NATIONAL ACADEMY OF SCIENCES

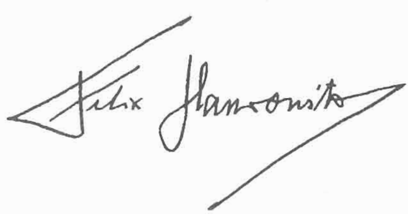
FELIX HAUROWITZ

1896—1987

A Biographical Memoir by

FRANK W. PUTNAM

Biographical Memoir



FELIX HAUROWITZ

March 1, 1896–December 2, 1987

BY FRANK W. PUTNAM

FELIX HAUROWITZ was born in Prague, then the capital of Bohemia and one of the provinces of the Austro-Hungarian empire. In his long life he saw many changes in the world, including the collapse of that empire at the end of World War I, in which he served, and the invasion of Prague by Hitler's army at the beginning of World War II. His flight with his family to Turkey was followed by a decade there before he moved to Indiana University at Bloomington, where he lived and worked the rest of his life. He survived successive political revolutions, and he participated in revolutions in science and medicine that have affected the condition of humankind. Felix and his wife, Gina, and family were displaced from the country and culture he cherished, but he never forgot either. In his last days he often talked about his early experiences in Prague. Yet he was fated to spend more than half his life in other countries, Turkey and America, which he also came to love. He was of a generation that will not be seen again. The product of centuries of European intellectual tradition-learned scholars, dedicated scientists, enlightened human beings—they were driven by barbaric intolerance to a new land to which they contributed so much. Their impact will be enduring, and Felix Haurowitz was one of the great ones among them.

Felix came from a family engaged in the textile trade but interested in literature, music, and foreign languages. German was his native language, but because Prague was predominantly Czech, he also spoke fluent Czech since his early childhood. His early education was at home with private teachers, then in a Catholic school run by a German order, and finally in a gymnasium. There for eight years he had Latin lessons daily and also studied Greek. No doubt this contributed to his linguistic fluency, for he later mastered Turkish well enough to lecture and write books in that language. Although the gymnasium taught a variety of subjects, including mathematics in which he excelled, it offered very little chemistry. He detested the required sports and gymnastic lessons but later became an enthusiastic mountaineer and skier. During the gymnasium years he also took private lessons in English, French, and Italian and also piano lessons. In later life he played the piano daily. He said he never practiced or played perfectly but that he played for personal satisfaction and relaxation.

On completing the gymnasium he enrolled in a textile school to please his father, although his mother wanted him to become a doctor. He enjoyed the textile school and said he learned much there of use for his later work in the laboratory. However, in November 1915 he was drafted for military service. He was assigned to an Austrian artillery battalion and sent to officers' school in Hungary. He made the highest grade in his class and was promoted to Fähnrich (ensign). He was made commander of the artillery battalion and assigned to the Austrian front in the southern Tirol. However, because they occupied an inaccessible ridge, there was little activity, so he began to prepare for medical school by reading textbooks of inorganic and organic chemistry by Holleman. These he found fascinating. In April 1918 he was given leave to enroll in the medical school of the Ger-

man University in Prague. The war ended in October 1918 with the disintegration of the Austro-Hungarian empire, and Czechoslovakia became an independent republic.

In his first year in medical school Haurowitz worked as a volunteer assistant in the Department of Physiological Chemistry for Professor Richard von Zeynek, a hemoglobin chemist, and thereby began a life interest in this critical respiratory protein. His initial assignment was to work with Dr. Hedwig Langecker from whom he received his first introduction to the techniques of the biochemistry laboratory. Haurowitz analyzed the lipid-rich gonads of the jellyfish *Rhizostoma cuvieri*, which von Zeynek had collected. The latter was so pleased with the young student's report that he edited it and sent it off to the *Hoppe-Seyler's Zeitschrift für physiologische Chemie* with Haurowitz as the sole author. This was the latter's first publication. Von Zeynek gave him a half-time paid assistantship, which he held until he received his M.D. in 1922, when it was converted to a full-time position. He was asked to prepare crystalline horse hemoglobin and study it spectrophotometrically, and this led to his main research interest in the period from 1922 to 1936.

Haurowitz did well in all his courses in medical school; as was the custom, he spent a semester elsewhere, at the University of Würzburg in Bavaria. There he met the famous protein chemist Franz Hofmeister. After receiving his M.D. in 1922, Haurowitz was awarded the Dr. rer. nat. (D.Sc.) in 1923 for several papers published between 1920 and 1923. Already engaged in hemoglobin research, he visited the laboratory of Leonor Michaelis in Berlin to learn physicochemical methods from P. Rona, especially pH measurement, which was then new. A paper on ion measurements in blood serum resulted from this period. In the summer of 1924 he worked in the laboratory of the Nobelist F. Willstaetter in Munich on the purification of gastric lipase.

This also led to a publication. The young Haurowitz was fast developing a reputation. The same year the colloid chemist R. E. Liesegang visited him in Prague and invited him to write a book on the advances in biochemistry and pharmacology since the advent of World War I in 1914. Haurowitz declined to write on pharmacology but wrote his first book, *Biochemie des Menschen und der Tiere seit 1914.* This began a series of "progress" books with new ones appearing in German in 1932, 1938, and 1948 and then in English in 1950 and 1959 after he moved to America. These books gave him international recognition, and he later felt that the series in German did much to develop interest in and enhance the status of physiological chemistry and biochemistry in the German-speaking countries at a time when there were very few such departments in Germany. However, the immediate result of his first book and the concurrent research was his appointment as a docent. This rank was similar to that of an assistant professor, but it also entitled the recipient to announce any course he wanted to teach provided it did not duplicate another. He introduced courses in Prague on biophysical chemistry and advances in biochemistry. In 1930 he was appointed a tenured associate professor in the same department and finally achieved independence as a research scientist.

On becoming a docent, Felix Haurowitz married Gina Perutz in June 1925. She was a student of art history to whom he had been engaged for some time. She became his lifelong companion, supportive of him in everything he did. A few months after the wedding, they moved to Heidelberg for a research semester in the new Protein Research Institute of Albrecht Kossel, known for his fundamental work on protamines and histones for which he had received a Nobel prize in 1910. On their return to Prague he devoted the next five years almost entirely to research on hemoglo-

bin. During this period he attended a series of international congresses where he gave papers on his studies of hemoglobin. He always recalled with pride the memories of the great biochemists he met at these early meetings, their gracious comments on his work, and the correspondence and personal contacts that ensued.

During the period of research on hemoglobin in Prague from 1925 through 1936, Haurowitz made a number of fundamental discoveries. Through spectroscopic studies of the combination of various oxidizing agents and other ligands with hemoglobin, he determined the absorption spectra of methemoglobin and other physical properties, and he crystallized several derivatives for the first time. He was the first to isolate fetal hemoglobin (Hb F) from fetal blood, and he crystallized it and determined its affinity for oxygen. He later pointed out that this was the first step in the search for further hemoglobins. However, his attempts to isolate abnormal hemoglobins from the blood of patients with anemias failed because there were no cases of thalassemia or sickle cell anemia in Prague. He also discovered the drastic change in the crystalline shape of deoxyhemoglobin from hexagonal plates to elongated prisms when oxygen was allowed to diffuse into the crystals. He showed this phenomenon to Max Perutz when the latter was in Prague visiting his cousin Gina while en route to Sir William Bragg's laboratory at Cambridge. Max later acknowledged that this surprising change gave him the idea to study the crystallographic structure of hemoglobin. Felix loved to tell of this meeting. He also claimed that this was the first observation of an allosteric reaction, and, in fact, it is sometimes cited as such. While at Prague he also published studies on other proteins and on methods of protein chemistry, but up to 1930 he was most noted for his work on hemoglobin.

A new and lifelong research interest began in 1930 and

was stimulated by a phone call from a colleague, Fritz Breinl, who had just returned from a year at the Rockefeller Institute in New York. Breinl, a virologist, was excited by the experiments of Karl Landsteiner with synthetic haptens. He asked Haurowitz to read the papers and discuss with him what could be done to solve the mystery of antibody production. Thus began an exciting but short-lived collaboration that led to what was later called the template theory of antibody formation. Equally important, it committed Haurowitz to an experimental study of the role of antigen in antibody production for the rest of his research career. As might be expected, they used horse hemoglobin as an antigen in the work for their first paper. Unlike Landsteiner, who used only qualitative indices for the amount of antigen-antibody precipitate (– or +, ++, +++), Haurowitz and Breinl used quantitative methods to determine the amount of hemoglobin in the precipitate, and they also indirectly determined the amino acid content of the nonhemoglobin portion of the precipitate. In his autobiography for the National Academy, Haurowitz underlined the following statement for emphasis: "I concluded that the antibody must be serum globulin and suggested therefore that the antigen interferes with the process of globulin biosynthesis in such a way that globulins complementarily adjusted to the antigen are formed." Thus began the template theory, as it was later called, to which he adhered with some modifications for the rest of his life.

Shortly after this startling theory was announced, Haurowitz began experiments to determine the distribution of the antigen in the organism. Because radioactive isotopes were not yet known, he employed protein antigens to which various colored dyes were attached covalently, for example, arsenic-containing azoproteins. The chemical groups used to derivatize and label the proteins were known as haptens.

Haptens can convey antigenic specificity to a protein carrier to which they are linked but by themselves are not antigenic. The antibodies specific for the protein carrier can be removed by a process called absorption so that the remaining antibodies are specific for the chemical hapten. This ingenious procedure pioneered by Landsteiner was further developed by Felix Haurowitz who employed many different haptens and used it for quantitative determination of the composition of the antigen-antibody precipitate, calculation of dissociation constants, and other parameters of the antibody-antigen interaction. It became the primary experimental basis for his further immunochemical research until the introduction of radioactive isotopes. Although he never met Landsteiner, Haurowitz exchanged many reprints with him, and at the Landsteiner Centennial he said that he considered himself "as a kind of student or pupil of Landsteiner."

In the mid-1930s immunochemistry was developing rapidly as an exciting new field. In the United States Michael Heidelberger and his co-workers, notably Elvin Kabat, introduced a parallel quantitative approach by using the Kjeldahl method to determine the antibody nitrogen in precipitates of antigenic polysaccharides. The template theory was widely discussed and generally accepted, although Linus Pauling proposed a different concept. However, little was yet known about protein structure, and nothing was even surmised about the role of RNA and DNA in protein biosynthesis. Moreover, the end of the Prague era was at hand, for in Europe war clouds were on the horizon. Breinl returned to his first love, virology, and later died a tragic death from rickettsial fever.

In the summer of 1938 when Haurowitz was working at the Carlsberg Laboratory in Copenhagen at the invitation of Albert Fischer, his stay was abruptly terminated by the

Munich agreement. Because of Hitler's threat of a Nazi invasion of Czechoslovakia, he decided to return to Prague as quickly as possible to be with his wife and their two children, who had been born in 1929 and 1931. Not daring to cross Germany with a Czechoslovakian passport, he traveled by boat to Poland and continued by train to Prague. He was soon mobilized as an M.D. by the Czech army, but returned to civilian life when Czechoslovakia abandoned the Sudeten area of the country to Germany. The German University became an independent university of the German Reich, and Haurowitz was deprived of his right to teach. Just at that time he received an offer of the chair of biochemistry at the University of Istanbul. Though reluctant to leave Prague, he visited Istanbul, found the conditions favorable, and accepted the offer. Soon after, Hitler's troops invaded Prague. Two weeks later the Haurowitz family left for Istanbul to begin a new life. Most of their property except their furniture and library was seized by the Gestapo. They arrived in Istanbul with only 2,000 koruny (about $70). Toward the end of World War II, severe inflation forced them to sell some of their furniture to supplement his salary.

The Haurowitz family loved their life in Istanbul and considered it the most beautiful city in the world both for its natural beauty and for the Roman, Byzantine, and Islamic monuments. Felix and Gina often spoke with pleasure of their life there. They adapted well. Since lectures needed to be given in Turkish, his lectures were at first translated during class, but by the end of the second year he lectured and examined in Turkish. In fact, he was put on a committee to help modernize the Turkish language and rid it of Arabic terms. He published papers in Turkish and also a textbook on biochemistry that went through several editions. He developed a group of hard-working Turkish co-

workers, some of whom later became professors in Istanbul and other Turkish universities. He maintained contact with them long after leaving Turkey, and in 1973 the University of Istanbul honored him by conferring the honorary degree of doctor of medicine.

At Istanbul Haurowitz's research was almost exclusively on problems of immunochemistry. Much of his time was spent in teaching large lecture and laboratory courses, and the budget was very low, especially during World War II. Yet in this period he published a number of papers in international journals, as well as in Turkish journals. He showed that the antibodies produced by the injection of a uniform antigen, such as an azoprotein, were always heterogeneous and could be fractionated by absorption with more or less modified azoproteins. He reported a method for purification of antibodies based on the dissociation of the antigen-antibody precipitate at low pH.

Despite the progress in research, the good life in Istanbul, and the satisfaction gained from the contribution he made to the development of medical education and extension of health care in Turkey, there was concern about the future of the children, who were reaching college age. In 1946 Gina and the two children, Martin and Alice, moved to the United States. However, Felix decided to stay in Turkey for two more years to fulfill his contract. Alice registered as a student at Indiana University in Bloomington and lived at the home of Harry G. Day, a professor of biochemistry in the Department of Chemistry. When Haurowitz visited the family in 1947 he gave a lecture at Dr. Day's invitation. This was followed by a reception where he met H. J. Muller, the geneticist and Nobel laureate whose wife was the daughter of a colleague in Istanbul. The next day Haurowitz was asked whether he would accept an appointment as professor of chemistry to teach biochemistry at Indiana Univer-

sity. He said he would be glad to do so but he had to return to Istanbul for one more year and also had been offered the chair of biochemistry in the Medical School at the University of Basel in Switzerland. While en route to Basel, he received the formal offer from Indiana University in London and accepted it. He moved to Bloomington in 1948 and spent the rest of his life there.

In 1948 Indiana University was expanding rapidly and was strong in chemistry and biology, particularly in genetics where it had a famous group: H. J. Muller, Tracy Sonneborn, and Ralph Cleland. Irwin Gunsalus and Salvador Luria were also there as assistant professors of microbiology. They asked Haurowitz to teach graduate courses in proteins and nucleic acids, which he gladly did. Among his students was Jim Watson, then a graduate student of Luria. Harry Day became a close friend and helped Haurowitz in many ways, as did his other colleagues in the Chemistry Department, particularly Frank Gucker, the chairman, who later became dean of arts and sciences. In 1950 while I was an assistant professor at the University of Chicago, Haurowitz invited me to give a seminar in the Department of Chemistry, my first such invitation. I was then a member of the Phage Group. I well remember the ferment and excitement in Bloomington at that time.

In Bloomington Haurowitz's research was almost entirely devoted to immunochemistry, but in addition to teaching courses in biochemistry and protein chemistry, he found time to write several books. Although he completed another book on the progress of biochemistry (from 1949 to 1959), he felt that the field had expanded too greatly to be covered any more by a single author, and he declined the publisher's request to become editor of a series of such volumes. In 1950 he published a book that had wide influence and the one of which he was most proud, *Chemistry*

and Biology of Proteins. This had great success. The book was soon reprinted, and a second edition was published in 1963. A later book *Immunochemistry and Biosynthesis of Antibodies,* was published in 1968. Both books were translated into Russian, Japanese, and several other languages.

Haurowitz's early research at Indiana University focused on the fate of the injected antigen and its persistence in phagocytic cells. For this study he used diazotized aromatic amino acids labeled with radioactive isotopes ^{35}S or ^{14}C. Contrary to previous views Haurowitz showed that antigen is taken up by the phagocytic cells not the lymphoid cells and persists in the organism for a long time. He also showed that antigen was deposited in the cytoplasm not in the nuclei. Radioactive isotopes were also used to determine the dissociation constant of antigen-antibody complexes. Over the years, with the help of his graduate students and postdoctoral research associates, Haurowitz made many attempts to identify the specific combining sites of antibodies. One unique approach was to use antigens with two different well-defined chemical determinants and inject the doubly labeled protein into a single rabbit to eliminate complications caused by genetic differences. This work showed that specific combining sites of antibody molecules directed against a single antigenic determinant are heterogeneous even if produced in an individual rabbit. Thus, the combining site, although complementarily fitting the rigid antigenic determinant group, can be formed by different amino acid sequences. Later experiments with rabbits heterozygous for certain immunoglobulin allotypic markers showed preferential expression of antibodies of high affinity by one allotype.

After forty years of research and teaching, and publishing some 350 papers and eleven books, Felix Haurowitz retired in 1966 at age seventy. Actually the word retired is a

misnomer, for he continued to go to the laboratory and his office every weekday and often on weekends, too, for almost twenty more years. For a time he continued immunochemical research with one assistant, and his work was still funded, for which he was very grateful. He attended seminars and asked penetrating questions. He and Gina attended scientific meetings where she watched over him carefully. She always had great difficulty persuading him to go to evening social affairs rather than work on his notes on the program of the day. He had major heart surgery at age seventy-seven, followed by complications from which he recovered, but except for that his health was good until almost his last year of life. He was never one to be interested in what he called "small talk" but always turned the conversation to some scientific theme. However, his own experiences had imbued him with a strong social conscience, and frequently he would raise issues related to world problems, especially those of Middle Europe.

International recognition came to Felix Haurowitz early in his scientific career, but major honors came rather late, perhaps because of the two mid-career moves resulting from the German invasion of Czechoslovakia. He was never active in professional societies though he did serve a term as chairman of the Division of Biological Chemistry of the American Chemical Society. He was a member of more than twenty scientific societies in half a dozen countries and was elected to honorary membership in several a decade after retirement. A rare honor was his election to the German Academy of Sciences (Leopoldina) in 1956. In 1960 he was awarded the prestigious Paul Ehrlich gold medal and prize, perhaps the highest honor in immunology and pathology. In 1970 he was elected to membership in the American Academy of Arts and Sciences. He was nearly eighty when elected to the National Academy of Sciences,

but he greatly enjoyed the fellowship, and he and Gina went to every meeting while she was still alive. At age ninety he was lauded at a meeting on the history of immunology at the Congress of Immunology in Toronto where he gave his last paper.

A biographical memoir of Felix Haurowitz would be incomplete without a tribute to Gina Haurowitz, just as he would have been incomplete without her. Her death in June 1983 left him devastated. In his autobiography for the Academy he wrote, "Teaching, doing research, writing books and keeping myself up to date with biochemical research done elsewhere was a full-time job. I would not have been able to do all this without the help of my wife." Indeed, this was true, for she took care of all his needs and shielded him from all the daily demands of the world. More than that, she was his lifelong companion, a fellow hiker, an enthusiastic gardener, and a landscape painter. She was a gracious hostess and presided over afternoon teas for conversation among friends or evening receptions for campus visitors. At Bloomington we saw little of their children, for they had already established their own careers. Alice got her A.B. in chemistry at Indiana University. She and her husband, H. William Sievert, earned a Ph.D. degree in biochemistry at the University of Wisconsin and later worked at Abbott Laboratories. Their son Martin changed his name to Harwit. He received a B.A. at Oberlin College and a Ph.D. in physics at the Massachusetts Institute of Technology and was professor of astrophysics at Cornell and for five years was chairman of the Department of Astronomy there. He married Marianne Mark in 1957. Now he is director of the National Air and Space Museum in Washington, the most widely visited museum in the world.

Felix and Gina were very happy in Bloomington. They loved the university and the countryside, and all who knew

them responded with affection and admiration. At Bloomington we honored him on his seventy-seventh birthday in 1973 with the Haurowitz Symposium. This drew several hundred distinguished immunologists from around the world. They told me they were drawn not just by his research but by their admiration for him as a person, for the ideas and encouragement he so freely gave to others, and for his acute insight and his thoughtful and helpful criticism.

His students knew him as a dedicated teacher, his colleagues as a leader of science. All who knew him will remember him as a fighter against intolerance who was also a wise, warm, and gentle human being.

IN PREPARING THIS BIBLIOGRAPHICAL MEMOIR I relied heavily on the autobiography and bibliography that Felix Haurowitz submitted to the National Academy in October 1975. Also, I had many conversations with him over a period of thirty years, especially in the last two years of his life. Harry Day supplied much valuable biographical material, including the transcript of a 1978 interview with Felix Haurowitz on his life and work. Many of the quotations and references to his personal recollections are from the autobiography and the transcript. I am indebted to family members and colleagues who reviewed this memoir.

ACADEMIC HISTORY AND HONORS

DEGREES

1922 M.D., German University of Prague
1923 D.Sc., German University of Prague

HONORARY DEGREES

1973 M.D., University of Istanbul
1975 Ph.D., Indiana University

UNIVERSITY APPOINTMENTS

1920–25, Assistant; 1925–30, Docent; 1930–39, Assistant Professor, Department of Physiological Chemistry, Medical School of the German University, Prague

1939–48, Professor and Head, Department of Biological and Medical Chemistry, Medical School, University of Istanbul, Turkey

1948–58, Professor of Chemistry; 1958–66, Distinguished Professor, Department of Chemistry, Indiana University, Bloomington, Indiana

MEMBERSHIPS

1960 Deutsche Akademie der Naturforscher Leopoldina
1970 American Academy of Arts and Sciences
1975 National Academy of Sciences

AWARDS AND HONORARY MEMBERSHIPS

1960 Paul Ehrlich Medal and Prize, Paul Ehrlich Foundation, Frankfurt, West Germany
1971 Award for Distinguished Services to Immunology, First International Congress of Immunology, Washington, D. C.
1972 Société de Chimie Biologique, Paris
1973 Société d'Immunologie, Paris

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1927

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