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Interview

A conversation with Frank Westheimer☆

Frank Westheimer's work has spanned physical chemistry, physical organic chemistry, and biochemistry. In biochemistry, he is primarily known for his work on enzymes involved in ethanol metabolism, acetoacetate decarboxylation, and photoaffinity labeling. He chaired the National Academy of Science's survey of Chemistry in 1964–1965 and served on the President's Science Advisory Committee from 1967 to 1970. A member of many honorary societies, Dr. Westheimer has received a number of awards, including the National Medal of Science.

BBRC: You started working in biochemistry just as the field was really growing. Did you intend to become a biochemist?

Westheimer: I drifted from physical chemistry through physical-organic chemistry to biochemistry.

I was James Bryan Conant's last graduate student. After he took me on, he became President of Harvard, and could no longer serve as my research advisor. When I got my Ph.D. at Harvard, I was awarded a National Research Council post-doctoral fellowship. The current plethora of post-doctorals didn't exist back then, and it was an honor to get one. Conant called me into the President' s office and wanted to hear what I intended to do the next year. With great pride, I told him about the post-doctoral I had won, and about the project I had submitted for which I got the fellowship. He sat back, put the tips of his fingers together the way he did, rocked back and forth, and then he said. "If you are successful with that project, it will be a footnote to a footnote in the history of chemistry."

I went to Columbia, and did the project as outlined, published it, and it was a footnote to a footnote, just as Conant had said. And because of what he had said, I made up my mind never again to do a project unless it was, at least potentially, really important.

While I was at Columbia, I somehow or other started reading the papers by Myerhof on intermediary metabolism, and became excited and charmed by them. That was my push toward biochemistry. Since I had been trained as a physical-organic chemist, I decided to work on (and solve) the mechanism of enzymic catalysis. I started some research directed toward that project as soon as I had got a job at the University of Chicago; it was a complete failure, but Conant couldn't have criticized it as being insufficiently ambitious. I had decided that, since amino acids were both acids and bases, therefore they were used for enzyme catalysis. I got that part sort of right. So I wanted to see whether there would be special catalysis by the amino acids themselves. There wasn't.

I continued at the University of Chicago, doing physical-organic chemistry, usually with an eye to biochemistry. One of my projects concerned the mechanism of the metal-ion catalyzed decarboxylation of beta-keto diacids in both chemistry and biochemistry. Rudy Steinberger and I worked out and firmly established the mechanism of the decarboxylation by some really elegant chemistry.

A great advantage of the University of Chicago (although I didn't think it was an advantage at the time) was that it had very few graduate students (actually not enough). The proper number of graduate students in any research group is one less than you absolutely need, because then every one is working on important projects. If in your research group you have one more graduate student than you absolutely need, you are searching for projects to keep the graduate students busy. In Chicago, I didn't just have one fewer coworkers than I absolutely needed; I had four fewer.

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I read in the literature some garbage about the mechanism of oxidation–reduction reactions involving the coenzyme, DPN+. The idea in this erroneous paper was that the reducing agent clamped onto the enzyme in one spot, the compound to be reduced clamped on in a distant spot, and the hydrogen atom for the reduction was transferred step by step up the amino acid chain from reducing agent to oxidant. This scheme seemed to me unlikely in the extreme; I postulated that the hydrogen atom for the reduction must be transferred directly from reductant to oxidant. Just at this critical moment, Harvey Fisher, an outstanding graduate student in biochemistry asked me for a research project. I happily put him on that one. We worked with the enzyme alcohol dehydrogenase, and invited Birgit Vennesland, a professor of biochemistry (who, incidentally, has just died) to collaborate with us. We demonstrated, through deuterium labeling, that the transfer of hydrogen took place directly from DPNH to acetaldehyde, and in the reverse reaction directly from alcohol to DPN+. I confess that I hadn't anticipated the most important part of this work: the hydrogen transfer turned out to be stereospecific. When we enzymatically synthesized monodeuteroethanol, and then reversed the reaction, the enzyme plucked off the same hydrogen atom from monodeuteroethanol that it had put onto acetaldehyde. Monodeuteroethanol, produced enzymatically, was chiral; we had produced a single enantiomer! And one could distinguish enzymatically between the enantiomers. This work got me into biochemistry with both feet.

Since I was already working on the mechanism of the decarboxylation of beta-ketoacids, I naturally embarked on the mechanism of the enzyme-catalyzed decarboxylation of acetoacetic acid.

BBRC: There have been many successful scientists that have come out of your lab. Do you have a philosophy of mentoring?

Westheimer: I don't know whether it is good mentoring or laziness, but I gave graduate students a great deal of latitude. I gave an exam in physical-organic chemistry at the beginning of my career that had a biochemical problem on it. One of the people who worked it out was Dan Koshland. He came up to me later and asked, "Are there any experiments that have been done to substantiate the mechanism that you suggested in this exam?" I said no, and he said, "Well, I am going to do it." And he did. He was probably the most successful graduate student I have ever had.

Another who was one of my best is Steve Benner, now at the University of Florida. He, too, picked his own problem, and carried it out in my laboratory. My only contribution was in approving the problem he proposed. It goes without saying that he published this work alone.

I had a number of superlative graduate students, and when I had a good graduate student, I gave him his head. One graduate student insisted on designing each experiment himself. On one occasion I saw a very pretty way of doing the next step in his project, and before I had time to bite my tongue, I had blurted it out. He did the next step, but by an entirely different method; he wasn't going to do anything that I had suggested. And I think that that's the way it should be; if graduate students are able, they ought to be allowed to do their own thing.

When I was a graduate student, and after Conant had deserted me, I continued my Ph.D. program doing organic chemistry with Elmer Peter Kohler. He gave me a project that turned out completely differently than he had expected. His mentoring of me consisted of coming around from time to time and asking me what I had done the previous week, what were these set- ups on my lab bench, and what did I plan to do in the coming week. Then he would pause, say, "Hmph!" and walk away. That was the sum total of advice I got from him; apparently he felt that I would work it out myself. I thought about it, and decided that that was good mentoring. With able graduate students, I tried to emulate Kohler.

BBRC: After your time at the University of Chicago, you moved to Harvard.

Westheimer: Chicago was a wonderful place, and it certainly was wonderful for me. There were a lot of good people there. In biochemistry, there was Gene Kennedy, Konrad Bloch, and Albert Lehninger. And after World War II, Chicago had the greatest chemistry department in America, at least in physical chemistry. Harold Urey, a fabulous scientist, was there, and Bill Libby, who invented radiocarbon dating. Joe Mayer was there in physical chemistry. He was skilled in mathematics and helped me out of a difficulty with the best work I've ever done. When I Invented molecular mechanics, I had got to the point where I thought I had to solve a huge determinant, and couldn't. This was just after World War II, before the computer age. I took my problem to Joe. He asked me to tell him about the chemistry involved, which took me about an hour. Then in half an hour, he devised a mathematical trick that avoided the determinant altogether. We published that work, the beginning of molecular mechanics, together.

Henry Taube was at Chicago in inorganic chemistry, and Herman Schlesinger, who co-invented lithium aluminum hydride and sodium borohydride.

But the neighborhood near the University was very dangerous, and a bad place to bring up two daughters, and the Department was starved for money, I had turned down several offers to relocate, but when I received an offer from Harvard, I accepted it. Harvard was strong in organic chemistry with Paul Bartlett and especially Robert Woodward. I don't think the Department as a whole was better than that at Chicago, but it was good, and in a much better neighborhood.

The Department at Harvard had decided to move in the direction of biochemistry when they hired Konrad

Bloch and me. This was over the strong objections of George Kistiakowsky, a fine scientist, and a powerful figure who lost his temper, or anyway pretended to lose his temper, to win arguments. He would scream at me (and others), but the next day would act as if nothing had happened. Apparently he had wanted to add a nuclear chemist to the Department, but Woodward and Bartlett wanted biochemists, and carried the day. This was an important departmental decision; I don't think you can have a modern chemistry department without a considerable emphasis on biochemistry.

Konrad Bloch, who was an outstanding biochemist, had begun his research on the pathway for the biochemical synthesis of cholesterol even before he went to the University of Chicago, and finished it at Harvard. An aphorism of mine is that a great scientist makes a discovery in his lifetime, a good scientist makes a discovery once a decade, and any damn fool can make a discovery every year. Konrad violated this classification; he was unquestionably a great scientist, and he made two great discoveries: the pathway for the biochemical synthesis of cholesterol, and suicide inhibitors.

Occasionally, others have violated my principle. Fred Sanger determined the amino acid sequence of insulin, at a time when no one realized that proteins had structures in the conventional sense of the term. Then, he invented the best method for sequencing nucleic acids. But such multiple great discoveries are rare. Sanger is a giant in biochemistry.

BBRC: What about your own work? What are you most proud of?

Westheimer: I did two pieces of biochemistry of which I am especially proud, and at least one piece of physical chemistry (molecular mechanics). The first project in biochemistry concerns the direct and stereospecific transfer of hydrogen in oxidation–reduction reactions involving DPN+ (a project that I have already discussed) and the second was the determination of the detailed mechanism of the enzymic decarboxylation of acetoacetic acid. This process involved an astonishing 5 pK unit shift in the ionization constant of an essential lysine in the enzyme. It was one of the first demonstrations that you could regard proteins simply as complex organic molecules and carry out organic chemical reactions with them.

BBRC: Finally, I wanted to touch on the Westheimer report [Chemistry: Opportunities and Needs (1965) National Academy Press] that is now 38 years old. Did it accomplish what you expected it to? Did things turn out differently from what you and the Committee had projected?

Westheimer: I think the results were reasonably good. We tried hard to justify increasing Federal support for chemistry. I took an outstanding social scientist to lunch and asked him how I could prove that chemistry was under funded. He laughed at me. He said there was no scientific way; we could argue, but there's no way to prove that it is to the Nation's advantage to increase funding for chemistry. Nevertheless, I tried. We counted how many references there were for specific instruments (e.g. infrared spectrometers) in selected US, German, British, and Russian journals over time, and so could prove that the use of instruments in chemistry had grown exponentially, not only in the US but in all our major scientific competitors. The National Science Foundation introduced a line item for instruments in their budget for chemistry, in response (I hope) to our report. Further, we pushed chemistry in the direction of biochemistry, i.e. toward our future.

My post-doctoral mentor at Columbia had been Louis Hammett, who was a fine scientist, if a little dry. (His wife said he had been born two drinks under par.) I sent a draft copy of our report to Louis for his criticism. He wrote back that he didn't like it at all. He found that, just in the summary, there were numerous references to proteins, enzymes, and nucleic acids. He complained that work on these subjects had been done by people who didn't even call themselves chemists. Thus Louis criticized the aspect of our report of which I am most proud: the emphasis on biochemistry. The report was forward-looking and predicted where we find chemistry today.

The federal funds for chemistry increased considerably after we submitted our report. The federal funds for astronomy, physics, and biochemistry also increased sharply, perhaps in response to the National Academy's reports in those sciences. We will never know how much influence our various reports had, but I hope and believe that it was considerable.

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