

HAUROWITZ AND PAULING

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In the fall of 1948, I had the honor and pleasure of introducing to one another two giants in the field of immunochemistry, Felix Haurowitz and Linus Pauling. There was some drama in this meeting, which occurred at Indiana University, and the story merits the telling.

These two certainly were familiar with each other's work through the scientific literature, but by the nature of world affairs during the previous 10 or 15 years, it is unlikely that Linus Pauling ever anticipated meeting Felix Haurowitz, upon whom he had relied so heavily in developing his theories of antibody formation, and certainly not in a small town in Indiana.

Felix Haurowitz was born in Prague, the capital of Bohemia, in 1896. After serving in the Austrian Army, he enrolled at the German University of Prague, where he received the Doctorate in Medicine in 1922 and the Doctorate in Science in 1923. His natural interest was in chemistry and mathematics, so while in school, he volunteered to work in the Department of Physiological Chemistry, headed by Prof. Dr. Richard von Zeynek, a hemoglobin chemist. Later, von Zeynek appointed Felix to a half-time assistantship and then to a full-time appointment, after Felix received the M.D. degree (1922). During his student days, Felix also spent a semester at the University of Wurzburg in Bavaria, where he spent some time in the organic preparative laboratory of Prof. Stephen Goldschmidt. He also found time to visit the famous, but retired, biochemist Franz Hofmeister.

Following completion of the D.Sc. in 1923, Haurowitz spent the summer months in the laboratories of Rona and Michaelis in Berlin. This laboratory was internationally renowned for physical chemistry, and Haurowitz was anxious to learn the use of hydrogen electrodes and pH measurement, a new technique being developed in the Michaelis laboratory. He spent some time working on blood serum there. In 1924, Felix worked in Willstätter's laboratory in Munich. Willstätter was an organic chemist, who had received the Nobel prize in 1915 for his work on chlorophyll and porphyrins. Willstätter at this time was working on enzymes, and a paper on the nature of gastric lipase resulted from their collaboration. While Felix was in Munich, he felt the first severe impact of Hitler's insidious anti-Semitic propaganda, when Willstätter resigned from the University, because a qualified Jewish nominee for an important academic post was rejected by the Faculty. Even then, in 1924, some students wore the "hooked cross" but were embarrassed to wear it in Willstätter's presence. The whole tragic incident is described in Willstätter's autobiography (1949).

In 1924, Haurowitz, at the suggestion of the colloid chemist Liesegang, completed the first of his internationally acclaimed series of volumes on "Progress in Biochemistry." Later volumes appeared in 1931 and 1938, and Pauling must have been familiar with these.

In 1925, Haurowitz submitted his several papers on hemoglobin as a thesis for the docentship at the German University of Prague, and he began to give courses on Biophysical Chemistry and Advances in Biochemistry. Following his appointment, he received an invitation to work in the new Protein Research Institute in Heidelberg from its director, Professor Albrecht Kossel. Kossel was well-known for his fundamental work on protamines and histones, for which he had received the Nobel prize in 1910. He was also Editor of *Hoppe-Seyler Zeitschrift für Physiologische Chemie*, the oldest biochemical journal in the world. Following a semester at Heidelberg, Haurowitz returned to Prague and continued work on hemoglobin and derivatives.

In 1930, he was given tenure as Associate Professor of Physiological Chemistry in the Medical School of the German University of Prague. It was now that he began his work on immunochemical problems, the research area that became his principal life-time effort and for which he became internationally famous. A young colleague, Fritz Breinl, had just returned from a year at the Rockefeller Institute and spoke of Landsteiner's experiments with synthetic haptens. Haurowitz became immediately fascinated by the mystery of how antibodies might be formed. After some collaborative experimental work, these two advanced a theory (Breinl and Haurowitz, 1930) that antibodies are globulins whose molecules are adapted complementarily to the determinant groups of antigen molecules. This became known as the "template" theory, and it served as a great stimulus to research in the field. It was the first viable theory that differed from the early suggestions by Paul Ehrlich (1900) that antibodies against all possible antigens were already present in blood.

Haurowitz continued his work in the field and became an authority in immunochemistry. In the spring of 1939, the Nazis occupied Sudetenland, and the German University of Prague became an independent university of the German Reich. Haurowitz was mobilized by the Czech army and asked to organize a military hospital. Soon after, he was notified that he had been "temporarily deprived" of his privilege to teach and to examine students. An offer of a chair of Biochemistry at the University of Istanbul permitted him to leave Czechoslovakia with his family for Istanbul just as Hitler invaded Prague. He remained in Turkey until 1948. It is typical of Haurowitz that during this period of reduced research effort, he published a biochemistry text in Turkish.

Linus Pauling was born in Portland, Oregon, in 1901. He received a bachelors degree in Chemical Engineering from Oregon Agricultural College (now Oregon State University) at Corvallis in 1922 and proceeded immediately to the California Institute of Technology as a graduate assistant in chemistry. He received the Ph.D. in Physical Chemistry in 1925. He held a National Research Council Postdoctoral fellowship, 1925-26, at Cal. Tech, associating with Robert Millikan, then director of the Norman Bridge Laboratory of Physics and President of the University, and Arthur A. Noyes, Director of the Gates and Crellin Laboratory and Professor of Physical Chemistry. Among his good friends that year was another N.R.C. Postdoctoral Fellow, Frank T. Gucker, just out of T.W. Richards' laboratory at Harvard. Gucker was Chairman of the Chemistry Department at Indiana University at the time of Pauling's visit.

In 1926, Linus Pauling was awarded a Guggenheim Postdoctoral fellowship for study abroad and spent his time working in the laboratories of such noted

scientists as Arnold Sommerfeld in Munich, Niels Bohr in Copenhagen, and Erwin Schrödinger in Zurich. He returned to the California Institute of Technology as an Assistant Professor in 1927, where he rose rapidly through the ranks to Professor in 1931 and Chairman of the Division of Chemistry and Chemical Engineering and Director of the Gates and Crellin Laboratory in 1936.

Pauling's early work focused on crystal structure and the chemical bond. He published a series of seminal papers on "The Nature of the Chemical Bond" between 1931 and 1933 in the *Journal of the American Chemical Society* and the *Journal of Chemical Physics*. In the fall of 1937, he held the George Fisher Baker Nonn-resident Professorship of Chemistry at Cornell University, which enabled him to complete his book (1939), *The Nature of the Chemical Bond and the Structure of Molecules and Crystals*. This volume, which has gone through three editions, has been called one of the most influential scientific books of the twentieth century.

In 1934, Pauling began to apply his knowledge of molecular structure and the nature of chemical bonding to more complex molecules, particularly to the structure of proteins. His studies of the magnetic susceptibility of hemoglobin molecules during oxygenation must have overlapped with the work of Haurowitz, who had worked extensively with hemoglobin and oxyhemoglobin from 1922 to 1936. Indeed, Haurowitz, writing of his own work on crystalline hemoglobin and oxyhemoglobin, noted that after his first discovery of a second hemoglobin (hemoglobin F), hemoglobins S, C, M, and others were discovered a few years later by Pauling, Itano, *et al.* (Haurowitz, 1975).

Following this work, Pauling began a series of studies of protein, which led to a theory of the structure of native, denatured, and coagulated proteins. This led naturally to proteins involved in immunological reactions, and in 1940, Pauling published his now classic paper entitled "A Theory of the Structure and Process of Formation of Antibodies."

In the late summer of 1947, Indiana University was in the process of installing a new chairman of the Chemistry Department, Prof. Frank T. Gucker of Northwestern University. Gucker was considering Felix Haurowitz as his first appointment in biochemistry, on the recommendation of Prof. H.G. Day. Day had become aware of the availability of Haurowitz, who was at that time still on the Faculty of Medicine at Istanbul, through Alice Haurowitz, his daughter, who was then a student at Indiana University and had been living with the Days. Since I had received my degree in biochemistry from Northwestern (1940) and was at that time teaching some of the biochemistry laboratory work at Indiana, Gucker asked me to review the Haurowitz file of reprints.

As I translated the German of the Breinl and Haurowitz paper of 1930, I had the feeling that I had read this before. Turning to my files of the *Journal of the American Chemical Society*, I pulled out Pauling's 1940 paper and was amazed at the similarity of the proposals! In his opening paragraph, Pauling stated that the idea of complementary structures for antibody and antigen was suggested by Breinl and Haurowitz in 1930. After outlining his proposal that antibodies differ from normal serum globulin only in the way in which the two end parts of the globulin polypeptide chain are coiled, and that these end parts can assume a very great many configurations with nearly the same stability to conform to the configuration of the surface regions of the antigen Pauling noted (1940, p. 2654),

"The only data permitting a quantitative test of this relationship (predicting the valence of two or more different haptens in the same antigen) which have come to my attention are those obtained by Haurowitz and his collaborators by use of azoproteins made from arsanilic acid."

It was apparent that the Pauling paper was proposing almost identical ideas for the formation of antibodies! The major difference in the two theories was later described by Haurowitz (1960) in an historical review as follows: "I assumed that the antigen molecule is deposited in the sites of globulin formation and interferes with this process by directing the amino-acids, during the process of biosynthesis, into such positions that the synthesized globulin is spatially adapted to the determinant group of the antigen. Pauling later (1940) modified this view and assumed that the peptide chain, after formation, folds around the determinant group of the antigen in such a manner that a complementarily adjusted group in the antibody molecule is formed. I am inclined to share this view and to assume that the difference between normal serum globulin and antibody is indeed only a difference in the mode of folding of the peptide chains."

By 1968, Haurowitz had reverted to his original ideas, and wrote as follows: "Pauling's views seemed very plausible at the time, when nothing was yet known about the close correlation between primary structures and conformation of proteins. Pauling's idea was supported by reports of almost identical amino-acid composition of various antibodies, and by reports that the N-terminal pentapeptide is identical in rabbit antibodies and normal γ -globulin. Improved methods of amino-acid analysis have now actually shown small but significant differences between antibodies of different specificity."

In the fall of 1947, Felix Haurowitz accepted a position as Professor of Chemistry at Indiana University and planned to arrive in the United States from Istanbul in the summer of 1948. In the meantime, Professor Gucker had taken charge of the department on his arrival in September of 1947 and inaugurated a number of new initiatives. One of these was the establishment of a new local section of the American Chemical Society. Previously, the chemistry faculty, as members of the A.C.S., had to travel to Indianapolis, fifty miles away, over winding old State Road 37 (no four lane through-ways in those days) to attend the monthly meetings. Needless to say, attendance was poor. Frank Gucker was a strong supporter of Chemical Society activities and proposed that we have our own section. He appointed a two-man committee (with me as chairman and a graduate student for support) to collect the needed signatures and to carry out the formalities required by the national organization to establish a local section. The Inaugural meeting of the Southern Indiana Section of the American Chemical Society was set for October, 1948. The principal speaker was to be the President of the American Chemical Society, Linus Pauling, who was to speak on "The Formation of Antibodies."

As first President of the new local section, it was my duty to host the speaker and to introduce him around the department. I looked forward with pleasure to this honor, and when Pauling arrived for his lecture, which was scheduled for eight o'clock that evening in the Chemistry Auditorium, the first office I took him to was that of Professor Felix Haurowitz. I said, "This is Felix Haurowitz. You probably know him." Pauling exclaimed, "Not **the** Felix Haurowitz!" "Yes," I said, "you work in the same field."

I left Haurowitz and Pauling in animated conversation, but I couldn't help wondering what Pauling would say that night when he talked on "The Formation of Antibodies." The two men differed very much in their styles. Haurowitz was very quiet and reserved. He never made a statement in his scientific work which did not have solid experimental backing, and in his proposed theories, he always indicated areas which needed experimental backing. He himself stated, discussing his template theory, "As a chemist, I have tried to translate this picture into the language of chemistry." He didn't draw many imaginary pictures of antigens and antibodies, as Ehrlich had done earlier. Pauling, on the other hand, was much more willing to go out on a limb. He loved to apply what he called the "Stochastic" method, the application of intuitive hunches based on chemical facts, for which he had a phenomenal memory. He used many diagrams and visual images of proteins, antigens, and antibodies in his first paper (1940) and in his lecture. "His success as a scientist is based on his capacity for quick insight into new problems, his ability to recognize interrelationships, and the courage to put forward unorthodox ideas. While his concepts have not always been correct, they have always stimulated discussion and investigation" (Encyclopedia Britannica, 1979).

The difference in these men is illustrated in a story Haurowitz later told. In follow-up experiments based on his theory, Pauling claimed that he could synthesize antibodies *in vitro* by exposing slowly renaturing globulin to antigens (Pauling and Campbell, 1942). Haurowitz repeated these experiments and showed that antibodies were not formed in this way; the observed precipitate did not involve complementary reaction. Haurowitz wrote this up, submitted the manuscript to Pauling with the suggestion that Pauling submit a correction, and offered not to publish in that case. Pauling, of course, said "no." Felix should publish his results, and let the scientific world be the judge. Haurowitz (Haurowitz, *et al.*, 1946) did publish and later, a postdoctoral student of Pauling's, working at Cal. Tech in 1948-49, was unable to confirm that claim (Morrison, 1953).

The lecture hall was filled that night, and there were many laymen present to hear the great man speak. Pauling was equal to the occasion. He is a flamboyant speaker and a popular lecturer. In order to be better seen and heard in the large auditorium, he climbed up on the lecture demonstration desk, which was large enough so he could walk back and forth. He began, "I visualized that if God was going to form antibodies, He would form them in the simplest way, and these antibodies are therefore merely coiled up chains of amino-acids, and nobody ever thought of that before except HAUROWITZ," and he turned and pointed at the Professor, sitting in the front row! He continued to present the various aspects of his theory, each time ending with a spectacular, "and nobody ever thought of that before, except Haurowitz," pointing to the man in the front row. The evening was a great success. A layman in the audience reported, "I didn't understand a word he said, but it was one of the best lectures I ever heard."

Since that autumn day in 1948, both men have gone on to greater honors. Haurowitz won the Ehrlich medal in Germany, was elected to the Leopoldina Academy, the U.S. National Academy of Science, the American Academy of Arts and Sciences, and an honorary M.D. from the University of Istanbul and an honorary Sc.D. from Indiana University. Pauling continued to occupy the public eye and received numerous honorary degrees, both here and abroad. He received the Nobel Prize in Chemistry in 1954, the Nobel Peace Prize in 1962, and the International Lenin Peace Prize in 1972. For a while, he served as Research

Professor at the Center for Study of Democratic Institutions and is now Research Professor in the Linus Pauling Institute of Science and Medicine, where his proposals on megavitamin therapy, especially vitamin C, are still stimulating discussion and investigation.

ACKNOWLEDGMENTS

In addition to the specific references given, I am indebted for general insight into the character of these two gentlemen to the following works:

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I am also indebted to Marvin Carmack for assistance in translating the pages of Willstätter's (1949) autobiography.

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