CHEMICAL HERITAGE FOUNDATION

KONRAD E. BLOCH

Transcript of an Interview
Conducted by

James J. Bohning

at

Harvard University

on

22 March 1993

(With Subsequent Corrections and Additions)

THE BECKMAN CENTER FOR THE HISTORY OF CHEMISTRY

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KONRAD E. BLOCH

1912 Born in Neisse, Germany on 21 January

Education

1934 Chemical engineering, Technisches Hochschule, Munich
1938 Ph.D., biochemistry, Columbia University

Professional Experience

1934-1935 Research assistant, Schweizerisches Höhenforschung's Institute, Davos, Switzerland
1939-1946 Instructor, Department of Biochemistry, Columbia University

University of Chicago, Department of Biochemistry
1946-1950 Assistant Professor
1950-1954 Professor

Harvard University
1954-1982 Higgins Professor of Biochemistry
1968-1971 Chairman, Department of Chemistry
1979-1984 Professor of Science, School of Public Health
1982- Higgins Professor of Biochemistry, Emeritus

1982 Newton-Abraham Visiting Professor, Oxford University

Honors

1953 Guggenheim Fellow, Eidgenössische Technische Hochschule, Zürich, Switzerland
1956 Member, National Academy of Sciences
1958 Medal, Société de Chemie Biologique
1961 Guggenheim Fellow, Imperial College, London, England
1964 Fritzsche Award, American Chemical Society
1964 Nobel Prize in Medicine and Physiology
1964 Distinguished Service Award, University of Chicago School of Medicine

1965	Centennial Science Award, University of Notre Dame
1965	Cardano Medal, Lombardy Academy of Sciences
1966	Honorary Member, Lombardy Academy of Sciences
1966	Honorary Degree, University of Uruguay
1966	Honorary Degree, University of Brazil
1966	Honorary Degree, University of Nancy
1966	Member, American Philosophical Society
1967	Honorary Degree, Columbia University
1968	William Lloyd Evans Award, Ohio State University
1968	Honorary Degree, Technische Hochschule, Muenchen
1968	Guggenheim Fellow, Harvard University
1970	Honorary Degree, Brandeis University
1971	Honorary Member, Phi Lambda Upsilon
1976	Honorary Member, Japanese Biochemical Society
1976	Corresponding Member, Bavarian Academy of Sciences
1976	Honorary Degree, Hokkaido University
1977	Foreign Member, Accademia Pattaviana
1985	Foreign Member, Royal Society, London
1987	Award for Excellence, Columbia University
1988	National Medal of Science

ABSTRACT

The interview begins with Konrad E. Bloch describing his childhood in Neisse, Germany, and his undergraduate education at *Technische Hochschule* in Munich. During a research assistantship in Davos, Switzerland, Bloch became aware of the cholesterol molecule for the first time. He also produced and published three papers that Columbia University later accepted as partial fulfillment for a Ph.D. in biochemistry, earned in 1938. Bloch describes his teaching and research in biochemistry at Columbia and later the University of Chicago, where he developed an interest in the mechanism of protein synthesis from amino acids. Throughout his career, Bloch's primary research interest was the biosynthesis of cholesterol. In 1954, he became Higgins Professor of Biochemistry at Harvard University and served as Chemistry Department Chairman for three years. He won the Nobel Prize in Medicine and Physiology with Feodor Lynen in 1964 for his work on cholesterol and fatty acid metabolism. Shortly before his retirement, he was appointed Professor of Science at the Harvard School of Public Health. Bloch closes the interview with some comments on nutrition research, blondes in Venetian Renaissance Art, the difference between biochemistry and molecular biology, and the Human Genome Project.

INTERVIEWER

James J. Bohning is Professor of Chemistry Emeritus at Wilkes University, where he was a faculty member from 1959 to 1990. He served there as chemistry department chair from 1970 to 1986 and environmental science department chair from 1987 to 1990. He was chair of the American Chemical Society's Division of the History of Chemistry in 1986, received the Division's outstanding paper award in 1989, and presented more than twenty-five papers before the Division at national meetings of the Society. He has been on the advisory committee of the Society's National Historic Chemical Landmarks committee since its inception in 1992. He developed the oral history program of the Chemical Heritage Foundation beginning in 1985, and was the Foundation's Director of Oral History from 1990 to 1995. He currently writes for the American Chemical Society News Service.

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INTERVIEWER: James J. Bohning

LOCATION: Harvard University

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BOHNING: I know that you were born in Germany on January 21, 1912. Could you tell me something about your parents—your father's name, your mother's name, and the family background?

BLOCH: My father's name was Frederick. He came from a family which had lived in this little town [Neisse] in upper Silesia for three or four generations. We could date our time in the province back to 1800. My father studied law and got a law degree. He practiced law very briefly, and then he had to move to take over my grandfather's business. He was very unhappy about it and never enjoyed it.

BOHNING: What was the business?

BLOCH: It was a business making draperies modelled on some Belgian designs which were very popular at the time. Neisse, a country town of some thirty thousand, had an interesting history. Here the peace treaty was signed by the empress Maria Theresa of Austria and Frederick the Second of Prussia, who had defeated the Austrian empress in the 1740s.

So we were Austrians before we became Prussians. There are strong feelings about where you come from and where you belong to. There's a famous painting by Adolf von Menzel, a portrait painter quite well known in Germany, showing the Austrian empress Maria Theresa, handing the key of the city over to Frederick the Second. The empress was quoted as saying, "This province of Silesia," which was, of course, then taken over by Germany, "was the most beautiful pearl in my crown."

It was nice to grow up in a rural environment. The town was heavily fortified and noted for churches and a Town Hall dating to the eighteenth century. We had a marvelous time playing in these fortifications, both in the winter and the summer. It was marvelous for playing hide-and-seek, and skiing and sleighing. This small town of maybe twenty-five to thirty-five thousand inhabitants had three high schools. And the high schools' orientations were different.

One was the classical or humanistic high school, a Gymnasium. Here the classical languages, Greek and Latin, were taught, but very little science, and very few foreign languages. Then there was the so-called Realgymnasium—I don't know what the Real means. Here only one classical language was required, either Latin or Greek, but it emphasized modern foreign languages, and much more math, including calculus, and sciences such as chemistry and physics.

Finally, there was an institution called Oberrealschule. Here the emphasis was on a technical education rather than on liberal arts. After graduation you were eligible to enter any university if you graduated from either of the three schools. You probably know that in Germany one went directly to the university from high school.

So at the age of eighteen, you went to the university of your choice. But the number of high school graduates who went on to the university was very small. I think at the time, in the 1920s, it was less then ten percent. That is in contrast to American high school graduates, of whom probably fifty to sixty percent now go to college.

I think the continental system at the time had some lessons for our problems in secondary education. All my high school teachers, with the exception of the gym instructor and the music teachers, had Ph.D. degrees. The degree was called a doctor of philology [D. Phil.], not philosophy. This degree was somewhat less demanding than the American Ph.D. degree. I don't know how long it took, but importantly, the high school teachers could use a doctor's title. That gave them standing in the community, and also a relatively high standard of living. This is something we lack in this country.

BOHNING: Could I back up for just a moment? How was your family affected by World War I?

BLOCH: In World War I, my father was an officer. He served at the Russian Front, and later at the French-German border in the Ardennes mountains. For one brief period, he was stationed at the German-Danish border. Do you know Schleswig-Holstein? This province borders on Denmark.

For some reason or other, the Danes had sided with the Allies and not with Germany. So there had to be some troops to protect an important port on the Baltic Sea, although there was no danger that the Danes would join the fray.

When my father was stationed there, he said it was so quiet at that front, why didn't we come and spend our summer vacation there? It was a lovely place on the Baltic Sea, with beautiful beaches for swimming. So the whole family—my sister, my mother, and I—went to spend our summer vacation at the front. [laughter] I was two years old, and these are very early memories, but I had a marvelous time.

Of course, after World War I, Germany had economic depressions, like most other countries, but things went reasonably well in my family. I remember the unprecedented inflation of the German currency. At its peak, the Deutsche Mark was stabilized, 1 billion Reichsmark became 1 "Rentenmark"! Then the war clouds [World War II] were gathering. Most of us, including my family, were optimistic that this period would be a relatively brief episode. We were so naive!

BOHNING: From other people I've talked to, it seems to be a very common feeling at the time.

BLOCH: Yes. It was naively believed that someone like Hitler could persuade the German people to accept his extreme policies and theories. Germany had never been exposed to this kind of a dictator, and significantly Germany never had a revolution. It's one of the few countries which became a democracy without the populace going to the barricades. By contrast, in France and in Britain, and I guess in other countries as well, and certainly in Italy, in Germany, this was a very quiet revolution.

The spirit of a democratic society evolved only very slowly. As was true elsewhere, you couldn't vote unless you owned property of a certain magnitude. We enjoyed the spirit of the Weimar Republic, but it was politically so unstable that it collapsed without a fight.

In the early 1930s it became very clear that we had to leave Germany. I was the first of my family to emigrate. I was able to complete what was the equivalent of a master's degree at the Technische Hochschule in Munich. It wasn't really a final degree, but after four years of university study you got a diploma. In 1934, I was told by the dean of the school in Munich that I had to leave, because Jews were not allowed to do graduate work.

He wrote me a letter saying that my professor, Hans Fischer, a very distinguished chemist, had denied my application to become a graduate student in his group. Therefore, I could not continue. This was not true. Fischer had said he would be delighted to take me on, but he had doubts that he would be permitted to do so. That was obviously a signal. Then, naively, both professor Fischer and I thought we might look at other universities in Europe for my degree. At that point, I was determined to become an organic chemist.

Earlier, during my first semester, I entertained the idea that I might be interested in metallurgy rather than chemistry. In the late 1920s, I had read a text on alloys by the metallurgist Gustar Tammann (1), and that was a period when alloys, among them stainless steels, were invented. Texts of the time were saying, "We now know how to make or design alloys with any desired properties." Well, it wasn't quite like that. I think metallurgy remained a largely empirical science.

The professor who taught the metallurgy course was a poor lecturer. He turned me <u>off</u> completely. At the same time, I had to take a course in organic chemistry, and that subject turned me on. I think it underlined, at least in my case, the importance of the instructor's pedagogic skills. What is important, I learned, is the content of the course, not the style of the lecture. The lecturer was Hans Fischer. He was noted for the total synthesis of heme, the blood porphyrin. He spoke in a monotone. He never cracked a joke. But at the end of the course, I knew I had found my field. You don't realize and recognize how well or how poorly a course is organized and structured until the very end; only then you realize what you have learned.

BOHNING: I would like to come back again to your childhood. After World War I, Germany had a depression. I think it was in the 1920s when it was really bad. How was your father's business affected at that time?

BLOCH: It managed to survive, but no more than that. The factory building had a relatively small number of employees, maybe up to fifty. Most of the work was done in the employee's homes. It isn't a bad idea. Homework was an early opportunity for women to find jobs.

I remember distinctly that we had very little food during the war. In the wintertime, we had carrots, potatoes and yellow turnips. We had practically no meat or eggs. It's interesting, because there were few health problems. The incidence of many of the major diseases actually went down, for example, diabetes during World War I. Diabetes is sometimes associated with overeating—excess caloric intake—or certainly aggravated by it.

We survived quite intact from this war. During that time my father came back home probably two or three times a year. What else do I remember from that period? I had some very good friends among my classmates, few of whom are still alive. I resumed contact with them, some of them, after the war. I'm still corresponding with one, a painter, a reasonably well-known artist. He was a professor at a school of art in Berlin.

He came from an interesting family. His father was a letter carrier, very lowly paid. He managed to get two of his sons through high school and through the university, and both became academics. One tends to think that only in America you can rise above your social background. But in Germany there were isolated incidents of moving up. With my class-mate, a painter—although I must say I don't care for his paintings at all, they're ultramodern—I've had a very good relationship ever since.

BOHNING: How would you describe your pre-high school education? Was it pretty rigid? Was that typical of the time?

BLOCH: I have very little memory of that period. The pre-high school, or elementary school, you attend from ages six to nine. Then you go to high school for nine years. Each of the grades had latin names. The lowest one is Sexta, and the next one is Quinta, followed by Quarta, Tertia, Secunda, and Prima. We all wore different colored caps, like those that German University students in the fraternities used to wear. All that has disappeared now.

High school you didn't have to complete, unless you aimed at a University degree, but instead you could transfer to what was called a middle school or a technical school [Technicum] to learn certain trades, institutions needed in greater numbers in this country.

I think I had a good education.

BOHNING: You said that you had three high schools to choose from. Why did you choose the one you did?

BLOCH: At the time I was interested more in physics, engineering, and related subjects. My father had gone to the so-called humanistic Gymnasium, the one my brother also attended. My family knew the principal of my high school socially. He and his family were lovely people. He

was the principal of the so-called Realgymnasium, one of the reasons for my choice. This school was also the only in town to have a school orchestra.

BOHNING: You've written about the cello and canoe story at your Bar Mitzvah (2).

BLOCH: I'm not sure whether that is the section I entitled, "Your Parents Are Always Right."

The Bar Mitzvah is a major event, even for families not very religious. But in a small town like Neisse, with a very small Jewish community, there would have been much unhappiness in the congregation, had I disregarded the ceremony. At the time, I was said to be the best Hebrew scholar in that town. I had private lessons from the rabbi.

There is this little episode which accompanied this event. My uncle—and I think I was his favorite nephew—said, "You know, Bar Mitzvah is a great event. For a present of mine, pick anything you like, within reason, you want to have. Perhaps you would like a canoe, or something quite different, a musical instrument, such as a cello. You make the decision." After several days of reflection, my mother said, "Konrad wants the cello." I was absolutely furious. As it turned out, or I believed, this decision was a conspiracy of my parents with the music teacher.

The music teacher, who was also the conductor of the high school orchestra, needed a second cellist. He had only one to play this instrument. He persuaded my parents that I should be the second cellist. I guess my parents thought the cello was a good idea. The cello was also safer than a canoe. They never told me the story until many years later. Of course, I was intensely unhappy. I would have preferred the canoe because it was fun and didn't involve dreary practicing. When I finally had learned enough to join the school orchestra, I always had to play the second cello. It was no challenge whatsoever. Only the first cello played the melodies. At the time the cello and I did not become friends. I don't know whether I mention in the same article how the cello helped me to get into Columbia graduate school.

BOHNING: Oh, yes. You were asked in the interview if you played a musical instrument.

BLOCH: Hans T. Clarke, the chairman of the Department of Biochemistry at Columbia University, was a fine musician. He played both the viola and the clarinet.

I had reason to hope that I would be accepted as a graduate student in the department, because my research in Switzerland had produced three papers which were accepted and published (3). These papers Columbia University later accepted in partial fulfillment of the Ph.D. degree. I did have to do a bit of research at Columbia, but that didn't take more than a year.

Whereas I flunked the Ph.D. exam in Basel. Do I go into this?

BOHNING: A little bit. But I'd like to come back to that, if I could. In high school, you had chemistry and you had the other sciences.

BLOCH: Yes. The chemistry course was probably the worst course, it didn't inspire me at all. I remember reading in my spare time on two subjects. One, as I mentioned, was metallurgy, and the other one was airplane design and engineering. This attracted me. Then I attended the Technische Hochschule, an institution similar to MIT or Caltech. I enrolled in a metallurgy program, but chemistry was an essential part in my curriculum. It was chemistry that turned me on.

[END OF TAPE, SIDE 1]

BLOCH: However, the kind of chemistry which I ultimately did evolved very much later.

BOHNING: Why did you select Munich?

BLOCH: There were only few similar institutions, apart from Munich, also Breslau, Berlin, and one in Karlsruhe. As you know, the number of these institutes in the States is also very small compared to Universities. Munich had an excellent reputation, and I was very eager to see a different part of Germany. I had heard a great deal about the Bavarian Alps, ideal for skiing.

Bavaria was sort of an uneasy "occupied" component of the German Reich. They didn't like the Prussians and vice versa, but they were supposed to be very easy-going. I had a great time in Munich, where I spent four and a half years, until I was kicked out.

BOHNING: You had occasion to hear some very famous chemists there. In addition to Fischer, there was [Richard] Willstäter . . .

BLOCH: . . . and [Heinrich] Wieland and occasionally Adolf Windaus. These were the great, the very great chemists of the time. The German word is Koriphae, meaning emminent experts. It must be of Greek origin.

In "Summing Up," (2) I report on a monthly meeting of the Munich Chemical Society, usually attended by these four great organic chemists. These meetings really turned the scales, convincing me that chemistry, organic chemistry, natural product chemistry was my métier. But since I had to leave Germany, I didn't know what was going to happen to me.

There's probably quite a bit in this "Summing Up," about how I got into the United States by the courtesy of professor R. J. [Rudolph John] Anderson at Yale. He was a great man, a crusty Norwegian, but his heart was as good as gold. The incredible thing was that after I wrote

to him, he responded. I was an undergraduate, and obviously he had never heard of me. In Germany, if an undergraduate wrote to a professor, you would not expect to get an answer, at best a form letter. He took a real interest in what I was doing, and on the strength of that, he made the effort to get me to the United States.

When I visited him at New Haven, on the first trip I took after arrival in the U.S., and asked if I could become a graduate student in his laboratory, he said, "I don't think I can teach you very much more." [laughter] He was in his early sixties, in those days close to retirement. Instead, he sent me to Hans Clarke at Columbia.

BOHNING: Going back yet to Munich, you've commented on Wieland's seminar on the butterfly pigments, which I found very interesting.

BLOCH: He worked on pigments from the so-called cabbage butterfly. In German, it's called the Kohlweissling. Wieland organized the German school children to provide him with the material he needed. If you work with butterflies, you have to go out and catch them.

Then at a meeting in 1934, Wieland said he had to stop this work. I remember the quotation. "The current government considers my procedure for collecting butterflies cruelty to animals, not in accord with the ethics of the party." [laughter] Ironical. One of his students continued the research. I believe his name was Purrman. He also left Germany and completed the work abroad.

BOHNING: Do you have any memories of Willstätter?

BLOCH: I visited Willstätter before I emigrated because he had so many connections. I didn't ask him, but he offered to write a letter of recommendation, although his entire knowledge of me was that I had visited him, and he had talked to me, and that I was a student of Fischer's. He wrote two pages of a letter, which I took with me. I had two letters of recommendation, one by Hans Fischer and one by Willstätter. I think I mentioned that Fischer's letter was very brief. It simply said, "Herr Bloch ist gut." [laughter]

That was essential Fischer. Fischer was known not to go overboard; this was a very sober assessment. Fischer said, "You go to Max Bergmann at Rockefeller." Max Bergmann, a student of Emil Fischer, came from Leipzig or Dresden originally, and became a member of the Rockefeller Institute in the 1930s. At the time, it was called Institute, not University. So Hans Fischer said I should go and visit him, and that he probably could help me, which he did. He recommended Clarke's department at Columbia, as Anderson had done.

BOHNING: At Munich, what was the hierarchy of professor and student? What was that kind of relationship?

BLOCH: H. Fischer may have been an exception. He saw every student every day, at least once. He had a group of approximately one hundred students. There was no distinction between undergraduate and graduate students. When you do organic chemistry, Fischer was the professor whose course you took, which means not only the lectures, but also the lab. I spent two full years in his organic lab. You start with simple experiments. Are you a chemist?

BOHNING: Yes, I'm a chemist.

BLOCH: Do you know the [Ludwig] Gatterman preparations? A manual for relatively simple organic preparations.

BOHNING: Yes.

BLOCH: I did a hundred Gattermans, then progressed to more difficult syntheses called literature preps, which were taken from recent or current research and mostly, if not exclusively, pyrroles and porphyrins. It was sort of a production line. The undergraduates made the pyrroles and the porphyrins for the graduate students, who then tried to synthesize heme.

About ten hours each day, you spent in the organic lab, with some interruptions for lectures. You also worked on Saturday morning, but that was it. The stock room was closed at twelve o'clock on Saturdays.

I made some good friends during this period, but my best friends were mostly at the university. I went across town to the university by streetcar. I took courses on art, given by the famous art historian Pinder, and met students who became good friends. Courses like this were not given at the Technische Hochschule.

BOHNING: You really didn't do any research at that point. You were just doing literature preps and that kind of thing.

BLOCH: Yes, I spent about two thirds of my time working in the Munich laboratory. After I left Munich, I spent a year-and-a half in Switzerland. This period was a rewarding one, introducing me to the kind of research that I was going to do later on. Do I mention my rereading *The Magic Mountain* (4) by Thomas Mann in the 1980s?

BOHNING: Yes.

BLOCH: I've recently written an essay on the history of the receptor concept, especially the morphine receptor predicted by Thomas Mann. In essence, he foresaw the enkephalins and

endorphins, the body's own opiates, which interact with the same receptor that binds morphine, a fascinating subject.

BOHNING: Were you ever able to find out where he got his sources?

BLOCH: I have a vast file of correspondence on the subject. I wrote letters to the Thomas Mann Institutes, one in Zürich, and one at Yale University. I also contacted members of his family—one of his daughters and one his sons, an historian. I also read all the diaries. He kept diaries throughout his adult life, but he burned several of them, apparently because they had too many intimate details.

But he kept diaries for the crucial period during which he wrote *The Magic Mountain*, from 1915 until 1921. For each of the *Magic Mountain* chapters he had numerous footnotes and references in the diaries. But, he makes no mention of the fascinating conversation he describes among the TB patients in Davos.

A famous French physician, Claude Bernard, is said to have been puzzled by the curious fact that some plant substances interact with animal cell surfaces or receptors. Why should plant substances have an affinity for an animal receptor? Since the 1970s, starting with the discovery of the endogenous opiates, enkephalins and endorphins, there have been additional plant drugs which have endogenous equivalents in animals. Now, the body's own marijuana and the body's own digitalis have been isolated and there will undoubtedly be other plant alkaloids in this category.

In all these instances, you have to be careful that the body's own opiate, et cetera, doesn't come from the outside. So far, at least, it's very difficult to see any structural analogy, for example, between the endogenous opiates or the plants morphine alkaloids.

I think I do point out that I was lucky to reread *The Magic Mountain* in the 1980s. Prior to writing "Summing Up," I wanted to refresh my mind about my stay in Switzerland, so I struggled through the novel again. I had previously read it in high school. When I came to the pertinent section, my eyes really popped.

I was highly impressed by the research on the endorphins and enkephalins in the mid 1970s. I had covered this subject in my last Biochemistry lecture at Harvard. So when I read this astonishing passage, I thought, "My God, how did Thomas Mann get this idea?" By the way, I have not found a single neuroscientist, whether old or young, who was aware of this prophecy. Experts in the field, Sol [Solomon H.] Snyder at [Johns] Hopkins or Dr. [Avram] Goldstein at Stanford, ought to have known, but they were unaware.

My explanation is that my generation probably read *The Magic Mountain*, whether in this country or in Germany. But very few people reread it. [laughter] It's one of these very learned tomes. I probably was the only one to reread it. The younger generation wouldn't have been struck by this passage, even if they came across it. Besides, I very much doubt that in American high schools the novel is required reading.

BOHNING: You've also commented about the fact that when you were getting ready to leave Munich, you had two negative replies from [Alfred] Butenandt and [Fritz] Kögl.

BLOCH: From my student days I remember in 1934, the same Munich Chemical Society sponsored a lecture by Kögl, then one of the most distinguished European organic chemists. He had reported the isolation of two new plant hormones he called auxins a and b. All the famous organic chemists I mentioned earlier were in the audience. As a student, I knew enough organic chemistry to appreciate the fascinating lecture claiming to have isolated, from several hundred liters of human urine, the two crystalline substances, known for several decades as auxins a and b (6).

At the time, the only known plant growth hormone was indoleacetic acid. But the auxins were not indoleacetic acid derivatives; they were of an entirely different chemistry, heterocycles of some kind. Kögl presented analytical data, such as they were in those days—an elementary analysis, melting point, and so on. Maybe UV spectra, although I don't remember that.

All the distinguished organic chemists in the audience had made very complimentary remarks, except Willstätter. Kögl had said he had isolated a hundred milligrams; (it was an astonishing achievement). When Kögl recited the wealth of analytical data, Willstätter remarked, "Dr. Kögl, how could you have done all this work with a hundred milligrams including the elementary analysis?" There may have been a semi-micro method, but it was pre-[Fritz] Pregl. But Kögl was very smooth and answered, "Well, I should have said that we have developed a new micro method," or something like that. [laughter]

The structures were a total fiction of the imagination of a woman co-worker.

The story continues then in the U.S., when I was at Columbia. I stayed there from 1936 to 1946. In 1939, one of my professors was G. L. [Goodwin LeBaron] Foster, who was an authority on amino acid chemistry and analysis. I remember to this day, he held up a copy of the *Zeitschrift für Physiologisches Chemie* and said, "Here's a paper, which is a total fraud from beginning to end (7)."

The paper, one of a series, dealt with the content of unnatural amino acids in cancer proteins from the same two authors who had done the auxin work. The purported results were astounding: twenty percent unnatural glutamic acid, and twelve percent lysine and so on. The main idea was that there's something unusual, chemically, in tumor protein. Unnatural amino acids were not unreasonable. Some unnatural amino acids were known to occur in bacterial polysaccharides, but not elsewhere.

The findings by the Dutch group were so exciting that Fritz Lipmann and Otto Warburg, two of the most distinguished biochemists at the time, tried to reproduce these results. After a year they gave up. They wrote to Kögl but didn't get an answer. Germany in the meantime, had occupied Holland, so there was no communication with Kögl. His papers were never retracted.

I should mention why Professor Foster reading this paper considered them a total fraud. As a chemist, Kögl had given elementary analyses for all the amino acids—carbon, nitrogen,

oxygen. Among others he claimed to have isolated racemic lysine. In those days, you isolated crystalline amino acids for analysis; there was no chromatography. The data were given for the free amino acids.

Now, free lysine has two amino groups. The pK one is very high, the pK_b, I guess. It is so alkaline that it picks up CO_2 from the air. It's very difficult to get it to crystallize. The standard analytical technique was to convert lysine to its monohydrochloride, which is crystalline and can be handled very easily.

Foster said, "The data are given for lysine, not for lysine monohydrochloride." He found a few other minor things, but this was the most glaring one. So he never believed it, and he was the only one who was skeptical. When Warburg and Lipmann finally gave up, the whole thing was forgotten, and there was no explanation until the 1960s.

In the mid-1960s, two young chemists in the same Utrecht department found some vials, which were labelled auxin a and auxin b, respectively. That goes back to the first story published in 1934, also never retracted. They analyzed these samples by mass spectrometry. The mass spec analysis showed that one of the auxins was, in fact, cholic acid. Then they found a bottle of commercial cholic acid on the same shelf. This so-called auxin had the same impurities, in the same proportion, as the commercial cholic acid. Unbelievable!

As for the unnatural amino acid story, a large bottle of δ-glutamic acid, which was claimed to be the most racemized amino acid, had been provided by the I.G. Farben to Professor Kögl. A copy of the letter was found in which he requested it. On the face of it, if you looked at Kögl's papers—the professor never worked with his own hands—one person, whether woman or man, could not have done all this work. It's just impossible.

But Kögl had done very good research earlier on the chemistry of biotin for example. So he was misled. There are several theories why these frauds occurred.

[END OF TAPE, SIDE 2]

BLOCH: I think the most likely one is, according to former students, that this woman somehow fell in love with the professor. He was a very handsome man and a bachelor. He didn't respond to her advances. She obviously was a psychopath, and finally, after all her efforts to seduce him, or whatever, failed, she decided to do him in. And she succeeded completely. As is the case with so many scientific frauds, by reading the paper, even if you know a lot about the subject, you cannot find out what's wrong with it. That's why I think these frauds will continue.

There was an example in my own department of an undergraduate painting mice or rats. This paper, which dealt with some immunological problem, the so-called Transfer factor, was done by an undergraduate, in collaboration with a postdoctoral student and a young staff member. The paper was read by three distinguished immunologists in the community, both at Harvard and MIT. Jim Watson also read it, and he was willing to sponsor this paper to the PNAS [*Proceedings of the National Academy of Sciences*].

Even now, fifteen years later, from the paper itself, you could not find out what was wrong. The way this perpetrator was unmasked had nothing to do whatsoever with the published paper. The culprit was a senior pre-med student, and then came the day he applied to medical school. A member of the admissions committee got a letter that said that Mr. X was an outstanding class-1 student, and he would do very well in medical school. The candidate in this letter was praised in the highest possible terms. A member of the committee called the student's supervisor, an assistant professor. "Is Mr. X really all that good, as your letter says?" My colleague said, "I've never written such a letter." The student's fabricated letter was his undoing, not someone discovering that claimed results couldn't be repeated.

The reason why we have so much trouble solving the mysteries of scientific fraud is, undoubtedly, the perpetrators have brilliant minds. In my opinion, in the most spectacular cases, the individuals are psychopaths, the pattern you see in all walks of life. I think that a very small percentage in each professional group are psychopaths. Their behavior is typically an unawareness of their eventual fate. It's suicidal, ultimately.

So it was certainly a lucky escape when Kögl turned me down.

BOHNING: What about Butenandt? Why were you turned down there?

BLOCH: I applied three months before Hitler marched in. He must have known what was coming. He knew that I was Jewish; my name is Jewish. I don't remember that I spelled this out, but he turned me down, and I'm glad that he did.

BOHNING: You left Munich in 1934 and went to Davos for . . .

BLOCH: . . . a year and a half.

BOHNING: How aware were you of the political situation in Munich and also when you went to Switzerland? Were you still thinking that this would not last, or were you becoming more aware that this was becoming more serious?

BLOCH: Obviously, the fact that I couldn't continue in Munich made it very clear that I had to emigrate. The countries open to refugees were limited in number. The United States, obviously, offered the greatest opportunities. First of all, my future wife was already in America. That was a very strong incentive.

BOHNING: You had met her in Germany?

BLOCH: I had met her in Munich. I tried desperately to get to the United States but I had no relatives who would have provided an affidavit of support the U.S. required. Strangely enough, I didn't know anyone in my family, on either side, who had emigrated earlier to the U.S. I therefore turned to Professor Anderson at Yale as I mentioned earlier.

BOHNING: What about the rest of your family?

BLOCH: All of them escaped. My older sister went to England. She had studied law. We had some relatives in Britain. I don't think I helped her. I may have sent her a check. I brought my younger brother over.

A hundred dollars was all I had when I came to the United States. [laughter] I made some money at night teaching the biochem lab for dental students. That was a hard way of making a living. [laughter]

But after a couple of years, I had saved enough to pay for the passage, first of my younger brother, and then for my parents, who were still in Berlin. Somehow they managed to leave at the very last moment, two weeks before the Germans invaded Russia, which was in 1941. They settled in New York and within a few months were able to support themselves.

BOHNING: What did your future wife do? Why was she in the United States?

BLOCH: She had many relatives here. She was taking a year off to go to Columbia. This is an interesting subject, and I've been very intrigued by it. My wife was born in Munich, and her whole family came from southwestern Germany, Bavaria and the Palatinate. I came from Prussia. My wife had hundreds of relatives in this country, but I had none. Most of my wife's forebears had emigrated to the U.S. in the mid-nineteenth century, the 1840s and 1850s.

Why this difference? My explanation—and I have confirmed this—is that most who had lived in Prussia did not emigrate until or shortly before the second world war. The reason was that the laws allowing or giving privileges, such as freedom to choose a profession, were much more liberal in Prussia than in Bavaria or the German Laender outside Prussia. So the pressure to emigrate was much less in Prussia.

The Prussian Freiherr von Stein [Heinrich Friedrich Karl von und zum Stein], introduced certain liberal reforms in the 1840s. At that time, the Prussian king, Friedrich Wilhelm IV, was also very liberal. In the 1840s there was a minor, democratic revolution, but totally bloodless. No one went to the barricades.

My great grandfather studied medicine and got his M.D. degree in Berlin in 1819. That wouldn't have been possible in Bavaria. Whenever I met someone who had also came over here during the Hitler days, I asked them, "Where are you from? Do you have any relatives in this country?" The correlation stood up very well.

BOHNING: In the Davos period, what kind of a person was [Frederic] Roulet, the person who headed the institute?

BLOCH: He was helpful. Like many Christians, he wanted to be helpful. He had two physicians, refugees from the German Reich, apart from myself working in his institute. At the time, the institute was dedicated to the study of tuberculosis. His academic appointment was in Basel, but he went there maybe once a month to give a lecture. He was a privatdozent, not a professor.

I don't know how Fischer, my professor, made contact with Roulet. In any event, one letter arrived from Switzerland saying, "We would be delighted to take you on for a year or so." And so I went. I hadn't done any research, only a cookbook kind of chemistry.

I remember the first thing you did when you entered an organic lab in those days was to distill and purify solvents. None of the organic solvents could be used as such without rectification. I needed acetone. I was working on phospholipids, and acetone was the solvent. I couldn't raise the boiling point. It stubbornly remained at fifty-two degrees, until it dawned on me that at five thousand feet, this is what it should be. [laughter]

There were many hurdles to overcome. There was no library. Roulet, a pathologist, was interested in the phenomenon that not only dead tubercle bacilli give the same response as live ones when injected into the skin, but also organic solvent extracts from the dead bacteria or live bacteria, cause the same histological picture, such as the so-called tubercular granulomas.

I isolated these materials, which turned out to be phosphatidic acids, both from the bovine strain of TB bacilli and the human strain, because the question was, how specific were they? We had to test them. We couldn't very well test them on cows, but we could test them on humans. And who should be the experimental animal? Of course, the young assistant! These are the scars from the human phosphatidic acid, injected internally in my right arm.

BOHNING: My goodness!

BLOCH: This is fifty years after the experiment! And this is the scar from the bovine injection in my left arm. I think the only surgeon in Davos was a vet. [laughter] Today, this kind of experiment would not be possible.

BOHNING: There was some question about contradictions with a report by [Erwin] Chargaff.

BLOCH: Yes, exactly. The first problem I had was to find out whether or not cholesterol occurs in tubercle bacilli. I had a predecessor, an M.D., [Eugen] Hecht, before I came to Davos. He had published a paper claiming to have isolated cholesterol from tubercle bacilli (8). During the same period a paper appeared from Yale. Erwin Chargaff, one of the authors, was also a

refugee working with Anderson. He had not found any traces of cholesterol in tubercule bacilli. Anderson (9) was the great expert on the chemistry of these bacteria.

Yet my predecessor in Davos had claimed to have found it. He used a faulty method, and I knew exactly what was wrong with his procedure. Certain branched-chain hydrocarbons present in mycobacteria also form insoluble digitonides, supposedly specific for cholesterol. I confirmed what Chargaff and Anderson had reported. Roulet, the director of the institute, was in an embarrassing position. A paper coming from his Institute contradicted, or could not confirm, the results obtained at Yale. He was anxious to find out who was right and who was wrong. That was my job.

It was my first awareness of the cholesterol molecule. Only a few years later this molecule came to my attention again, after I became a postdoc at Columbia with [Rudolf] Schoenheimer. He was a brilliant scientist, full of ideas and enthusiasm. It was he who introduced novel methodologies for one of the main objects of modern biochemistry—intermediary metabolism.

If you look at chemical structure of biomolecules, you ask yourself, how is this molecule made? What is biosynthesis? It's rarely, if ever, organic synthesis, i.e., test tube synthesis. One molecule that intrigued him was cholesterol. He was the first to find out that cholesterol is made in the animal body. He established this in Freiburg in the lab of the very famous pathologist [Ludwig] Aschoff, an early student of atherosclerosis.

When Schoenheimer came to this country, he was one of the first to take advantage of the availability of isotopic tracers. The history is not quite clear, but apparently Harold Urey gave a seminar on the separation of stable isotopes of carbon and nitrogen and oxygen and hydrogen. At this seminar, in the Columbia Chemistry Department, Urey suggested that these stable tracers should be ideally suited for tracing metabolic pathways in the body.

Schoenheimer said, "I would love to do that, provided you can give us some of these isotopes which are not available commercially. Secondly, I need someone familiar with the methodology to measure these isotopes." Urey was a very generous person. He could have hired people himself, because he was world-famous. But he said to Schoenheimer, "I'll send you my best graduate student." The graduate student, who had just finished his degree in physical chemistry, was David Rittenberg. He built the first mass spectrometer at Columbia. He also assembled the apparatus for measuring heavy water. Do you know the [K.] Linderstrom-Lang method for determining the deuterium content of heavy water?

BOHNING: Oh yes, the falling-drop method. I didn't know it by that name.

BLOCH: First of all, you have to burn or combust enough organic material to give you three drops of water, roughly a hundred milligrams. This water had to be highly purified, by high-vac distillation. Then you had to transfer this sample to an automatic pipette, which would deliver drops of uniform size into a water bath which had a constant water temperature varying by no more than 0.002 degrees centigrade. [laughter] The procedure was a nightmare, but it was the only method available before the mass spectrometer. That, of course, was developed later.

I was starting out this section by mentioning the brilliant mind and intuition of Schoenheimer. He looked at the structure of cholesterol and said, "There's one oxygen in this molecule, and all the rest carbon and hydrogen. Where does this oxygen come from? From water, or does it come from molecular oxygen? Let's try it."

This was in 1940. The prerequisite was to develop a method for getting the oxygen out of the organic molecule in the form of CO_2, so you could equilibrate it in the form of water. Then the water had to be equilibrated with CO_2, which you then, in turn, could analyze in the mass spectrometer. It was a very complicated procedure.

I spent more than a year trying to develop an analytical procedure for teasing the potentially continuing H_2O^{18} from these large, complex organic molecules, but I failed. Had I succeeded, I would have found the answer, which was that it comes from molecular oxygen, not from water.

It was the first example of what we now know as P_{450} systems, so-called oxygenases discovered later by O. Hayaishi and W. Mason. Prior to that, there was only water thought to be the source of oxygen organic compounds in biological systems.

Schoenheimer had numerous other ideas, and it was wonderful to work for him. As to why he committed suicide, I think it was quite clear that he was an unstable person. We learned later that he had attempted suicide on a few earlier occasions.

BOHNING: That's interesting, because my reading on that was that it was depression over the events in Europe. If he had a previous problem, that may not be totally correct. When did he come to the United States?

BLOCH: He first came in 1932. He had a visiting professorship in Chicago and also Columbia. He impressed Hans Clarke, the chairman at Columbia, so much that, after Schoenheimer had gone back to Germany, Clarke invited him to join the department. He was an electrifying person, and potential graduate students would line up to work with him. He had by far the largest group in the department.

BOHNING: Did you see any signs of this other side of his behavior at all?

BLOCH: No, except that at some times, his exuberance and enthusiasm were a little frightening. Six months before his death, we were wondering why he would closet himself in his office every afternoon for a few hours, apparently writing very busily. It turned out later that he was drafting future research projects for each one of his collaborators, both postdoctoral and graduate students. Since he had a very large group, this took a great deal of time.

We found these notes, they were incredibly detailed. There were three senior postdocs of Schoenheimer's. One was David Rittenberg, another was David Shemin, and I was the third one. I think I mentioned that Hans Clarke called us to his office after Schoenheimer's death and said, "There's still lots of unspent money from a big NIH grant, which will run for another three or

four years. NIH has told me that I can use these funds for projects that make good sense in my judgment. You, the three senior associates of Schoenheimer, go ahead and use the funds."

[END OF TAPE, SIDE 3]

BLOCH: The problem was that Schoenheimer had almost covered the entire waterfront of intermediary metabolism. The three major metabolic areas were lipids, i.e. fatty acids and cholesterol, protein synthesis and what Schoenheimer had called metabolic turnover, the synthesis and degradation of proteins. The three of us had dabbled in all these fields. We had to ask ourselves, "Who's going to do what? How are we going to make the choices?"

None of us was really committed to lipids, to proteins or amino acid metabolism. They were all interesting. Ultimately, I think it was I who suggested that we draw lots. That's how I got the lipids. It was not a very rational decision, but from then on lipids were my major interest.

BOHNING: Didn't your Ph.D. work use some of the work from Davos, or didn't they use any of it?

BLOCH: The Columbia Faculty Committee accepted the three publications as part of the requirements for the Ph.D. degree. The experimental work I had to do at Columbia was inspired by Clarke's interest. It was purely organic chemistry. Specifically, the synthesis of various cysteine derivations and their sensitivity to alkali. They were to be model compounds for thiamin, a project that Clarke was engaged in, in collaboration with Roger R. Williams, then at the University of Texas in Austin, Texas. It took me exactly one year to get results which would satisfy Clarke. I needed a job after I got my Ph.D. This was in 1939, and there were very few available jobs. Schoenheimer was first reluctant to hire me, because he didn't think my Ph.D. thesis was very impressive. [laughter]

BOHNING: You've also mentioned the seed crystals that you gave to . . .

BLOCH: . . . [Vincent] du Vigneaud. In classical organic chemistry, crystallization was not only essential for analytical work, but for the investigator also a triumph and an aesthetic experience. The compound was N-methylcysteine monohydrochloride. At first, I obtained an amorphous mass, a goo sitting in a desiccator for weeks. I looked at it daily and occasionally tickled it with a glass rod. [laughter] After a month, all of a sudden, a small crystal appeared in the center of the flask. I waited for a few days and the crystals gradually spread. This is or was one of the great and enviable sensations for a chemist.

Then I called Clarke and said, "Would you look at the crystals?" He always had a little magnifying glass [Lupe in German] in his pocket. Organic chemists always looked at crystals, you know. [laughter] He certified that they were crystals. "Well, that's great. I'm very pleased. Besides, I know that Dee is interested in the same compound." Dee was Vincent du Vigneaud.

He was a close friend of Hans Clarke's, and the professor of Biochemistry at Cornell Medical School. "Can I tell Dee to come up to 168th Street with a test tube and to fetch a seed crystal?" For a graduate student, it was a very special thrill, to provide a seed crystal to a professor. [laughter]

BOHNING: Did du Vigneaud make any comment?

BLOCH: He gave me a footnote in one of his papers.

I knew that there were about four or five young men and one young woman in the Department, all roughly at the same stage of their careers. They all were in need of a faculty position. During the war, there were no openings. No department made new appointments. The existing staff was kept for teaching purposes, particularly in medical schools. But after the war in 1946, the universities in this country expanded enormously. There were numerous opportunities. My very close friend, an early graduate student of Schoenheimer's, was Earl Evans at Chicago. He was chairman of the Chicago Biochemistry department. He offered me a job as an Assistant Professor. So I went.

BOHNING: Let me come back to some of the other work you did with Schoenheimer, because you went off to Mt. Sinai Hospital for a short period of time.

BLOCH: My salary in the 1930s gradually rose from $500 to $1,000 dollars a year. I was anxious to get married. In those days, you didn't dare get married, unless you had a job which would support a family. At Mt. Sinai Hospital a retired surgeon had a great deal of private money. He wanted to have some fun and do some cancer research. He needed a biochemist to isolate certain active fractions from the thymus gland.

I went across town. He offered me twice the salary I was paid at Columbia. I accepted immediately, because I thought this would support me more comfortably. My future wife also had a job. Yet after I started my assignment, the hopelessness of the project soon became obvious. I prepared tissue fractions for the pathologist, who tested them for their effects on mouse adenocarcinomas. Six weeks later you got an answer whether or not a fraction reduced the size of the tumor. In the interim, I had nothing to do. After a year had gone by, Schoenheimer called me to say, "Why don't you come back? Columbia will pay you the same salary as Mt. Sinai." [laughter] So it was a good move for more than one reason.

BOHNING: Your first work with Schoenheimer was with nitrogen-15.

BLOCH: Yes, it dealt with creatine, its biosynthesis and conversion to creatinine. The two compounds were closely related; one is an anhydride of the other. Other people had tried. In pre-isotope days, you gave compound A to an animal, a rabbit or rat, and then you isolated B, the suspected conversion product from the tissues, from the urine, or from blood. If there is

more of B than in the control experiment, you conclude that A has been converted to B. This so-called balance technique sometimes gave the correct answer, but more often for inherent reasons there was no proof. This is why the tracer technique was such a fundamental advance.

Before I could start by biochemical experiments, the organic synthesis of the isotopically labelled molecule had to be carried out. I administered the N-15 creatine I had synthesized to rats and found that it was converted to creatinine (10). We also did some interesting work on the biosynthesis of creatine—where it came from (11). That really set the tone for my interest in the ultimate and never a priori obvious origins of organic molecules. It remained, by and large, my major interest.

BOHNING: How difficult was the synthesis of the labelled compounds at that time?

BLOCH: You obviously had to use a method which not only gave good yields, also one that would allow the recovery of all the unreacted material. We had finite amounts of N-15, from Urey. Mother liquors had to be worked up and converted into ammonia, in the case of nitrogen. Then the ammonia was precipitated in whatever form, and reused; recycled, as it were. There was no commercial source for a few years.

Then, after World War II, the Atomic Energy Commission produced C-13 and N-15 for a few years, until the Commissioner, Bill [Willard F.] Libby, declared, "I don't think we need stable isotopes anymore." In his dating method he used C-14, so he didn't see any need for stable isotopes.

Deuterium came from Germany or Norway as D_2O. Fortunately, Merck (Canada) continued the production of C-13 and N-15, as did Eastman Kodak. The Atomic Energy Commission also withheld C-14 from the scientific community until 1947, for no obvious reasons.

BOHNING: Where was Urey getting his N-15?

BLOCH: He made it by thermal diffusion, the feat that earned him the Nobel Prize in 1934.

BOHNING: Just thermal diffusion?

BLOCH: Yes. Here is an amusing fallout due to the uncertainty of stable isotope availability. In the building in which I was located, the Conant building, laboratories named after Harvard's President, and the most modern building (1959), there is an open space extending from the basement to the fourth floor. Its purpose, at the time when Frank Westheimer and I came [to Harvard], was to allow us to set up thermal diffusion columns. The bigger the column, the better the separation. This was Urey's method for preparing stable isotopes. P-32 was available

commercially, but for many of our purposes, carbon, hydrogen, and nitrogen were the obvious stable isotopes.

BOHNING: How much incorporation of the isotope into the compound would you get? Ten percent?

BLOCH: It depends whether stable or radioactive isotopes are involved. C-13, N-15 or D contain normally a small fraction of the heavy isotope referred to as natural abundance, and you express the data in terms of atom percent excess. In one of our experiments, the isotope concentration was limiting the conversion of cholesterol to pregnanediol (12). I isolated the glucuronidate of pregnanediol from pregnancy urine and analyzed the sample by mass spectrometry. It contained 0.1 percent excess of deuterium. This was about ten times the natural abundance. The paper was accepted (12).

You may have heard about the first paper on the enzymatic synthesis of DNA, by Arthur Kornberg (1958). The results were submitted to the *Journal of Biological Chemistry*, and the responsible, anonymous editor turned it down. Also, one major criticism was the inadequate characterization of the radioactive product as DNA. Arthur Kornberg was stubborn and insisted, and the paper went back and forth. He did not provide additional data, but convinced some of the other editors, especially John T. Edsall, to accept the paper. Kornberg's results stood the test of time. His paper became a classic.

BOHNING: But in the 1930s this must have been an incredible thing, to go from conducting animal experiments to labelling, to be able to follow these things.

BLOCH: Yes. The information, the knowledge given, explosively following the discovery of isotopes.

I learned my biochemistry from a slim text of three hundred pages by [Meyer] Bodansky (13). The type was relatively large and the margin was wide, but it contained all the knowledge in biochemistry at the time. Today, we have texts like one by [Lubert] Stryer, which is 1,060 pages, has a much larger format and smaller print (14). The information it contains is enormous.

Textbooks of biochemistry today include a subject which isn't strictly biochemistry, but molecular biology. Before long, we will have to separate the two areas. One is biochemistry; that is, the chemistry of the transformation of molecules in living systems. It is fundamentally a problem of organic chemistry. Molecular biology does not involve or minimally involves detailed chemical structures, mostly acronyms. Few molecular biologists know the precise chemical structures of amino acids or the nucleic acid bases with which they work.

Here is a classical example, an episode reported by Jim Watson in *The Double Helix*, his autobiography (15). At one time Watson and Crick were at an impasse in building space-filling models of DNA. Their models did not fit the x-ray data. One day, an organic chemist, Jerry Donohue, walked into their lab to inspect their 3-dimensional models. Looking at the structures

of the purine and pyrimidine bases, he said, "You're using the wrong tautomers of the bases, the enol tautomer, not the keto tautomer. That's wrong." Watson and Crick responded, "That's what all the textbooks say; we simply copied the structure. We didn't know anything about the chemistry. All the textbooks show these structures." Donahue said, "They're wrong. In aqueous solution at neutral pH, ninety-eight percent of the bases are in the form of the keto tautomer." That comment broke the log jam, and immediately everything fell into place.

I think Donahue's comment is one of the most important contributions of chemists to the structure of DNA. That is hardly known. Jim Watson mentions this episode in his *Double Helix*, but it is rarely mentioned elsewhere.

BOHNING: It's an interesting point, because I did teach biochemistry to nursing students. It was at a very low level, but I always felt that they needed to know and have some appreciation of molecular structure and reactivity, because otherwise you're just working with names.

BLOCH: Exactly.

BOHNING: The ASBMB [American Society for Biochemistry and Molecular Biology] was originally a society for biological chemistry [American Society of Biological Chemists] and then changed its name to include molecular biologists.

BLOCH: Our department here started out in 1967 as the department of biochemistry. When Jim Watson joined the department a few years later, he said to his colleagues, "I don't think I'm a legitimate member of a department of biochemistry. I don't know any biochemistry; I never took a course. You have to change it somehow." The compromise was the "Department of Biochemistry and Molecular Biology."

Interestingly, the molecular biologists such as Watson and Crick and many others, came not from chemistry, but many of them were trained physicists. They wanted to approach biology from the physicist's background, but bypassing chemistry. In their case, it worked. But today, many of the molecular biologists, how little feeling or understanding they have for key chemical structures. For macro-molecular interactions yes, but not for covalent interactions.

BOHNING: Was it 1941, then, when Schoenheimer committed suicide?

BLOCH: Yes.

BOHNING: How did he do it, if I may ask?

BLOCH: Cyanide.

BOHNING: That's what Isaac Asimov calls a chemist's suicide. That's something that was used by a large number of chemists.

BLOCH: That's right.

BOHNING: That was right after [Wallace] Carothers.

BLOCH: Carothers, and Emil Fischer.

BOHNING: That's right. Emil Fischer.

BLOCH: With Emil Fischer, there was also an element—I'm not certain about this—that the defeat of Germany in World War I weighed very heavily on him. He was a great patriot. I think he was a bachelor and his work was his all-consuming interest. Hans Fischer also committed suicide.

BOHNING: Really?

BLOCH: For two reasons. First of all, during World War II, his entire institute in Munich was levelled to the ground. Secondly, he apparently had bone cancer and it was very painful. He had no family; he was always a bachelor.

BOHNING: I can't remember the exact date that Carothers committed suicide, but I think it was just before 1941. I was interested in the close relationship in timing, because Carothers also had stability problems, which he was aware of. He had a long history of the same kind of problems that Schoenheimer apparently had.

You had a number of papers that were coming out at this time. You even got a paper out of the Mt. Sinai work (16).

BLOCH: Yes.

BOHNING: As you said, you lost interest in the cholesterol-oxygen problem.

BLOCH: I didn't lose interest, but I gave up temporarily. Then a German paper appeared in the *Liebig's Annalen der Chemie* from Wieland's laboratory, showing, or indicating, that acetic acid might be utilized specifically for the synthesis of yeast sterols (17). Wieland had worked on yeast metabolism a great deal. His associates analyzed the sterol fraction, the unsaponifiable matter, rather than crystallizing the sterol. But that seemed to us sufficiently intriguing to repeat the experiment with animals. We fed isotopic acetate to rats, and then purified the cholesterol. That's what Rittenberg and I did, experiments that ultimately led to the localization of the two atoms of acetic acid in the sterol structure (18).

[END OF TAPE, SIDE 4]

BOHNING: You said you did that experiment the next day after you found that paper. Was that the paper that was delayed by the war?

BLOCH: Yes, that was a 1937 paper we did not see until 1941.

BOHNING: You also commented that it was at this point that you finally had set the stage for a lifelong interest in the biosynthesis of cholesterol and fatty acids.

BLOCH: I looked at speculations of this process in the literature. Organic chemists, especially once retired, tend to speculate. Sir Robert Robinson and all the greats have speculated on what they called biogenesis—they never called it biosynthesis—how nature might assemble complex molecules, such as the sterols. Sir Robert was on the right track. He proposed that the branch-chain hydrocarbon squalene, $C_{30}H_{50}$, might be the precursor [*J. Chem. Soci. Ind.*, 53 (1934): 1062]. Other proposals were oleic acid by way of Zibeton, carotene, and others.

[Taddeus] Reichstein, who was also one of the greats, pioneered the structural analysis of adrenocortical steroids and had some scheme in which glucose breaks down into three carbon units, which might be reassembled. None of the hypotheses were sufficiently convincing to encourage experimentation. The solution to the puzzle had to await the arrival of the isotopic tracer technique.

Heinrich Wieland was interested in the metabolism of acetic acid, not in sterols. He used labelled acetate to study the fate of this small molecule. One important result from his lab was that the yeast saccharomyces will not grow on acetate as a carbon source, unless you wait a long time. Yeast growth is preceded by a long lag period, and then something happens to adapt the yeast to grow on acetate. He was very intrigued by this adaptation phenomenon. He concluded that somehow acetate, added as the sole carbon source to the growth medium, has to be activated. So he postulated "activated acetate," which then turned out to be acetyl-CoA, the structure that his son-in-law Feodor Lynen solved.

And then the deuterium analysis of yeast fractions in Wieland's laboratory was probably—do you know what the German word Gründlichkeit means? Thoroughness. [laughter] Using labelled materials, the postdocs or the students had to analyze every fraction, and found a rather high deuterium concentration in the nonsaponifiable material. This part of a routine analysis had very major consequences, certainly for us. A priori, we wouldn't have picked acetate as a carbon source for sterols.

BOHNING: How rapidly did labelling techniques spread throughout biochemistry? I'm curious about the availability of isotopes. You said they weren't easy to get.

BLOCH: It was a question of how much money you had and whether you had a collaborator, someone like David Rittenberg who could build a functioning mass spectrometer. In the North American continent, up to 1950, no more than three or four mass spectrometers had been built.

BOHNING: Harland Wood was one of the early ones.

BLOCH: Harland Wood. [Alfred O.] Nier had a special design for mass spectrometers and I believe Harland built the instrument with his own hands. Martin Kamen was certainly another pioneer. He showed that in photosynthesis, oxygen came from water, not from CO_2 gas. It was a very fundamental discovery. It had to await the advent of isotopes.

In the early days, mass spectrometers were certainly not routine equipment in laboratories, and it was an expensive technique. Schoenheimer had a large grant from the Rockefeller Foundation. The general methodology became very routine, once radioactive isotopes of elements such as carbon, phosphorous and hydrogen became widely available. The equipment was much less costly than for stable isotopes. The Geiger counter did not cost very much, compared to a mass spectrometer. I got my first Geiger counter in 1946 or 1947, when I was in Chicago.

BOHNING: Before you left for Chicago, in those last years at Columbia, you had as your goal the complete elucidation of the biosynthesis of sterols, but you spent a lot of time looking at the precursor role of cholesterol for bile acids and steroid hormones.

BLOCH: Right. The rationale was that the cholesterol molecule has very diverse functions, reasoning on structural grounds. Cholesterol shares the same ring system with bile acids and steroid hormones. When the structure of the bile acids was shown and established, it was quite obvious that cholesterol should be the precursor; it's the same for steroid hormones. All of these structures were identified chemically in the 1930s.

But for nature, one cannot always predict relationships.

BOHNING: You are quoted as saying, "Structural similarities do not prove biochemical relationships."

BLOCH: Yes, that's right. But "not necessarily," I think I should have said. Do not prove, in that sense it's correct. I've been interested recently in the parsimony of nature or actually the opposite of parsimony, i.e., profligacy. Nature is not always parsimonious, but wasteful in some instances. This wastefulness is illustrated by the fact that you have more than one pathway to a given biological compound. One recent example: δ-aminolevulinic acid, the precursor of porphyrins, is made on biological systems by two totally separate pathways, one starting from succinic acid and glycine, and the other from glutaumic acid. One of the pathways may be redundant, perhaps vestigial.

I've been a member of two departments at Harvard, chemistry as well as biochemistry. I was a full-time member of both departments, which meant I could vote in two departments. [laughter] And I was chairman of both, at different times.

The two types of chemists really differ in approach, outlook and temperament. I'm now comparing organic chemists with biochemists. The organic chemist, when he or she devises routes to the synthesis of a natural product off-hand, several modes are chemically reasonable. Obviously, a good chemist can devise more than one route to the same product, without knowing which one, if any, nature uses.

Chemists delight in the intellectual thrill of predicting one or more reactions which will be successful in the test tube. Moreover, the investigator is in charge. He can vary conditions—temperature, catalysts, pressure, solvent, what have you—and the skillful combination of variables will lead to the desired product. Now, this doesn't allow you to make any prediction of nature's design for the same process. For example, the origin of none of nature's macromolecules—e.g., protein or nucleic acids, alkaloids, et cetera—has been predicted by organic chemists. The pathways were always rationalized post factum. Then they would say, "Of course! It had to be this way."

I think one of the wisest statements about biochemical or biological research I have quoted frequently, we owe to François Jacob (19). "The biologist is a tinkerer, whereas an organic chemist is an engineer, working from a certain blueprint, and he knows exactly the ultimate goal." There are more than one reasonable procedures to reach it.

Clearly, you need different temperaments to do synthetic organic chemistry or biochemistry, ingenuity in the former and intuition in the latter. In a sense, you have to be less ambitious, or more humble, and recognize that we cannot yet foresee the motives of nature.

BOHNING: You went to Chicago in 1946? You've already commented about that, through your earlier associations with Earl Evans, even though you did say that you missed the opportunity to ski in the Wasatch Mountains in Utah.

BLOCH: Yes. [laughter]

BOHNING: What were your goals when you went to Chicago?

BLOCH: Do you mean scientifically, or as far as career is concerned?

BOHNING: Both.

BLOCH: The department in Chicago was attractive, first of all because Earl Evans and I were good friends. Secondly, the University of Chicago was a very lively place, particularly after the war. Many of the people who had worked on the Manhattan Project in physics and chemistry and also biology remained. So, it was a first-class institution. It also had the reputation of hiring young people whom they would later on promote, which Harvard didn't have. [laughter]

So it appealed to me very much, including the closeness of the university to living quarters, although the residential area later on deteriorated. But, in the mid-1940s, the atmosphere was very lively, in part because of [Robert Maynard] Hutchins, and in part in spite of Hutchins. He was a very controversial figure who didn't like science at all.

BOHNING: Yes, I've heard that.

BLOCH: Yes. [laughter] Well, it was not a question of liking, he despised it as an inferior intellectual pursuit.

BOHNING: You did continue the cholesterol work, but you also did some work on protein biosynthesis.

BLOCH: Yes. Like a number of others, I was interested in the mechanism of protein synthesis from amino acids. But coupling mechanisms require energy, and what was the energy which drove the synthesis to form the peptide bond? I decided to use glutathione as a model system. It's a tripeptide, widely distributed.

There had been very little earlier work, and again, isotopes provided the opportunity. We isolated two specific enzymes, one would make a dipeptide and the other a tripeptide. We showed the mechanism of activation, that ATP is needed. We had evidence, but not necessarily convincing, that sort of mixed anhydrides were formed, carboxyl phosphates and things like that. I think our enzymology was in good shape, but the question was whether the mechanism was related to protein synthesis.

In 1954, when I came East, I attended a cancer meeting on Cape Cod, and listened to a paper given by Paul Zamecnik. Do you know him?

BOHNING: No, I really don't know him.

BLOCH: He was at the MGH, Massachusetts General Hospital, for many years, and there he did the early fundamental work on protein synthesis, e.g., the involvement of RNA, which came as a revelation and total surprise. At this meeting, I was going to give a talk on glutathione, which I did. It turned out that our work was irrelevant to protein synthesis. We still don't quite know all details of protein synthesis. Central issues remain, such as information transfer from DNA to RNA, specifying amino acid segments in the various proteins.

So I stopped work on glutathione as a model for protein synthesis. The tripeptide is of interest once again, because it is an antioxidant. Antioxidants are very popular these days, such as vitamin C, E, glutathione, and vitamin K. We ingest all these fish oils which are sensitive to oxygen, give rise to toxic oxidized intermediates, and therefore we need antioxidants for protection. [laughter]

Shortly after I moved East, I became interested in unsaturated fatty acids, their origin, because in some instances, the process depends on oxygen. By chance I learned of a paper by two plant physiologists, A. A. Andreason and T. J. B. Stier (20), who found that yeast will not grow in the total absence of oxygen, contradicting Pasteur's notion of "la vie sans air," meaning anaerobic yeast will grow well in the absence of oxygen. It turns out that yeast will ferment sugar, but cells fail to multiply under strictly anaerobic conditions.

Andersen and Stier showed in the 1950s that if you rigorously remove oxygen from the atmosphere, yeast will grow, but only if provided with cholesterol or ergosterol and oleic acid. Clearly, yeast needs oxygen for biosynthetic purposes but not for fermentation.

We had already shown at the time that you needed oxygen to provide the -OH group of cholesterol. The question then arose, "Is this true also for making oleic acid?" The process is a dehydrogenation or desaturation without oxygen entering any intermediate. We discovered an enzyme called acyl-CoA dehydrogenase, which is an oxidase of a special kind. The enzymes have been purified, but to this day, the detailed mechanism is not known. For me it became a major research interest, and ultimately led to the last accomplishment in my career, a phenomenon called "enzyme suicide." I don't know whether you've heard about it.

BOHNING: I know the term.

BLOCH: It's a term I do not use, because it is inaccurate for reasons I will give below. It is a common practice to prepare inhibitors of enzymes by modifying the substrate, inserting an extra or foreign group into the substrate. Enzyme specificity can be explained by making analogs of the substrate. We then turned from yeast to an E. coli enzyme. I should mention here that in many bacteria, unlike yeast and animal tissues, long-chain olefinic acids are formed anaerobically

by dehydration of hydroxy acids, not desaturation. The E. coli system includes an $\alpha,\beta,\rightarrow\beta,\gamma$ isomerization.

In order to assay the enzyme, we had to make an olefinic Co-A derivative of a 10-carbon fatty acid. This was not commercially available; we had to synthesize it. What was commercially available was the corresponding acetylene, at the same position, β,γ, C-10 acetylene, which you reduced by Raney nickel to yield the cis olefin. It was a very nice method—we thought!

This was the substrate. We had made several batches of it. But one of the samples from a later run was totally inert; it was not converted to product. We were very puzzled, and finally found that in our chemical reaction to make the substrate from the acetylene, the Raney nickel reduction to the olefin had been incomplete. Five percent of acetylene remained, contaminating our substrate. It killed the enzyme, in effect, by reacting covalently with the active site of the enzyme. What happens is that the enzyme was unable to distinguish between the acetylene and the olefin, converting the acetylene by hydrogen abstraction into an allene. This allene is exceedingly reactive and then attaches covalently and irreversibly to an imidazole ring of histidine at the active site. The normal substrate binds non-covalently to the active site. As a result of this mistake, the lack of specificity seals the enzyme's fate.

As I said, biochemists have called the phenomenon "enzyme suicide." I don't think it is descriptive, because the enzyme is deceived. It does not commit suicide. A widely accepted alternative for naming inhibitors of this type is "mechanism-based." It is innocuous, but rather bland.

In any event, it is now recognized as a novel, rational method for drug design, if the aim is to reduce abnormally high levels of some enzymes. One of the successful examples is a drug called Ornidyl which is used to successfully control sleeping sickness in Africa. It is one of the examples I describe in an essay entitled, "The importance of being contaminated."

[END OF TAPE, SIDE 5]

BOHNING: If I have the sequences correct, part of this came out of a meeting you had with Roy Vagelos in 1961.

BLOCH: Yes. I'd like to talk about this episode, because competition in science sometimes has an unpleasant connotation. Roy and I had published papers simultaneously and independently, on a small heat-stable protein, ACP, acyl carrier protein, which turned out to be very important for fatty acid biosynthesis (21). He had worked with Clostridium and we chose E. coli as enzyme source. It was obvious that these two proteins were closely related if not identical. Neither of us had pure protein.

A month or two before the Federation meetings in Atlantic City, I decided to get in touch with Roy and his group to explore our mutual plans. Two of my associates and two of his group met for cocktails in Atlantic City. We decided not to race each other.

As it turned out, our eventual interests were quite different. Vagelos wanted to determine the amino acid sequence of the protein, and we wanted to know the role of ACP in the synthesis of unsaturated fatty acids. I think that's how science should operate.

BOHNING: You say that with the indication that you've experienced the opposite as well. Is that correct?

BLOCH: Yes, I have experienced the opposite as well. In retrospect, I would not quite put it this way.

I have actually competed with Lynen, with whom I shared the Nobel Prize. Both of us were interested in the biosynthesis of mevalonic acid especially the identity of the biological isoprene unit, isopentenyl pyrophosphate. There, we raced each other, without really wanting to. Our lab was the first to determine its structure, while Lynen and his associates designed its first chemical synthesis. But our results were such that we had no choice but to go ahead, also, in the interest of our co-workers who did these experiments. It turned out that in the pathway of eight steps, Lynen found half of them, and my group found the other half. Probably accidentally, we concentrated on different phases of the project.

BOHNING: I remember a time as a graduate student when I was told that so-and-so is coming through the lab on a visit; hide your notebooks. [laughter]

BLOCH: There are indeed unpleasant stories. I think these competitions tend to be at their most intense when people are still insecure. Let's say, they almost have made it, but not quite. There's also the Nobel Prize syndrome. No question about it. It is human nature; when you compete, you don't want to be beaten at the draw. I must say, I've always had an amiable relationship with my "competitors."

BOHNING: When did you first become aware of Lynen's work?

BLOCH: Very early. Right after the war, he sent me a sample of succinic acid. "Could I analyze it by mass spectrometry?" He was interested in succinic dehydrogenase; his laboratory did not have any facilities for analyzing heavy atoms. So he asked me whether I could have this analysis done. Then we met at a Ciba Foundation meeting in London. Then he invited me to come to Munich. I had spent a sabbatical in London, and we became very friendly, even though we realized that we were now competing—not totally, but partially.

I had one other group of very capable, brilliant competitors. You may have heard the names of [John W.] Cornforth and [George] Popják, who also worked on cholesterol biosynthesis. So on the one hand, there was Lynen who had three times as many collaborators as I had. There were the British, truly brilliant organic chemists and highly capable biochemists.

Altogether there were three groups all working on the same general subject. I think in the end, it turned out to be good for science. To some extent we overlapped, but it was not a waste of time for any one of the groups.

BOHNING: I had some other questions, but why don't we talk about this period now, since we are talking about Lynen? I hadn't realized he was Wieland's son-in-law. You mentioned that earlier.

BLOCH: He was the graduate student who married the bosses' daughter. [laughter]

BOHNING: You mentioned the Nobel syndrome before. As your work on biosynthesis proceeded, was there a point where you said, "Maybe this will do it?"

BLOCH: No. I think I can truthfully say that I thought someone with my interests and my position had a finite chance, but no more. It was not a thought that preoccupied me or was an incentive. It came as a total surprise. I was fifty-two, and what I set out to do was by no means complete. I think the reward was for the cumulative impact of research, not only on cholesterol biosynthesis, but also fatty acid synthesis. That is what the citation says. We spent as much time on fatty acid biosynthesis as on cholesterol synthesis.

Today, biochemists either are more chemically oriented or use the methodologies of molecular biology, and I think more and more of the latter. Chemists have taken over the mechanism of enzyme action, requiring a background in physical organic chemistry, for which biochemists are not equipped or prepared.

It's difficult to predict future directions, but it seems that metabolism or pathways will not play the same role as in the past. The first fifty or fifty-five years of this century were a golden age of metabolic biochemistry, intermediary metabolism. Macromolecules dominate the second half, how DNA, RNA and protein interact, and metabolic regulation, i.e., cell biology. Somewhat separately, but also related, of course, is neurochemistry.

My last four graduate students all became neurochemists, or neurobiologists. Just to find out how one compound derives from another, unless it is done with great chemical sophistication, is no longer a center-stage subject.

BOHNING: Didn't departments of biochemistry historically come out of medical schools?

BLOCH: Yes, certainly in part. In this country, there are two sources. One of the major preoccupations of biochemistry was nutrition, and nutrition in turn was part of agricultural biochemistry. So the Land Grant colleges, like Madison [Wisconsin] and Illinois are the earliest ones which had biochemists in their chemistry departments. William Rose at Illinois determined

the identity of the essential amino acids thirty years ago, and he was in the chemistry department. Roger Adams appointed him.

Before the war, much biochemistry often named physiological chemistry came from physiology in Medical Schools. There was no biochemistry section, either in the National Academy, or in the Federation. It was not a separate discipline. In a sense, biochemistry as a separate discipline was a post-war development.

In Europe, Britain was the first European country to found separate departments of biochemistry, at Oxford and Cambridge. In Germany, biochemistry entered the scene very late. The only way to become a biochemist was either to study chemistry, and then do a postdoctoral in biochemistry, or to have first a medical training. The German universities were opposed to setting up separate departments of biochemistry. You couldn't get a degree in biochemistry in German universities until the 1960s.

Some of the best-known biochemists were located in Max Planck Institutes, or what was called Kaiser Wilhelm Institutes, before the war. Now, much of the outstanding research in Germany is done in Max Planck Institutes. There are over fifty of them today. They appoint and attract the best people, because they are princely positions; they are not required to teach and their research is guaranteed. There's some unhappiness in Germany about this. I think the best scientists should also do the teaching.

BOHNING: When you came here from Chicago, your teaching really changed quite a bit.

BLOCH: It did substantially. I was one of maybe three or four staff members who taught the biochemistry course at Chicago. But this was not the Harvard system, or at least in certain departments. I joined the chemistry department at a time when biochemistry was not taught in the Faculty of Arts and Sciences. I was expected to teach either two courses or one-and-a-half courses all by myself. The practice was one undergraduate course and one graduate course per year.

Before I came to Harvard, I worked all summer on my biochemistry course, which was known as Chem 192. It was addressed to students who had taken organic chemistry and some physical chemistry. Then in the spring I taught a special topics course on hormones, membranes and regulation.

I retired about twelve years ago, no longer fully informed who teaches what, but I think that biochemistry, per se, is no longer given in the biochemistry department, but is either part of the curriculum in chemistry or in biology. They divided up the field. It reflects the major changes that organic chemistry and biology have undergone.

BOHNING: Why did you come back here from Chicago? Why did you leave Chicago?

BLOCH: I asked myself that question later on. We were very happy in Chicago. We had good friends, and our children went to a good school. But living had its problems, the physical aspects of living on the south side. We had an apartment faculty building, across the street from the midway, a three minute walk to my lab. But it wasn't safe to walk after dark.

Our children also went to the laboratory school affiliated with the university. My wife was worried if they didn't come back on time. Then it got worse and worse. Not until fifteen to twenty years ago did the university make great efforts to build housing for the faculty.

Maybe one reason was that the country around Chicago was flat. I like the mountains. The idea of ski areas very close in the East was attractive to me. There was no intellectual reason to leave Chicago, none whatsoever, except the physical environment, which the university wasn't responsible for. I also had offers from the West Coast.

I was about forty at the time. If I were to leave Chicago, it was now or never. Today most of my colleagues are made full professors in their mid-30s, or sometimes even earlier. That's a fairly dramatic change.

BOHNING: You took a microbiology course with [Cornelis B.] van Niel. Is that the summer after you came here?

BLOCH: No, it was in 1957, three years later. It was a major turning point in methodology, the choice of biological objects or materials biochemists work with—from rat liver to E. coli. And this meant to me new, microbiological techniques. That's primarily why I went to Van Niel's Marine Biological Station at Pacific Grove, California.

BOHNING: You finally did show, around 1956 if I have the paper correct, that the oxygen in cholesterol was indeed from molecular oxygen (22).

BLOCH: Yes, with T. T. Tchen. Dave Rittenberg was still alive then. He offered us the highest concentration of 0-18—about 80 percent excess—that was available, and it came from Israel, which is remarkable. My co-worker, T. T. Tchen, went to New York by train, and he returned to Cambridge carrying a glass containing this precious balloon containing O-18 gas. The experiment was very simple. Tchen did it both ways, with H_2O^{18}, which was easier to handle, and oxygen gas.

BOHNING: I am not clear when you did come here to Harvard whether you sought them out or you had been getting offers?

BLOCH: [laughter] One day I got a letter saying, "Dear Mr. Bloch: We are pleased to appoint you professor of biochemistry." It came out of the blue. I had not visited formally before. I had given an organic colloquium in the Chemistry Department about two years earlier. Louis Fieser

was my host, but there was no mention whatsoever of a faculty position. I was unaware that the Chemistry Department wanted to appoint a biochemist. The first inkling, the first letter, was the offer.

I didn't accept right away. But I did not have a long wish list. I surely wanted to find out where to live, what kind of space and facilities were available. In those days, however, one didn't bargain. Nowadays, people bargain, particularly about laboratory space and equipment, et cetera. You couldn't make an appointment like this today. No one would come, or accept the appointment, without a visit. I ended up having the basement floor of Converse, because the only cold-room was there—we called it the lower depth. I stayed there for five years until the Conant Laboratory opened. E.J. Corey took over those basement labs for several years.

I mention here what I only learned much later. In the early 1950s the Harvard Chemistry Department debated whether to expand in new directions. The fields under discussion were Nuclear Chemistry and Biochemistry. Biochemistry won by a vote of 5 to 4.

BOHNING: In working through the cholesterol, there was a series of events which you included in "Summing Up," which I'd just like to review. There was a report by [Harold J.] Channon on squalene (23)?

BLOCH: Yes. Channon was a biologist. What was known about squalene was the molecular weight and that it was a C_{30} hydrocarbon, but the exact structure was not known. That was in 1926. Ian M. Heilbron, the Professor of Chemistry in Manchester, was interested in squalene. I think he had determined the elementary composition and that it was a branched-chain hydrocarbon. Cholesterol, in a way, was also known to be a branched-chain hydrocarbon molecule. Channon was persuaded, maybe by Heilbron, to feed rabbits some of this hydrocarbon, which was easy to obtain from shark liver.

He found that there was more cholesterol in rabbit liver when the animal received squalene in the diet. This was a typical pre-isotopic experiment, when you had to rely on quantitative changes, which could be due to a direct conversion, or other metabolic changes. There was no proof. It was a black box kind of experiment [laughter], known as the balance technique.

[END OF TAPE, SIDE 6]

BLOCH: Then Sir Robert Robinson picked up this Channon paper, and he reluctantly formulated a folding mechanism of the hydrocarbon chain into cholesterol. This I mentioned earlier. He was rather diffident about his paper in the *Journal of the Society of Chemical Industry* in 1934 (p. 24). In it he says, "I am not very enthusiastic about this idea of mine. The findings of Channon support this conversion, but I don't think that the biochemical tail should wag the chemical dog." [laughter]

I've quoted this paper any number of times. I talked to him later about it in a long discussion, and he finally was convinced, accepting the squalene-sterol conversion. He wanted to make sure that there was no harm stating it, but he didn't really believe it. [laughter]

BOHNING: Part of that led you to go to Bermuda and work with sharks for a summer?

BLOCH: Yes. I knew that all members of the genus squalidae contain this hydrocarbon squalene as a major liver constituent, and dogfish as much as the larger sharks. I said, "Well, you can go to Cape Cod any time, but it would be more fun to go to Bermuda." I was still in Chicago at the time. I wrote to the director of the Bermuda Biological Station and asked him, "Is it a relatively major or a minor effort, to catch some dogfish in the waters around Bermuda?" He said, "No problem. Please come, and we will try to have the equipment ready for you."

When I arrived, it turned out that the station had a single dogfish in the aquarium. [laughter] They weren't interested in catching any others. Obviously, I couldn't get the one from the aquarium. But that was after I had arrived in Bermuda, and it was very difficult to get a small shark. To catch a big shark is no problem. [laughter] But a small shark, weighing less than two hundred pounds, was difficult. The idea was to inject a small shark with labelled acetate, and then look at the squalene in the animal's liver.

Liver slices were to be made with a razor blade, which was a common technique at the time. Shark liver proved totally unsuited for this purpose, because it had the consistency of blubber. Slicing it with a razor blade yielded a semi-solid mass with the consistency of porridge, which was difficult to handle. By that time, we were nearing the end of our stay in Bermuda. We finally found a small shark and injected labelled acetate into the animal. We then "sacrificed it" a few hours later, but we couldn't find any radioactivity in the shark's liver.

In any event, the problem was solved by my graduate student, Robert Langdon, who did the experiment in Chicago using the so-called carrier technique. He fed both unlabeled squalene and radioactive acetate to rats, and recovered liver squalene which was labelled, thus convincingly showing the conversion (25). But, we had a good time shark fishing in Bermuda. [laughter]

BOHNING: That was around the same time that you gave this talk here at Harvard.

BLOCH: We had been showing the isotope content of squalene and the distribution of the two carbon atoms in squalene and sterol all fitted in very nicely. At this colloquium in 1952, I was told by [Robert B.] Woodward that the Swiss chemists at the ETH had shown that in lanosterol, a C_{30} sterol, the attachment of the aliphatic side chain is the same as in cholesterol, at C_{17}. This structural detail had earlier been a matter of controversy between British and Swiss organic chemists.

But the day that I gave the colloquium, the latest issue of *Helvetica Chimica Acta* contained a paper with the correct structure for lanosterol, which was really a trimethyl derivative of cholesterol (26).

BOHNING: Was that [Leopold] Ruzicka?

BLOCH: He was the senior author and Voser, Mijoric, Heusser and [Oskar] Jeger the collaborators. Clearly, it was the Ruzicka school. That information was crucial for formulating the cyclization mechanism, which was proposed and rationalized by Woodward and myself in an evening session after my seminar, I think around midnight. [laughter]

BOHNING: Was that your first interaction with him?

BLOCH: No, I had met with him before in Chicago. He had given a talk at the local ACS section, and I think we had met at Gordon Conferences. Our joint paper is the only biochemical publication with Woodward as an author (27).

BOHNING: Really?

BLOCH: Yes, and also his only collaboration with a biochemist. It was the mechanistic problem which challenged him. We had some discussion on the matter of first and second authors for the JACS publication: was the order of authors agreed upon in this instance a reflection of then current practices, that senior chemists listed themselves first while senior biochemists listed themselves last?

BOHNING: What was your reaction, in terms of his coming to you and sitting down with him at midnight and working out this scheme?

BLOCH: It was fascinating. Woodward was a night owl. He was known to work fourteen to sixteen hours a day. [laughter] One of the visitors at the time was the professor of organic chemistry at Cambridge, Sir Ewart Jones. We called him Tim. He was a student of Heilbron's. He was a visiting professor for a term. He and Woodward and I sat down together. He had been steeped in lanosterol research, which was Heilbron's major enterprise.

I went back to Chicago and did the necessary experimental documentation. I had the labelled material around, and the hypothesis predicated which carbon atoms had to be labeled, and which should not be labeled, to conform with our hypothesis.

We had no doubts that our hypothesis was correct, but I thought that additional evidence would be helpful. When I arrived in Zürich—it was my first sabbatical—and talked to Ruzicka, he asked me what did I want to do? I said, "I would like to find out the origin of carbon atom seven in the sterol structure, because its origin should be different, depending on whether the hypothesis is correct or false." Ruzicka said, "We have a desk for you, and now we have to find a student to do the work." I said, "I want to do the work myself. That's what I came here for!" He replied, "I think you are very naive. How long ago did you get your Ph.D?" I think I said it was about nineteen years ago. Ruzicka said, "Now don't fool yourself. You don't know any more how to do even the simplest operation! You have to rely on students. You are no longer an experimentalist." I said, "Well, I'll try."

Well, I tried. I was given a bench among the graduate students. First I had to distill all the solvents; there wasn't a single commercial solvent pure enough to be used as such. Next, one had to stand in line and queue up in front of the stockroom. [laughter] The stockroom was open only two hours in the morning and two hours in the afternoon, and there was usually a long line. It took me six weeks before I could get the needed equipment to get started.

I had a good time, and this problem worked out very well, and the predictions proved to be correct (28). Then I went to Prelog, who was to succeed Ruzicka as the Head of the Department. He had a good sense of humor. He looked at me and when I told him my positive result, as predicted, he said, "How dull." [laughter]. Only the results that are not predicted are interesting, because they pose a new problem." [laughter] There is some truth to that.

BOHNING: You mentioned earlier that the Nobel came as complete surprise to you.

BLOCH: Yes.

BOHNING: What about the sharing of it with Lynen?

BLOCH: No problem.

BOHNING: What kind of immediate reaction did you have to that announcement?

BLOCH: To the announcement? Disbelief, and great fun. It was eight o'clock in the morning, and I had a class at ten o'clock. Some friends called me, who had listened to an earlier radio report. I didn't really believe it, until eleven o'clock when the Swedish Ambassador to the U.S. said, "Dear Mr. Bloch, let me be the first to congratulate you."

I'd known for three hours. [laughter] Nowadays the Nobel Committee has much tighter control of the news, to make sure that they themselves are the first ones to announce it.

After breakfast, I went into Cambridge and gave my lecture, but I changed the subject. I talked entirely about the biosynthesis of cholesterol, not what was scheduled for this day, and I think I probably had the best ever attendance in my class. [laughter]

Going to Stockholm was a great experience. My children and my wife had a marvelous time.

BOHNING: What was the longer impact of receiving the Nobel?

BLOCH: There is no question that there are certain fallouts. You are, for example, invited to join whatever—a committee, or visiting committee, or things of that kind—there is a difference. Also you get a number of attractive offers from other institutions, all of which I turned down. Long before this event, I had an offer in Zürich, while I was still on the staff in Chicago. Ruzicka asked me to become the first professor of biochemistry at the ETH and start an institute, a proposition which was very attractive. Zürich is a lovely place in every respect.

I thought a great deal about the invitation. It spoiled my whole sabbatical, because on the day I arrived, Ruzicka asked me that question—would I come? Every day he asked me, "Have you made up your mind?" It was very difficult.

Finally, before I definitely decided to say no, I thought about my children as much as about myself. I think ultimately the major factor was that I wanted my children to grow up in the United States.

BOHNING: How old were they?

BLOCH: My daughter was five, and my son was eight. From the beginning, I was very well treated in the U.S. What appealed to me, especially, was the open academic system in the United States. Beginning with Anderson, who answered the letters of an unknown undergraduate, helped me to immigrate, and then telling me that I should go elsewhere, because he didn't have anything to teach me—all this impressed me greatly.

In Europe, at the time, this attitude, the democratic style of academic life, was unknown. Even now, it has been very slow in coming into some countries in Europe. The professor is still a very powerful person, and very often he is the only one of that rank in the department. The rest of the staff members are dependent on him. The open structure of American universities in contrast to European universities, at the time, was one of the major factors for my decision not to leave the USA.

BOHNING: You said you came to Harvard with appointments in both chemistry and biochemistry. Then you were chair of the chemistry department for three years. How did that come about?

BLOCH: That was and is nothing out of the ordinary in the Faculty of the Arts and Sciences. James Conant, the President of Harvard University until the end of the war, introduced the system of rotating chairmanships, a term appointment of three years. Senior faculty members serve as chair for a three-year period, and the only criterion is seniority. Earlier, the professor was chairman for life.

The chemistry department, of which Conant was a member for thirty years before he became president, had gone downhill. The permanent chairman made the new appointments, promotions, and so on. The system was very structured and hierarchical as in Europe.

I was chairman because it was my turn. The only reason why I was also chairman of biochemistry later on was that the dean couldn't find someone who was willing to serve. The person in line was unwilling, or he had some good reasons, to be chairman. [Henry] Rusovsky, the dean at the time, asked if I, by any chance, would be willing to serve as chairman of the biochemistry department. I did it, but I said not for the entire term; I did it for two years and was rewarded by the Dean by extension of a sabbatical period.

Because I was willing to serve, not because it was a special honor. You know the chairperson of your own department, but not the chairperson of physics or of the several departments of biology. You're not interested, because he or she has no real power. Important decisions such as promotions are done by committee. The chairman is the faculty representative who reports to the dean. And that's it. Everyone here is very happy with this system. And if you were not, you would move elsewhere. But this never happened in the Harvard Chemistry Department, certainly not during the last fifty years.

BOHNING: You also had an appointment in the School of Public Health.

BLOCH: This was shortly before I retired. The School of Public Health had some problems at the time—inability to attract staff in some of the biological sciences, especially nutrition, and graduate students. I was appointed chairman of search committees for new faculty, and drives for funding student stipends, and so on. It wasn't a very exciting or successful experience, because my responsibilities were administrative.

One of the problems was that at Harvard, the School of Public Health and the Medical School are contiguous. Graduate students in the Life Sciences—not the medical students—have a choice to go either to a Medical School department or a similar one in the School of Public Health. Most of them choose the Medical School, because it has more prestige. In recent years, the School of Public Health has stressed the social sciences, more and more, which are distinct from the ones in the Medical School, primarily health care and things like that.

At that time I no longer taught the Biochemistry course in Cambridge. I had some extra time and spent a day or so a week in the School of Public Health. There I learned a great deal about nutrition, the major benefit I derived from this association.

BOHNING: You recently had a paper on that (29).

BLOCH: Yes. It's in a nutrition journal or something like that.

BOHNING: It had an unusual title, "Concepts and Approaches to Scientific Inquiry."

BLOCH: Right.

BOHNING: But it's in a nutrition journal.

BLOCH: Yes. I think there are aspects of nutrition which need to be changed.

[END OF TAPE, SIDE 7]

BLOCH: Nutrition had its heyday. The essential dietary constituents had been identified, the essentially amino acids, fatty acids, vitamins, and so on. That was bona fide science, and it was done mostly by nutritionists early in this century. Today the major concerns are not what to eat, or what is essential, but how much. Nearly all the debates are about how much or how little, and that varies from individual to individual.

In an earlier interview, I quoted some rather typical nutritional experiments. For example, you take three human cohorts, individuals receiving 2,000 calories daily. All 300 participants were young adults, matched according to physical parameters as closely as possible. It was a very well-designed experiment, controlled for dietary intake as well as physical activity. Possible variables were eliminated. At the end of six months, on a regime of 2,000 calories, one-third of the sample had gained weight, in one-third of the individuals, weight had not changed, and one-third had lost weight. How do you evaluate such results?

All of the efforts of matching humans are clearly inadequate. At best, you could do such experiments with identical twins. That is the problem which nutrition faces. What is good for one of us may not be adequate for the next person. I know of one very famous biostatistician who states that every study in epidemiology, which means human biostatistics, is flawed. There is always one parameter no one thought about which is not entered into the equation. So that's the trouble with nutrition. Nutrition tries to give us guidelines, so-called RDAs, recommended daily allowances which apply to everyone, because you can't have separate guidelines for every individual. There's an enormous waste of time and money in doing such studies.

BOHNING: Is that paper "Folklore and Food Selection" along the same line (30)?

BLOCH: Yes. It is one of the topics in a little book, edited by the physicist [Nicholas] Kurti at Oxford University, who was interested in food. It is called *The Crackling is Superb*, and published by Adam Hilger. The only copy I have is at home. It really is not worth having.

BOHNING: You also became interested in the evolution of organisms. How did that develop?

BLOCH: I've been interested in the role of oxygen in metabolism, and the very fundamental changes which occurred when oxygen appeared in the atmosphere. Then I saw a graph, which plots the frequency and diversity of cells or organisms, as a function of time, since life began, what is known as the pre-Cambrian explosion. In other words, at a certain point of time, about two billion years ago, [drawing graph; see following page] the frequency and diversity of organisms began to change dramatically, probably in an exponential manner.

Why? I have speculated that this increase parallels an equally exponential rise in the concentration of atmospheric oxygen until it reached the current level of 21 percent. None of this has been proven, but it appears to me that biological diversity of cells was driven by the level of oxygen availability. A few experimental data are consistent with the hypothesis.

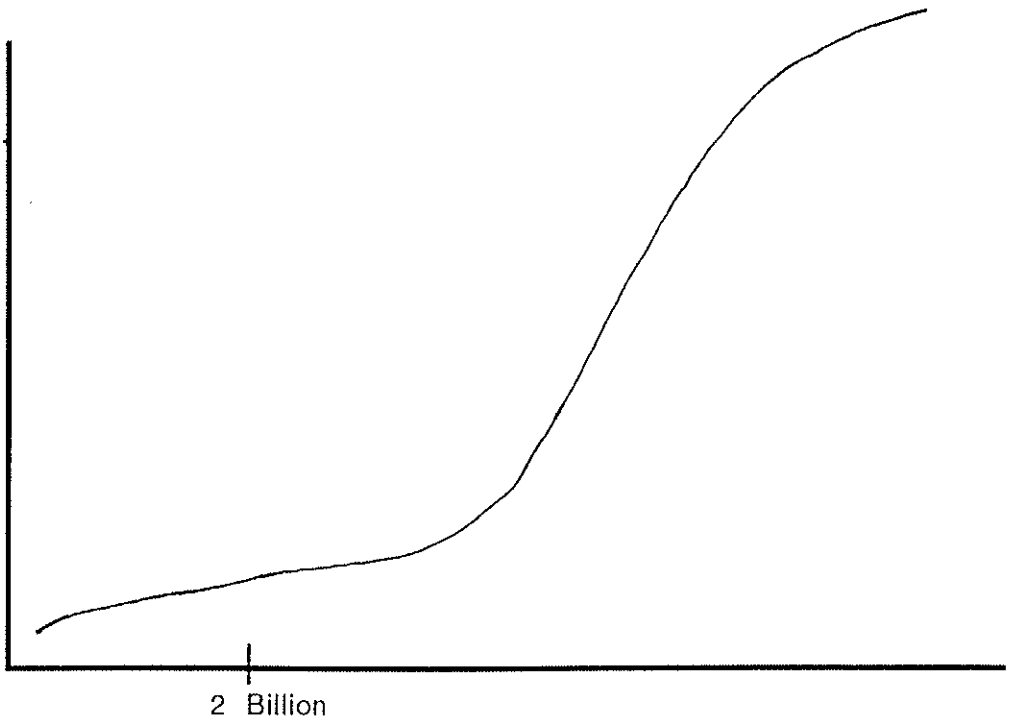
Both we and others have found that in the sterol pathway, starting from the hydrocarbon squalene, a minimum of four oxygenase reactions participate. In the sequence in which they proceed throughout time, reaction I will occur at exceedingly low oxygen concentration about 0.01 percent; reaction II, somewhat higher; reaction III, even higher; and, the final oxygenase reaction in the cholesterol pathway requires 1 percent O_2, the highest one. In other words the completion of the biosynthesis of the molecule is presumably dependent on the prevailing level of atmospheric oxygen.

One can well imagine that there is an exponential increase in the concentration of atmospheric oxygen. Oxygen production by photosynthetic cleavage of H_2O started in an ecological niche invented by the blue-green algae or cyanobacteria. Oxygen diffusion, depending on the rate of multiplication of the organism, could well have been exponential.

Yet, we know nothing about the time course from the very early period, when the atmosphere was anaerobic until it reached the present 21 percent.

Except for the sterol pathway I mentioned, there are no published data on pO_2 values for the hundreds of oxygen-dependent reactions catalyzed by the so-called P_{450} enzymes. If I still had a lab, I might pursue these problems. What would be interesting are the results, not the experiments themselves. In a sense it would be an effort complementing the Human Genome Project, yielding perhaps an independent approach to phylogeny.

BOHNING: Are there any particular graduate students who stand out?


2 Billion

BLOCH: I will mention a few of my associates, undergraduate and graduate students, and also postdoctorals. William Lennarz was trained at Illinois in organic chemistry by Harold R. Snyder and came here to learn biochemistry. He participated in the research which led to enzyme suicide inhibition. After he left he had a very successful career, first at Hopkins, and now he is chairman of Stony Brook's biochemistry department.

He recently discovered a new protein which is necessary for sperm and egg to interact. It had long been known that a protein called acrosine causes the sperm to penetrate the membrane of the egg during fertilization. He has now found an even earlier stage for sperm-egg interaction that might be a useful tool for population control. He is working with sea urchin eggs, the classical system for developmental studies. He is one of the most successful ones, having turned from classical biochemistry to developmental biology.

Bernard Babior, trained as an M.D., came to my lab to work for the Ph.D. He is now a professor at the Scripps Clinic in La Jolla. In his independent work, he clarified the mechanism of B_{12} catalysis, notably the demonstration of free radical intermediates, by homolytic cleavage. He then turned his attention to macrophages, the phenomenon of phagocytosis. He is well known as an expert in the field.

Robert Rando is also an organic chemist who turned into a biochemist here. He is now Professor at the Department of Biochemistry and Pharmacology in the Harvard Medical School. He has made major contributions to the chemistry of the visual process. There are many others who became very successful in their research careers. There are now about twenty-four full professors among my former graduate students and postdocs. It has been very satisfying to me, that the majority of my former associates have chosen in their careers research unrelated to the work they did in my laboratory.

BOHNING: You commented, in "Summing Up," that the first group in Chicago was apparently not like the Schoenheimer group, where you worked as a team, but that they wanted to work on their own ideas.

BLOCH: First of all, these students were three or four years older than those who came later. Having served in the Armed Forces, they were all on the GI Bill. More mature, they had given much thought to their careers while they were in the Army. Younger graduate students tend to be less mature.

It has been a policy of mine to assign to every student a self-contained problem, not dependent on a fellow student or postdoc. I was fortunate enough that this system worked. Also, the student benefits, because the published Ph.D. thesis will have no co-author except the supervisor. Actually, I had three students who published their dissertation alone, without my name.

I still have very close contact with my students. They organized a marvelous meeting a few years ago. It was not the occasion for a special birthday. About one hundred of my former associates came to Banff in the Canadian Rockies. This was great. I also gave a paper at this symposium (31).

I'm not sure whether that is mentioned in "Summing Up." Did I discuss in there my interest in blondes in Venetian Renaissance paintings?

BOHNING: No.

BLOCH: My family was fortunate to have acquired an old farmhouse in Northern Italy, not far from Venice. We didn't look for a summer place thousands of miles from Boston; it just happened. We love to go there, and you can't help but become fascinated Venetian Renaissance paintings of the fifteenth and sixteenth century.

I was struck by the fact that many women painted notably by Titian, Tintoretto and Veronese, obviously from the upper classes, had light blonde hair. If you meet a blonde in northern Italy, she is most likely a tourist from Scandinavia or Germany, or a peroxide blonde. I found dozens of Renaissance paintings, showing blonde women and often Venuses from Greek mythology.

It struck me that in the same paintings, the hair of the males is invariably very dark, in fact black. Another hint in the Venetian blondes, blonde hair does not go together with blue or grey eyes. When visible, their eyes are dark brown or black, and not blue.

I put all these clues together, and concluded that the ladies in question must have known about bleaching hair centuries before hydrogen peroxide was discovered in 1812. With the help of a an art historian friend, I came upon French and Italian literature, including a tome which listed in an appendix thirty-five recipes for bleaching hair, dating from the sixteenth century. The recipes, given in great detail, all are based on plant extracts, mostly from conifers, myrtle, herbs, and sometimes mixed with inorganic salts such as alum and potassium carbonate.

The procedure is to place the aqueous plant extracts into shallow trays and expose them to the sun for a couple of weeks. The Mediterranean sun is very bright and strong. The effects could be concentration or oxidation, in any event, production of an oxidizing agent.

Historically, this concoction is called aqua bionda, and you find relevant references to it in the fifteenth and sixteenth century literature. Apparently, this trick was practiced in Florence as well as in Venice. There are no chemical clues beyond what I just mentioned. But it seems to me that terpenes, widely occurring in higher plants, are candidate precursors or sources of H_2O_2, perhaps by way of endoperoxides.

Ascaridole, a terpene product which has an endoperoxide bridge, comes to mind. Under certain conditions, endoperoxides give rise to hydrogen peroxide. Thus, I ventured to postulate a mechanism for such plant extracts to be potent bleaching agents. This thought came at a time when I had closed my lab and, besides, I thought the effort wouldn't be all that interesting. But I've had a good time. My hypothesis has been published in an Italian art journal (31). [laughter] This article, in English translation, is about to be published as one of the chapters in "Essays on Biochemistry" (Yale University Press, 1994).

None of the many art historians I consulted was aware of aqua bionda. They had not even been struck by the fact that there are numerous blondes in the Venetian Renaissance

paintings. But art historians view art differently. Besides, only chemists know that hydrogen peroxide was not discovered, unknown until 1812.

BOHNING: That's amazing.

[END OF TAPE, SIDE 8]

BOHNING: You raised an interesting point, because it's the old saying of being so close, you can't see the forest for the trees.

BLOCH: The Renaissance literature revives the ideal of beauty dating to ancient Greece. Homer described many of the Greek goddesses as being blonde and blue-eyed.

Some of the technical information on hair bleaching I owe to the Clairol Company, a subsidiary of Bristol-Myers. I wrote to the company's research director, Dr. L. J. Wolfrans. He described to me Clairol's research on melanin formation, the chemistry underlying the bleaching of hair by peroxide.

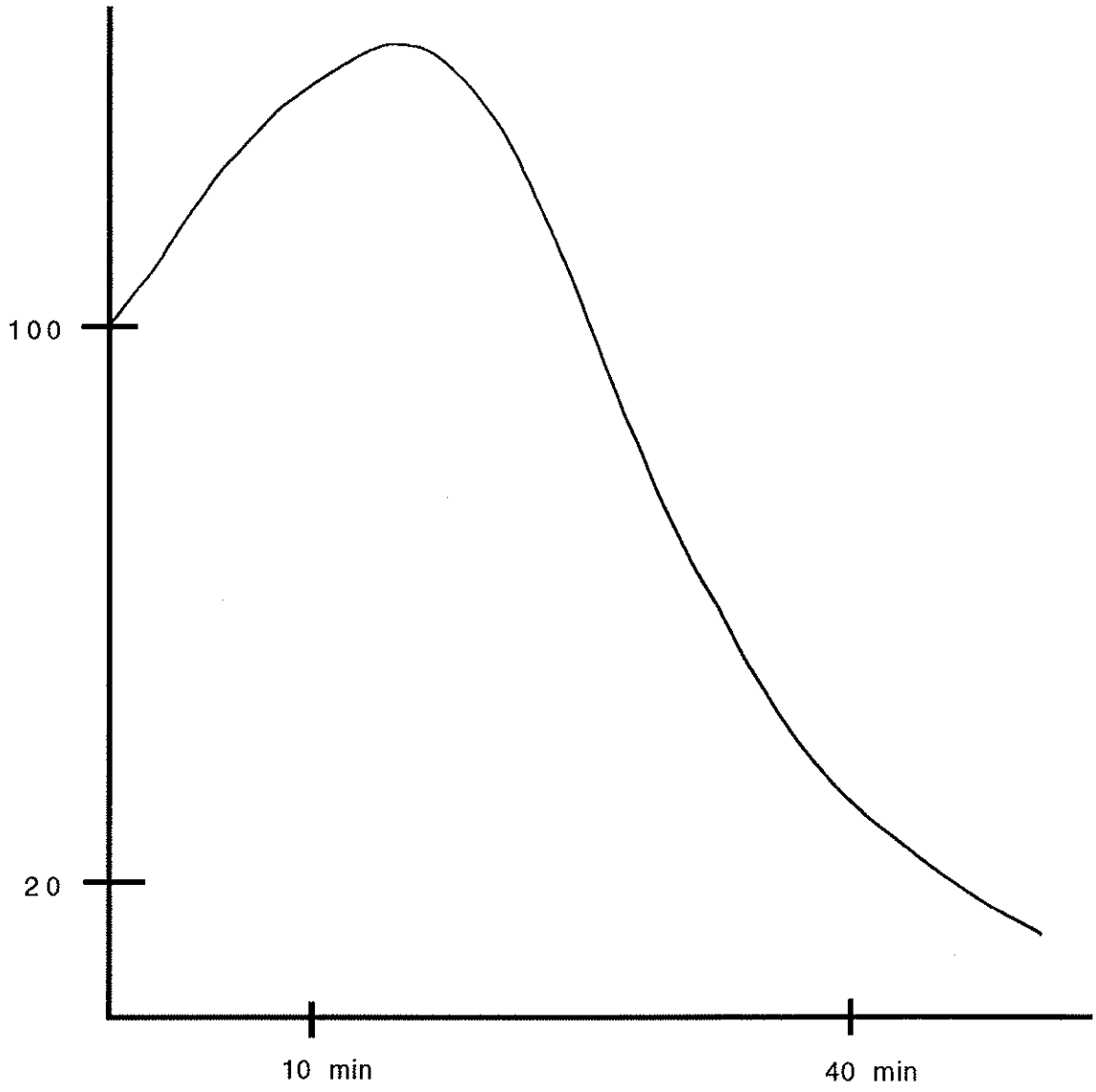
I have been very pleased by the willingness of experts in both academia and industry to share information, but I ran into some difficulties in two cases. I have been interested, and I've written an essay, on the importance of being contaminated, one of the chapters in "Essays on Biochemistry" I just mentioned. In earlier days, commercial biochemicals often contained impurities. They were pure only by the standards then available. Let me give you an example of what I call the importance of being contaminated.

The standard test for insulin is or was to administer to a rabbit a load of glucose along with insulin, and then measure the blood glucose level, forty minutes later. The normal blood glucose level in mammals is 100 milligram percent. It will decline to 20 milligram percent three-quarters of an hour after insulin injection. [See diagram, following page]. That was probably the standard assay for insulin.

But someone, maybe by mistake, determined the blood sugar much sooner, ten minutes after the insulin injection. Lo and behold, the blood sugar had gone up, rather than down. What you observe is first hyperglycemia, followed by hypoglycemia [referring to diagram]. Well! It seemed unlikely that insulin has both these properties intrinsically.

It took about thirty years to find out that early insulin preparations were contaminated with another hormone from the alpha-cells of the pancreas, now known as glucagon. The two hormones are not easily separated, although they are rather different molecules. Only relatively recently, insulin became a pure compound. It does not show an antagonistic behavior, but an immediate hypoglycemia, as it should. Only the contaminating glucagon causes hyperglycemia.

In more recent years, insulin samples from various companies contain none or very little glucagon. It's not a serious problem, because the amounts are too small to seriously affect the


100
20
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hypoglycemic effect of insulin. I don't want to mention names, but some of the companies that are involved in insulin production have been very reluctant to disclose when and how they got pure instead of contaminated insulin. Apparently there are patents; but although the patents must be thirty or forty years of old, some companies don't share such information. I found this on two occasions. Clearly, competitive advantage is no longer an issue. It may be a question of professional pride.

BOHNING: Might there also be some legalistic aspects to it as well?

BLOCH: Maybe early on, but probably no longer.

BOHNING: It's all public domain. After that time period, it would be.

BLOCH: That's right. If you look at situations like this, you depend on the major players. In industry they are not easy to identify, unless you know them personally.

BOHNING: Earlier you commented about the difference between biochemistry and molecular biology. You've really seen it all happen in your career. You've seen biochemistry appear and then molecular biology appear. Do you have any general comments about your view of that developing period?

BLOCH: Molecular biology is becoming more and more a novel and unique methodology for studying biological events. There are now at least two members of this Chemistry department, professors of chemistry who were trained in organic chemistry. They are using all the modern methodologies of molecular biology, including cloning genes and determining sequences and so on. But their skills involve sophisticated organic chemistry, synthetic as well as mechanistic. I would characterize their research as chemical biology.

The category of bioorganic chemistry describes only part of these new developments. Some classical organic chemists became interested in enzyme mechanisms. They worked primarily with enzymes which were commercially available—trypsin, chymotrypsin, pepsin, and so on. You will find that all the early work on enzymes is done with these extracellular enzymes which you can buy, because they are commercially used in the dairy industry, for example.

But the intracellular enzymes are of much more interest from the regulatory point of view, and they are more difficult to get, particularly in adequate quantities. This is where molecular biology comes in. It allows you to obtain and produce essentially unlimited amounts of enzyme, certainly at the gram level. One enzyme we looked at in detail in the 1960s, it took us a year-and-a-half to get maybe one hundred and fifty milligrams by traditional methods. Now you can do this in less than a week, especially with microbial systems and genetic techniques.

Necessarily, all of this new breed of chemists will become more and more interested in truly biological problems. For example, what is very much in evidence today is the interest in regulation of the cell cycle—the various phases in cellular development, until recently a classical problem, tackled only by biologists. Here nucleic acids and proteins and their interactions are the major players.

Site-specific mutagenesis is one of the most popular techniques today in bioorganic chemistry, allowing deductions on the evolution of organisms. Classical phylogeny is in very poor shape so far, on certain levels. You need protein sequences, replacements and homologies in order to study evolution. The trend I describe seems irresistible; science will benefit.

BOHNING: What is your opinion about the Human Genome Project?

BLOCH: My opinion is very much influenced by what should be priorities in science. If you talk about meritorious problems you must pay attention to prevailing conditions—culturally and economically. I'm not well enough informed to say anything about the time scale for completion of the Human Genome Project. Many of the genes are being identified, independently of the Human Genome Project. The genes for diseases such as Lou Gehrig's and Huntington disease, and others, are already being identified, independently of the Project.

Ultimately, when the Human Genome Project has been completed, will we have solved such problems as the evolution of the brain? I would like the Genome Project to reveal the mystery between the human brain and that of the highest animal—a non-human primate brain. Can thoughtful reasoning be expressed in terms of genetic sequences? That would be my primary interest. Intellectually, there may be other practical differences.

I'm much more concerned about the future prospects for young scientists. In many of the study sections at the NIH, roughly twenty percent of the applications are being funded, compared to sixty percent a few years ago. I think the young investigators are always the first ones to be more seriously affected by economic restraints. A more mature or a more senior investigator has a much greater chance of being supported, not only from federal agencies, but also from Howard Hughes or other foundations and the private sector. Pharmaceutical companies tend to go to the scientific elite and say, "Will you do this or that, with company support and with the following understanding on patents, et cetera."

A number of efforts have been made to improve the lot of the junior investigator, but with limited success. I made a suggestion to the NIH director—I forget who it was—a number of years ago, when this first became a problem. I suggested a cap on the amount of grant money given to an individual investigator from federal sources; let's say half a million. Anything above and beyond this amount, a really well established investigator can get from sources such as the ones I just mentioned. The young investigator has no such access, because he is not yet sufficiently known.

I must say, I was very lucky. I've been supported generously from beginning to end. I always had some money left over, I never overspent. [laughter] I didn't have very large groups. On the average, I had ten to twelve people. At one time, the group reached fifteen or sixteen, but that was only temporary.

I'm somewhat disturbed by the fact that the number of authors of a given paper is growing, partly because you need so many approaches and tools for an interdisciplinary problem, and therefore you need so many specialists on your team. That is dangerous, because one member of the team who is a specialist in a certain field won't fully appreciate or understand the contributions of his co-investigator, or will not be familiar with the field.

This is one reason why it is sometimes difficult to detect flaws or frauds in a paper. Let's say, the senior author submits a paper. He gets the approval, of course, of all his co-workers for the portion of a paper that he or she writes. If there are fifteen authors, not all of them fully understand what their co-workers are doing. So the opportunities for mischief are very great in multi-authored publications.

BOHNING: Doesn't NIH have now have its own fraud investigation group?

BLOCH: That's right, yes.

BOHNING: I guess that's an outgrowth of the Baltimore case.

BLOCH: Yes, I think so. It's still not clear to what extent the federal agents have been stonewalling on the [Robert] Gallo controversy. This is now all taken out of the hands of the NIH, this part of the Health and Human Services Department. I don't know the individuals, only some of the members of the advisory committees.

BOHNING: Is there anything else that I haven't covered that you want to add to this, at this point?

BLOCH: I think you get this response quite often, that if people are asked if they had the choice of doing their career over again, would they do it, or would they change to a different field? I must say, I have no regrets about the field I fell into. I have enjoyed it from beginning to end. I've been lucky, exceedingly lucky.

There is some nostalgia about things past, and at this stage of one's career, one spends a great deal of time at the desk. In the absence of a lab, interaction with your junior colleagues and students is limited. That is the only thing I miss. I still occasionally go to one of the undergraduate houses to have dinner at a science table. But that is not a substitute for having constant exchanges of ideas with your younger colleagues and co-workers. Well, I'm not complaining.

[END OF TAPE, SIDE 9]

BLOCH: There is a company in Luxembourg which made this video tape program to be shown in Europe, primarily in Germany. The only reason I'm giving it to you is that I do comment in somewhat greater detail on education and some of the more secondary subjects. You're welcome to borrow it, but it's is the only copy I have.

BOHNING: I will make sure it comes back to you in due course. Would you object if we made a copy?

BLOCH: I will not object. The question is the use of the copy. I can give you the address, which I don't have here, of the person who sent me this. By the way, the questioning is in German, and I respond in English. They did a simultaneous translation so they could show it in both English-speaking and German-speaking countries.

BOHNING: We would like an archive copy, and we're very careful about access to and use of the archive materials.

BLOCH: Do you have facilities for people to go to the archives, where they could play this?

BOHNING: We do not have video facilities at the present time, although they are available from the university. That's still something in the planning stages.

BLOCH: I see. What physical facilities does the Beckman Center have?

BOHNING: We're very limited in space right now. You may have heard about our possible move to a new site next year, which is the old Divinity School site at the university, which is a just a magnificent site.

BLOCH: Which university?

BOHNING: University of Pennsylvania.

BLOCH: I see.

BOHNING: Just off the campus, there's the old Divinity School site. There's a chapel which is on the National Historic Landmark registry, and an office building. We're looking at some potential contributions which would allow us to develop that into our own facility. Donald Othmer at Brooklyn Poly has given us a challenge in a substantial amount, so we're looking towards meeting that, to the extent that we would be able to move out of very cramped quarters.

One of our greatest assets is the collection in the library, and we want that to be available, just as the oral histories are available to people to use. It's a problem of space. We have most of it in remote storage some place right now, except for the very rare items. But a lot of things are just off in a warehouse, until such time as we can move.

BLOCH: How long has this program been in existence now?

BOHNING: The Beckman Center started just as the Center for History of Chemistry ten years ago.

BLOCH: I see, yes.

BOHNING: We've been doing oral histories off and on since 1985. I've been talking to Joshua Lederberg at Rockefeller recently (32). One of the people I would like to talk to is Chargaff.

Lederberg tells me he's still alive. But I've heard all kinds of different stories, and I am not sure whether going to see him would be profitable or not.

BLOCH: Profitable, in what respect? Have you read some of his publications?

BOHNING: Just a few.

BLOCH: He is one of the very disappointed men. He has received many honors, but not the biggest one. Watson and Crick got the correct base pairing by model building. Chargaff's analytical data, A equals C and G equals T, provided powerful support for Watson and Crick, but by themselves these base ratios would not tell you how the bases are interacting. Chargaff is a brilliant but difficult person—difficult in the sense that he likes controversies. The two traits often go together.

At an early stage in his career in Vienna, he had a hard time making up his mind whether to become a writer, a novelist, or a scientist. He writes very well. Also, he produced some very good students, but he could not come to terms with the vagaries of scientific progress. He hurt himself, but not anyone else.

Among my contemporaries at Columbia, there were many who became prominent scientists. DeWitt Stetten, Jr., later an outstanding member of the NIH. David Shemin went to Northwestern. David Rittenberg, Henry Walsh are no longer around. There were many foreigners who came as postdoctoral fellows.

BOHNING: Bill [William von Eggers] Doering was there when you were there.

BLOCH: But he was downtown at 116th Street, the main Columbia campus. At 168th Street was P&S, the College of Physicians and Surgeons. The only time I went to 116th Street was to be examined for the Ph.D. degree.

Finally, a few words about Hans Thatcher Clarke, the chairman of the department and my research supervisor. He created an outstanding department, probably the best at the time. He had no background in biochemistry. Previously he had been the director of the organic chemistry section of Eastman-Kodak. How he came to be chairman of biochemistry at a medical school is an interesting story.

A close friend of his was [Henry Drysdale] Dakin, a bioorganic chemist, who was responsible for making certain biochemical reagents. Dakin became famous as the inventor of chloramine-T, widely used as a sterilizing agent. He was a very influential advisor to Columbia University. He identified Clarke as a suitable chairman for the biochemistry department at the medical school. So that's the background. The Dakin-Clarke connection was certainly a major factor for chemistry-oriented biochemistry in the Columbia Medical School.

BOHNING: If there's nothing else at this point, I'd like to thank you very much for taking this time to talk to me today. I have enjoyed it.

BLOCH: Thank you. It's been a pleasure.

[END OF TAPE, SIDE 10]

NOTES

1. Gustav Tammann, *Lehrbuch der Metallographie: Chemie und Physik der Metalle und ihrer Legierungen*, 3rd. ed. (Leipzig: Voss, 1923).

2. Konrad Bloch, "Summing Up," *Annual Review of Biochemistry*, 56 (1987): 1-19.

3. K. Bloch, "Über phosphorhaltige Lipoide aus humanen Tuberkelbazillen," *Biochemische Zeitschrift*, 285 (1936): 372-385;

   F. Roulet and K. Bloch, "Beitrage zur Spezifitaet der Entzuendung mit besonderer Beruecksichtigung des tuberkuloesen Granuloms," *Virchow's Archiv*, 298 (1936): 311-326;

   K. Bloch, "Über eine Phosphatidsaure aus Humanen Tuberkelbazillen," *Zeitschrift für Physiologische Chemie*, 244 (1936): 1-13.

4. Thomas Mann, *The Magic Mountain*, translated by H. T. Lowe-Porter (New York: The Modern Library: 1932).

5. K. Bloch, "Some Speculations on the Structure and Function of the Sterol Molecule," in R. W. Straub and L. Bolis, eds., *Cell Membrane Receptors for Drugs and Hormones* (New York: Raven Press, 1978), 1-7.

6. Fritz Kögl, "The Chemistry of Auxin and Its Occurrence in Vegetable and Animal Matter," *Naturwissenschaften*, 21 (1933): 17-21. ["A lecture on the work of isolating crystalline auxin from urine," *Chemical Abstracts*, 27 (1933): 2167.]

7. Fritz Kögl and Hanni Erxleben, "Chemistry of Tumors. I. Etiology of Malignant Tumors," *Zeitschrift für Physiologische Chemie*, 261 (1939): 57-95;

   F. Kögl, H. Erxleben, and A. M. Akkerman, "II. Isolation of Glutamic Acid from Tumor Proteins," Ibid., 261 (1939): 141-153; Kögl and Erxleben, "III. Sterochemistry of Myoma and Other Tumors," *Zeitschrift für Physiologische Chemie*, 261 (1939): 154-171.

8. Eugen Hecht, "The Sterol Content of Bacteria, Especially of the Tubercle Bacillus, and the Detection of Cholesterol," *Zeitschrift für Physiologische Chemie*, 231 (1935): 29-38.

9. R. J. Anderson and Erwin Chargaff, "The Chemistry of the Lipoids of Tubercle Bacilli. V. Analysis of the Acetone-Soluble Fat," *The Journal of Biological Chemistry*, 85 (1929): 77-88.

10. Konrad Bloch and Rudolf Schoenheimer, "Studies in Protein Metabolism. XI. The Metabolic Relation of Creatine and Creatinine Studied with Isotopic Nitrogen," *The Journal of Biological Chemistry*, 131 (1939), 111-119.

11. Konrad Bloch and Rudolf Schoenheimer, "The Biological Precursors of Creatine," *The Journal of Biological Chemistry*, 138 (1941): 167-194.

12. "Deuterio cholesterol containing 4.18 atom per cent excess deuterium was administered to a woman in the 8th month of pregnancy." Konrad Bloch, "The Biological Conversion of Cholesterol to Pregnanediol," *The Journal of Biological Chemistry*, 157 (1945): 661-667.

13. Meyer Bodansky, *Introduction to Physiological Chemistry*, 2nd ed. (New York: John Wiley & Sons, Inc., 1930).

14. Lubert Stryer, *Biochemistry*, 3rd ed. (New York: W. H. Freeman, 1988).

15. James D. Watson, *The Double Helix* (New York: Atheneum, 1968), 189-197.

16. R. Lewisohn, C. Leuchtenberger, R. Leuchtenberger, D. Laszlo, and K. Bloch, "Action of Yeast Extract on Transplanted and Spontaneous Malignant Tumors in Mice," *Cancer Research*, 10 (1941): 799-806.

17. Robert Sonderhoff and Heinz Thomas, "Enzymic Dehydrogenation of Trideuteroacetic Acid," *Liebeg's Annalen der Chemie*, 530 (1937): 195-213.

18. Konrad Bloch and D. Rittenberg, "On the Utilization of Acetic Acid for Cholesterol Formation," *The Journal of Biological Chemistry*, 145 (1942): 625-636.

19. François Jacob, "Evolution and Tinkering," *Science*, 196 (1977): 1161-1166.

20. A. A. Andreasen and T. J. B. Stier, "Anaerobic Nutrition of Saccharomyces cerevisiae. II. Unsaturated Fatty Acid Requirement for Growth in a Defined Medium," *Journal of Cellular and Comparative Physiology*, 43 (1954): 271-281.

21. Peter Goldman, Alfred W. Alberts, and P. Roy Vagelos, "Requirement for a Malonyl Coenzyme A-CO_2 Exchange Reaction in Long-Chain but not Short-Chain Fatty Acid Synthesis in Clostridium kluyveri," *Biochemical and Biophysical Research Communications*, 5 (1961): 280-285;

W. J. Lennarz, R. J. Light, and Konrad Bloch, "A Fatty Acid Synthetase from E. Coli," *Proceedings of the National Academy of Sciences*, 48 (1962): 840-846.

22. T. T. Tchen and Konrad Bloch, "On the Mechanism of Cyclization of Squalene," *Journal of the American Chemical Society*, 78 (1956): 1516-1517.

23. H. J. Channon, "Biological Significance of the Unsaponifiable Matter of Oils. I. Experiments with the Unsaturated Hydrocarbon Squalene (Spinacene)," *Biochemical Journal*, 20 (1926): 400-408.

24. Robert Robinson, *Journal of the Society of Chemical Industry*, 53 (1934): 1062-1063.

25. Robert G. Langdon and Konrad Bloch, "The Biosynthesis of Cholesterol," *The Journal of Biological Chemistry*, 200 (1953): 129-134.

R. G. Langdon and K. Bloch, "The Utilization of Squalene in the Biosynthesis of Cholesterol," *The Journal of Biological Chemistry*, 200 (1953): 135-144.

26. W. Voser, M. V. Mijovic, H. Heusser, O. Jeger, and L. Ruzicka, "Steroids and Sex Hormones. CLXXXVI. The Constitution of Lanostadienol (Lanosterol) and its Relationship to the Steroids," *Helvetica Chimica Acta*, 35 (1952): 2414-2430.

27. R. B. Woodward and K. Bloch, "The Cyclization of Squalene in Cholesterol Synthesis," *Journal of the American Chemical Society*, 75 (1953): 2023-2024.

28. Konrad Bloch, "The Origin of C_7 in Cholesterol," *Helvetica Chimica Acta*, 36 (1953): 1611-1614.

29. Konrad Bloch, "Concepts and Approaches to Scientific Inquiry," *American Journal of Clinical Nutrition*, 45 (1987): 1054-1059.

30. Konrad Bloch, "Folklore and Food Selection," in Nicholas and Giana Kurti, ed.s, *But the Crackling is Superb: An Anthology on Food and Drink by Fellows and Foreign Members of the Royal Society* (Bristol, England: Adam Hilgar, 1988), 64-67.

31. Konrad Bloch, "Lei Bionde mei Dipinti Venezia ni del Cinquecento," *Edios*, (Asolo: Asolo Arti, 1990): 21-25.

32. Joshua Lederberg, interview by James J. Bohning at Rockefeller University, 9 December 1992 (Philadelphia: Chemical Heritage Foundation Oral History Transcript #0107).

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