. Probably the most drastic result refers to the hooking on the nucleotide chain to B_{12}'s corrin core. It had been clear in the planning phase of the B_{12} synthesis that the specific carboxyl function at ring D bearing the nucleotide chain in vitamin B_{12} must be differentiated chemically from all the others throughout the synthesis, because otherwise one would not be able to arrive at cobyric acid with its free carboxylic acid group at that position and its amide groups all around the periphery by eventually hooking on the nucleotide chain to the free carboxylic function of ring D. The "change in attitude" mentioned above led to the conjecture that this analysis may be unnecessary. The core of the B_{12} molecule itself might have the potential to direct the nucleotide chain to the specific carboxyl function at ring D, a potential that would correspond to the concept that a biomolecular structure which is elementary can form itself in a straightforward way. Straightforward means that its formation would not necessarily need complex instructions and regulations from outside. The molecule would regulate its own synthesis. Now, the fact we discovered is the following: if you activate all seven carboxyl functions of cobyric acid in the same way as cyanomethylesters and let the nucleotide chain slowly react with the undifferentiated heptaester, most remarkably this nucleotide chain

exclusively attacks the carboxyl function of ring D to give a hexaester derivative which, after treatment with ammonia, gives vitamin B_{12} and essentially nothing else. It looks like if the vitamin B_{12} molecule had its own code for attaching the nucleotide loop specifically at that special carboxyl group as ring D, in preference to all others.

KOEPPEL: This is amazing. So you actually are now interested in pre-biotic chemistry?

ESCHENMOSER: Yes.

KOEPPEL: Have you been able to reproduce this from an anaerobic primordial atmosphere, as [S. L.] Miller did (21)? Is that your goal?

ESCHENMOSER: No. Absolutely not. The questions we ask are quite different. In prebiotic chemistry, as far as it has been done (and Miller's work is the classical example) one tries to make a guess about the prebiotic environment, to simulate the environment and then to find out what organic molecules are formed in such an environment. What we would like to do is to conceive a pathways along which the structures of the fundamental biomolecules could be formed within a chemically defined framework of conditions and starting materials, and then to check such ideas experimentally. This is essentially an exercise in organic synthesis. We deliberately restrict ourselves to defined frameworks of conditions, and we ask which starting materials, which types of reactions, and which reagents are required to derive synthetic trees to which type of fundamental biomolecules. We also ask, for instance, what if we exclude water? In fact, we investigate rather systematically the chemistry of alpha-aminonitriles in the absence of water. Without worrying too much about fashionable assumptions on the geological conditions allegedly existing three billion years ago, what we just want to find out about is the chemistry of that special group of substances—the alpha-aminonitriles, adopting the current view that they played an important role in the prebiotic formation of α amino acids. At present, we think that the structures of many cofactors, such as the porphyrinoids or others like folic acid, may be related to precursors which are alpha-aminonitriles.

KOEPPEL: You could essentially start from HCN and reduce it and dimerize it like you have shown in some of your models. But you would not expect to be able to duplicate this?

ESCHENMOSER: No. The work we do at present is mainly concerned with chemistry at a somewhat advanced structural level. We would like to be able to show how the structure types of cofactor molecules such as the chlorophylls, the corrin structure of vitamin B_{12}—or factor F-430 from the methanogenous bacteria, the core structures, not necessarily the biomolecules as we know them—can derive in a straightforward, chemically rational way from a common precursor, namely uroporphyringogen-octanitrile, a cyanide derivative which we were able to

show can be derived from glutamic acid dinitrile. There is much new chemistry to be discovered in such work on various levels of molecular complexity.

In an autonomous chemical investigation on such problems, one doesn't worry too much about what people think of so-called prebiotic conditions that might have existed on our planet. What seems essential is that comprehensive chemistry, or more specifically synthetic chemistry, may by itself have to play a more active role when it comes to develop experimentally supported views about the beginning.

KOEPPEL: You think that chemists should pay more attention to these questions? That they are too involved in their own specialties?

ESCHENMOSER: That is quite problematic. A young chemist can hardly make a career with this type of research. Whatever he does, his research must be significant also from a purely chemical point of view, and to achieve this with work in this special field is very difficult. Each age period of a scientist has its own adequate research problems. I would not necessarily encourage a young chemist to become involved, except if he had brilliant ideas that nobody else ever had. That, of course, is possible and would be absolutely natural.

KOEPPEL: We have interwoven all of these relationships and questions into our talk so far. I would like to ask a few specific questions about your professional relations at the ETH. At some point, you were chairman of the department. Did you have this rotating chairmanship system?

ESCHENMOSER: We have an Abteilung and we have an Institute. I was chairman of the Institute of Organic Chemistry after Prelog's implementation of the rotating system. All of us have been chairman. For the next two years, I will be chairman again.

KOEPPEL: So, it's your turn again. It seems like a somewhat drastic change from Ruzicka's style, who managed everything by himself.

ESCHENMOSER: That's the great merit of our older colleague Vlado Prelog. He was one of the first Institute directors at ETH who proposed to the school that an institute should have a number of professors. Sciences like organic chemistry should not be represented by one professor, but by a number of them. They should rotate in the chairmanship, and that was in Europe a rather modern idea. He humorously claims that he did that not only as a consequence of principles, but also to evade a job that he doesn't care for. [laughter] The rotating chairman system is now established in essentially all institutes at the ETH.

KOEPPEL: Yes. It's in line with our times. Was there a special way of funding involved in your research? Who mainly sponsored your research?

ESCHENMOSER: I am a consultant for Ciba-Geigy in Basel and for Firmenich in Geneva. For many years they have supported my group very generously, without any strings attached.

KOEPPEL: That's amazing.

ESCHENMOSER: Yes. It was very important for us. There was also a large contribution over the decades from the Schweizerische Nationalfond.

KOEPPEL: The national science foundation, so to speak. Then of course, you have been in the United States many times. You have been a visiting professor about six times at MIT, Chicago, Cambridge, Harvard, Wisconsin, and Israel. Were you there for a semester?

ESCHENMOSER: Three months is the longest period that I have been away from this laboratory. It goes back to Ruzicka's time. Ruzicka told me and Arigoni, "You should not go away. You should stay here and work." That meant both of us had no post-doctoral year abroad. Ruzicka's theory was, if you don't know your chemistry already, you will not learn it. Well, he was quite demanding.

KOEPPEL: If you don't know chemistry?

ESCHENMOSER: If you know your chemistry and know what to do in your research, then it is waste of time to go abroad. Of course, this is an exaggeration of the esteem Ruzicka had for us youngsters.

KOEPPEL: So he did not encourage you to go?

ESCHENMOSER: No. He did the opposite. I think he quenched invitations in both our cases. I happen to know that he quenched an invitation I was supposed to receive from UCLA to come and be a visiting lecturer.

KOEPPEL: Oh, I see.

ESCHENMOSER: He simply cut off that invitation. When Donald [J.] Cram came to ETH from UCLA and wanted to extend the invitation to me, Ruzicka insisted that he was not going to. So I was told by Don Cram. Ruzicka believed that it was best for a young scientist to stay home and do his research. This is not necessarily completely wrong. However, my English would be better if I had been abroad.

KOEPPEL: It's very good. Do you have anything to tell about your stay in the USA? Did you make any special friends?

ESCHENMOSER: I have many.

KOEPPEL: Did you lecture there?

ESCHENMOSER: Last autumn I had the unique pleasure to be the R. B. Woodward Visiting Professor at Harvard for three months. That was a major experience.

KOEPPEL: You lectured and researched? Or did you direct a research group?

ESCHENMOSER: No. I gave rather extended lectures in which I discussed what had been going on recently in our group.

KOEPPEL: Do you have a number of friends you would like to mention?

ESCHENMOSER: Do you mean in the United States?

KOEPPEL: Yes. Any special relationships?

ESCHENMOSER: Essentially the whole Harvard group in the organic division. And then the organic division at the University of Wisconsin. This group, at that time lead by Harlan Goering, played an essential part in my academic life, because they offered me a professorship in 1960. That induced ETH to give me a professorship here.

KOEPPEL: I see. They did not want to lose you.

ESCHENMOSER: Apparently not.

KOEPPEL: You had already gone to MIT by 1961. That was really before your B_{12} time.

ESCHENMOSER: Yes. I was Arthur D. Little Visiting Professor and lecturing about colchicine.

KOEPPEL: It wouldn't be fair not to mention the many awards you have been given like the Werner Prize, the Ruzicka Prize, the Marcel-Benoist Prize, and the A.W. von Hoffman Medal in Germany, the Davy Medal in England, and in the USA you had the Gunther Award, Robert Welch [Award], Arthur Cope [Award], Tetrahedron [Prize] and many others.

ESCHENMOSER: The British would say that the last mentioned is a British prize.

KOEPPEL: The Tetrahedron Prize is a British prize? You have been named an honorary doctor of several universities including the University of Chicago in 1970. You have about one hundred and fifty publications.

ESCHENMOSER: That is a small number.

KOEPPEL: Yes, but in addition there are all these name-lectures. I counted over fifty of them. How can you cope with all of this work?

ESCHENMOSER: It's the old saying that if you are privileged to enjoy your work, it's no longer work, it is pleasure. That is certainly true with me. I have a reputation of not doing something unless I like it.

KOEPPEL: That's wonderful.

ESCHENMOSER: That's a dangerous reputation.

KOEPPEL: I think that's also your privilege. You must have collected a great number of correspondence and letters and at some point you will decide where your collection goes. Are you going to put them into the ETH archives or have you selected any other place?

ESCHENMOSER: You are a little early with that question.

KOEPPEL: I am sorry but I am supposed to ask that question. [laughter]

ESCHENMOSER: I do not consider myself among those who should worry about collecting letters.

KOEPPEL: But you do collect what comes your way.

ESCHENMOSER: I don't. I do keep letters, but do not collect them.

KOEPPEL: You shouldn't throw them away. You surely have Woodward letters.

ESCHENMOSER: Yes. I have some marvelously beautiful letters.

KOEPPEL: Is there any significance for vitamin B_{12} therapy? Have you ever thought about this since you "created" it?

ESCHENMOSER: You must be careful about saying that. I mean, who "creates" a compound? I could say the scientist who isolates it creates it. I could say that the microorganism creates it, but that's not perhaps...

KOEPPEL: Yes. You reproduced it.

ESCHENMOSER: Not even that. Vitamin B_{12} today is a very inexpensive substance. It's made microbiologically in large amounts at a very low price. The chemical synthesis of vitamin B_{12} has not contributed anything to the production of it. It has only contributed to our understanding of a biologically very important and fundamental molecule. Quite apart from this, it was contributing, as R. B. Woodward would have said, to the art and science of organic synthesis. And what perhaps may even be more important, after all that work we look at the

vitamin B_{12} structure in a very different way.

KOEPPEL: So this is what you consider your main contribution?

ESCHENMOSER: I think what should be behind all such kind of work is to contribute to a better understanding of nature.

KOEPPEL: And behind all chemical synthesis. I think that more or less concludes our interview. You have given me a great deal of information and a great deal of your time too. I would like to thank you.

ESCHENMOSER: Thank you very much. It was a pleasure.

[END OF TAPE, SIDE 3]

[END OF INTERVIEW]

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