Emil L. Smith

1911–2009

BIOGRAPHICAL *Memoirs*

A Biographical Memoir by
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NATIONAL ACADEMY OF SCIENCES

EMIL L. **SMITH**

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By Alexander N. Glazer and Robert L. Hill

Emil Smith was among the pioneers in the invention of methods for purification, characterization, and sequencing of proteins. He was the first to show that in green plants, chlorophyll is protein-bound, and he was the first to demonstrate the widespread requirement for specific metal ions to enable the catalytic activity of diverse peptidases.

Early life and education

Emil L. Smith was born on July 5, 1911 in New York City. His parents were immigrants, his father from Russian Ukraine and his mother from Belorussia. They met in New York and were married in 1906.

Emil's father was a skilled tailor and initially worked for Saks Fifth Avenue. He then opened his own small shop and the income provided a decent living for the family. His mother was a homemaker and helped in the store.

The Smiths had two children: Bernard, born in 1907, and Emil. The parents, largely self-educated, valued knowledge and culture, and their sons went on to distinguished careers, Bernard as a highly regarded book editor, film producer, and writer, and Emil as a scientist and educator.

Emil progressed rapidly through the New York public schools, skipping several grades. At age 16 he enrolled in Columbia University School of General Studies. He described himself as an average student in school, but evidence of his wide-ranging talents emerged early. At age nine, influenced by a neighbor who was a pioneering radio engineer, Smith began to build small inexpensive receiving sets, which he and a friend sold for several years to relatives and others.

Midway through high school, Emil started playing the saxophone, and after two years of lessons from a very good, rigorous teacher, he progressed to working as a professional

jazz musician largely through the well-known Moss-Hallett agency. His earnings helped to pay his college tuition at Columbia. During his last club performance, on December 31, 1931, he was part of the Eddie Edward's augmented Dixieland Band, playing in New York at the famous Webster Hall, which was described as the "Jewel of the Village" by the playwright Eugene O'Neill. The following day, at a New Year's party, Emil met his future wife, Esther Press.

When he enrolled as a pre-med student at Columbia, Emil had an ill-defined interest in science. Then, in his sophomore year, he fell under the spell of two gifted teachers: James Howard McGregor and John Maurice Nelson. McGregor, a professor of zoology and a dynamic and persuasive teacher, made everything in biology very exciting. His course emphasized evolution and genetics. Nelson, who taught the organic chemistry course, was unusual among organic chemists at the time because of his interest in the chemistry of enzymes. (One of Nelson's PhD students, John Northrop, received the 1946 Nobel Prize in Chemistry for establishing that enzymes are proteins.) These two teachers set Emil on his lifetime course of studying proteins, a domain where the strands of biology and organic chemistry are tightly interwoven.

After receiving his bachelor's degree in 1931, Emil began his graduate studies in Columbia University's Zoology Department. The country was in the midst of the Great Depression, so the offer of a teaching assistantship was an important factor in his choice. For the next three years, he taught for twelve hours a week in parallel with his research.

In his first year as a graduate student, Emil took Selig Hecht's sensory physiology course and was captivated both by the instructor and the coursework. George Wald, who completed his PhD studies with Hecht in 1932, later wrote, "In Hecht, great scientific capacities combined with superb gifts as a teacher, writer, and lecturer" (Wald 1991).

Emil unhesitatingly chose Hecht as his mentor. Hecht was a research pioneer in the discipline of general physiology, as well as in the physiology of vision. He ensured from the start that Emil was exposed to rigorous research training in the biophysics of vision. This phase of Emil's graduate research resulted in three papers that he coauthored with Hecht (e.g., Hecht and Smith 1936).

For his doctoral work, Emil studied the dependence of photosynthesis on light intensity and carbon dioxide concentration (Smith 1936; Smith 1937). His results led him to conclude that green plant photosynthesis had "a complex reaction mechanism involving

more than one photochemical reaction," an idea at variance with the widely accepted work by Otto Warburg. However, later studies unambiguously verified Emil's conclusion.

Emil emphasized that his mathematical formulation of the photosynthesis rate limitation can be used as a criterion for the validity of any theoretical description of photosynthesis (Smith 1936). Indeed, this formulation has stood the test of time remarkably well. As of 2009, it remains the best empirical formulation of a photosynthetic-irradiance curve model as assessed by comparison to experimental data and observations on primary productivity (Grangeré et al. 2009).

Under the shadow of World War II:
Cambridge University, The Connecticut Agricultural Experiment Station, The Rockefeller Institute, E.R. Squibb and Sons

As soon as his thesis research was complete, Emil's focus shifted permanently to proteins. While still at Columbia, he investigated whether chlorophylls in the green leaf were protein-bound or free—a segue from his thesis work on photosynthesis to later work on proteins.

In Hecht's laboratory, native rhodopsin was routinely solubilized by extraction of retinas with an aqueous solution containing the detergent digitonin. When Emil applied this method to ground-up green leaves, chlorophyll was solubilized and the spectrum of the solution was very similar to that of intact leaves, but it shifted to longer wavelengths as compared with solutions of mixtures of chlorophyll *a* and *b* in organic solvent. Examination of the extract in the ultracentrifuge showed that the chlorophyll was sedimenting with particles of molecular weight in excess of 70,000, leading to the conclusion that "...the classical organic studies of chlorophylls and carotenoids were concerned with the prosthetic groups of extremely complex, specific catalysts perhaps analogous to hemoglobins..." (Smith 1938). This fundamental contribution was largely overlooked for nearly fifty years (Govindjee 1988).

At this stage, Emil's heart was set on broadening his expertise in the field of protein chemistry and enzymology. Towards the end of the 1930s, Cambridge University was a leading institution for studies of protein structure and function, and Emil decided that David Keilin's laboratory at the Molteno Institute was particularly attractive.

Hecht encouraged Emil to apply for a Guggenheim Fellowship, and Emil followed his advice successfully. He and Esther travelled to Europe, arriving in Cambridge in

September 1938. In an exploratory conversation with Keilin, Emil expressed an interest in trying to solubilize cytochrome oxidase with solutions containing bile salts, an approach found to be successful in the preparation of rhodopsin. But Keilin recommended that he should continue the investigation of the chlorophyll-protein complex. That work was abruptly interrupted in September 1939 by the outbreak of the Second World War, at which time Emil and Esther were compelled to return to New York.

Hecht welcomed Emil back to his laboratory at Columbia. There, Emil had access to the spectrophotometer and other equipment needed to complete his studies of the chlorophyll-protein complex and write up the results.

In studies of the size of native chlorophyll-protein complex, Emil collaborated with Edward Pickels, the co-developer with Jesse Beams of advanced air-driven models of the high-speed analytical ultracentrifuge. While they were unable to ascertain the true molecular weight of the chlorophyll-protein, it was estimated from the sedimentation constant to be at least 265,000 (Smith and Pickels 1941). These pioneering studies demonstrated that with appropriate detergents, the proteins of the photosynthetic apparatus could be solubilized, that the chlorophyll and carotenoids remained protein-bound, and that the spectroscopic properties of the chlorophyll complex in the visible region matched closely those measured *in vivo* in the green leaf. Half a century would pass before others would purify and rigorously characterize photosynthetic light-harvesting and reaction center complexes.

With the balance of the second year of his Guggenheim Fellowship still remaining, in January 1940, Emil moved to New Haven to work at The Connecticut Agricultural Experiment Station with Hubert B. Vickery, the station's energetic and productive chief biochemist (Zelitch 1985). During his stay in New Haven, Emil gained experience in methods of protein isolation and in the quantitative analysis for nitrogen and sulfur, as well as in gravimetric analysis for several amino acids.

Emil collaborated in an ongoing study to search for a substitute for edestin, the globulin of hemp seeds that had been shown to serve as an adequate source of protein in the diet of animals. Passage of the Marihuana Law of 1937 placed trade restrictions on hemp seed that amounted to prohibition. The amino acid composition of edestin had been extensively characterized, primarily in work by Vickery. Emil's research was successful in identifying a readily available substitute with very similar amino acid composition, the globulin of the pumpkin seed (*Cucurbita pepo*) (Vickery, Smith, and Nolan 1940).

Vickery was also a lecturer in the Department of Physiological Chemistry at Yale University, and through him, Emil became acquainted with the several young faculty members at Yale: Abraham White in Physiological Chemistry, with whom he formed a lifelong friendship; and two assistant professors of pharmacology, Lou Goodman and Alfred Gilman. Emil also met Horace Davenport, a postdoctoral fellow in physiology. These friendships proved to be very influential later in Emil's career.

As the end of his Guggenheim Fellowship neared in the autumn of 1940, Emil found no attractive opportunities for independent work. Jobs in universities were very scarce.

With strong backing from a Columbia classmate and close friend, Joseph Fruton, who had been working with Max Bergmann at the Rockefeller Institute for several years, Emil successfully applied for a fellowship to work in Bergmann's laboratory to further his experience in protein chemistry and enzymology. Bergmann, the last student of Emil Fischer, was regarded as the most eminent protein chemist in the world, and he attracted exceptionally gifted scientists. Emil's contemporaries in Bergmann's group included William Stein, Stanford Moore, Joseph Fruton, Klaus Hoffman, and Paul Zamecnik, all of who became his lifelong friends. The two years he spent at the Rockefeller Institute set the course for his future research.

Through the study of the stereospecificity of the reactions catalyzed by proteolytic enzymes on appropriate synthetic peptide substrates, Bergmann concluded that recognition of a chiral carbon by an enzyme requires that at least three of the groups surrounding the carbon atom must interact with the enzyme (Bergmann and Fruton 1937). Bergmann's theory was designated the "polyaffinity theory" (or the multi-point attachment theory).

A report that a crude preparation of intestinal erepsin hydrolyzed both L-leucylglycine and D-leucylglycine challenged the polyaffinity theory. Bergmann asked Emil to try differential denaturation of the crude preparation to show that these activities of the intestinal erepsin were due to distinct enzymes. Emil chose to use his experience in protein purification, along with methods developed in the Keilin laboratory, to purify a fraction (designated L-leucine-aminoexopeptidase) that had activity towards the L isomer with only a trace of activity towards the D isomer, providing "conclusive evidence that distinct enzymes cause the splitting of the two stereoisomeric peptides." In addition, Emil showed that the activity of the purified L-leucine-aminoexopeptidase depended on the presence of Mn^{2+} or Mg^{2+} (Smith and Bergmann 1941; Smith and Bergmann 1944).

Just as Emil immersed himself in very productive studies of peptidases, World War II intervened once again. Within a few days of the Japanese attack on Pearl Harbor on December 7, 1941, the United States was at war with Japan, Germany, and Italy. To contribute to national defense, Bergmann focused his research on synthetic, analytical, and inorganic chemistry problems in chemical warfare, especially on nitrogen mustards.

"We learned how to assemble the kind of stuff we needed with three-quarter-inch stainless steel pipe, because if we waited for the shop at Squibb to make this stuff, we'd still be waiting. They were so busy and overloaded and didn't have enough skilled people."

Emil was unprepared for this new direction in Bergmann's research. However, an inquiry from E. R. Squibb and Sons offered Emil an opportunity to make an important contribution to the war effort. Squibb was providing blood fractions to the U.S. Navy and marines and offered to hire him as a biophysicist-biochemist to work on the blood fractionation program. Emil accepted and at the end of June 1942, he and Esther moved to New Brunswick, New Jersey.

The challenges that Emil encountered on joining Squibb were daunting. He had no previous experience in industry, nor in managing a large crew that was ill-prepared to produce high-purity biological products. The need to start production was urgent. He summarized the situation in an oral history interview (Smith 1994):

> *"The methods devised in Edwin J. Cohn's laboratory [at Harvard] were largely devised working on a five to ten-liter scale. We would have to work on a thousand liter scale. Scaling was not simply a matter of arithmetic or multiplication; you had [to] devise different techniques to doing so. Moreover, we started with a crew of shift superintendents who were college graduates who had no experience with any of this…They had to learn how to use a pH machine, and make up buffer in quantity. They had to learn how to handle proteins and work in the cold…We learned how to assemble the kind of stuff we needed with three-quarter-inch stainless steel pipe, because if we waited for the shop at Squibb to make this stuff, we'd still be waiting. They were so busy and overloaded and didn't have enough skilled people."*

All of these obstacles were surmounted rapidly, and the group started to produce vials of sterile solution of serum albumin on a large scale, followed over time by gamma globulin,

fibrinogen, prothrombin, and other fractions. Emil was fortunate that his boss, Tillman D. Gerlough, who was also the head of his division, was an excellent scientist himself, as well as a good teacher, with more than ten years of experience at Squibb. The division handled all the protein therapeutic products, ranging from antitoxins to insulin. Emil and Gerlough worked well together. They even collaborated on the characterization of the proteins responsible for the antitoxic activity of hyperimmune horse plasma (Smith and Gerlough, 1947).

During the hectic period from 1942 to1946 at Squibb, Emil also managed to complete a substantial body of basic research to eventually fill eight papers published in the *Journal of Biological Chemistry* in 1946 and 1947. Emil left Squibb in 1946, but the company retained him as a general consultant for the next twenty years.

When the war ended, Emil was eager to return to academia and he shared his intentions with his close friends. Through a fortuitous set of events, he was soon to accomplish his objective.

University of Utah

In 1942, the University of Utah established a four-year medical school. Maxwell M. Wintrobe, a distinguished hematologist, was appointed in 1943 as the founding chairman of the Department of Medicine, with the challenge to recruit faculty and develop research programs. The faculty members he recruited included Louis Goodman as professor of pharmacology. As to the facilities for the new school, Wintrobe commented on arrival that the University of Utah offered "opportunity, but absolutely nothing more." The hospital's clinical facilities were run down and poorly administered. The medical school was housed in a dormitory constructed for World War I cavalry officers. The promised new medical center materialized only after twenty-two years (Valentine, 1990).

On the positive side, the Public Health Service Act, which was passed on July 1, 1944 authorized the Surgeon General to "Make grants in aid to universities, hospitals, laboratories, and other public or private institutions, and to individuals for such research projects as are recommended by the National Advisory Health Council, or, with respect to cancer, recommended by the National Advisory Cancer Council." Wintrobe applied to the NIH for a grant to support a program to study muscular dystrophy and other hereditary and metabolic disorders. Muscular dystrophy of a hereditary type affected many Utah families, and the wealth of Mormon genealogy data was a valuable asset to the

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proposed research. His application was approved and the very first NIH research grant, initially $100,000 annually, was awarded in 1945 to the University of Utah.

In the spring of 1946, Louis Goodman, the head of pharmacology at the university, called Emil to explore his interest in this new project. Wintrobe administered the NIH grant as principal investigator, with Horace Davenport (physiology), Leo Samuels (biochemistry), and Goodman as co-directors. Emil was offered a joint appointment as associate professor of biochemistry and associate research professor of medicine at the University of Utah, with the understanding that he would set up a laboratory for his research, but that its equipment would also be available for other activities in protein chemistry at the university. After meeting with this group, Emil accepted the offer without first visiting Utah. He later remarked that this was very fortunate (Smith 1982).

Emil, Esther, and their two-year-old son arrived in Salt Lake City in July 1946. The space available for Emil's laboratory would have discouraged those faint of heart. It was in vacant buildings that had belonged to the Army base at Fort Douglas and had been turned over to the university. "The principal laboratory was a tar-paper covered, temporary building that had been the venereal disease treatment center of the Fort. A former latrine had been converted to an animal house and a second-hand butcher's walk-in refrigerator served as a cold room" (Smith 1982).

Emil's reaction to this disappointing beginning was admirable. After ordering the benches, fume hoods, equipment, and supplies, and during the subsequent transformation of temporary building into a laboratory, he taught a course for medical students and a protein chemistry course for graduate students, wrote a paper on unpublished work he had done at the Rockefeller Institute, and wrote several other papers on the characterization of γ-globulins and seed globulins he had done at Squibb.

Emil's assistant at Squibb, Douglas Brown, joined him in Utah in January 1947 and provided much-needed help in setting up the new laboratories. Brown, who was also expert in the use of Pickels' new analytical ultracentrifuge and in the use of the Tiselius electrophoresis apparatus, made substantial contributions to ongoing research for many years and was a co-author on numerous papers. Their association and friendship

continued until Emil's retirement in 1979. After several years in the temporary quarters, the Metabolic Lab (as Emil's laboratory came to be called) took over a comfortable brick building that had been the dental clinic for Fort Douglas.

At the outset of his research in Utah, Emil's focus was on continuing studies of proteolytic enzymes he started while he was with Bergmann, with particular attention to the metal ion requirements for stability and activity. The work from 1947 to 1953 led to the publication of several papers on the tissue distribution, purification, characterization, and substrate specificity of numerous proteolytic enzymes from several different organisms. The stability and catalytic activity of many of the enzymes were dependent on specific metal ions (Smith 1951). Soon, Emil's highly productive laboratory was recognized worldwide as a leading center for the study of protein purification and characterization.

In 1949, Emil proposed that a metal ion was part of the catalytic site of metalloproteases and that it played a key role in substrate binding and hydrolysis through chelate formation with both the enzyme and substrate (Smith 1949). This paper drew attention to the structural and mechanistic details of enzyme catalysis and provoked a great deal of interest. However, at the time, no three-dimensional structures of proteins were known, and the nuances of enzyme catalysis were not understood. In his paper, Emil warned that "The present theory may of course be partially or completely incorrect," and this caution turned out to be appropriate. Looking back, he noted succinctly, "…many of the ideas turned out to be rather naïve and the postulated mechanisms are not correct…" (Smith 1991).

In the early 1950s, Emil saw the determination of the sequence of a proteolytic enzyme as an essential step towards elucidating the molecular basis of its catalytic activity. The time was ripe for this pursuit. In 1948, Sanger had completed sequencing the two chains of insulin, 21 and 30 residues long, respectively, demonstrating that "proteins are definite chemical substances possessing a unique structure in which each position in the chain is occupied by one, and only one, amino acid residue" (Sanger 1958).

At the Rockefeller Institute, Moore and Stein were developing methods for sensitive quantitative amino acid analysis and for ion-exchange chromatographic separation of peptides. They were also devising automated fraction collectors and an amino acid analyzer, using these tools to determine the amino acid sequence of ribonuclease, a single-chain protein of 124 residues containing four disulfide bonds. However, even with major advances in methodology, the complete primary structure of ribonuclease was not

determined until 1963.

Emil settled on papain, a sulfhydryl protease, as the enzyme he wanted to sequence. Starting with high quality dried papaya latex, an elegant method for the preparation of large amounts of crystalline papain was developed and the substrate specificity of the pure protein was explored (Kimmel and Smith 1954). The sedimentation coefficient of papain indicated a molecular weight of 20,500, predicting a polypeptide of ~170 residues, a sequence longer than that of ribonuclease by ~36 residues. Disappointingly, as the papain sequencing progressed, several challenges delayed the completion of this project till 1970.

Setting up the Metabolic Lab with state-of-the art instruments for protein purification, characterization, automated amino acid analysis, and peptide separation, along with increasing expertise in sequence determination, soon enabled other studies, which had exciting results. In 1959, Emanuel Margoliash arrived at the Metabolic Lab and, with strong encouragement from Emil, embarked upon determining the amino acid sequence of horse heart cytochrome c, a 104-residue protein. Within a year, he had nearly completed the sequences of most of the chymotryptic peptides.

Between 1961 and 1970 (first at Utah and continuing at UCLA), Emil's group determined the sequences of cytochromes c from human, monkey, dog, sheep, whale, dogfish, rattlesnake, *Neurospora crassa*, and wheat germ...

At that time, Emil learned from Hans Tuppy that he and Gunther Kreil in Vienna were working on the tryptic peptides of cytochrome c. The scientists immediately agreed to collaborate, which soon led to the joint publication of the complete amino acid sequence (Margoliash et al. 1961). Because cytochrome c is ubiquitous in eukaryotes, knowledge of complete sequences from a wide variety species would allow a comparison between phylogenetic trees based on protein sequences and those constructed on the basis of organismal biology. To that end, Emil and Emanuel Margoliash each embarked on sequencing other cytochromes c.

Between 1961 and 1970 (first at Utah and continuing at UCLA), Emil's group determined the sequences of cytochromes c from human, monkey, dog, sheep, whale, dogfish, rattlesnake, *Neurospora crassa*, and wheat germ, while Margoliash sequenced several others (Margoliash and Smith 1965). The independent trees were in good accord and

this result, coupled with data on hemoglobin sequences, led Zuckerkandl and Pauling (1965) to introduce the concept of the "molecular clock."

University of California at Los Angeles

In 1963, Emil left Utah to become the new chairman of the Department of Physiological Chemistry in the UCLA School of Medicine. The medical school was still in its early days. Classes for the first twenty-eight medical students began in 1951, while the school's first permanent building and the University Hospital were occupied in 1954 and 1955. Soon after arriving at UCLA, Emil changed the department name to the Department of Biological Chemistry and began a multi-year effort to build a strong, forward-looking faculty by recruiting promising, productive young scientists. Reflecting on Emil's seventeen years as chairman, Irving Zabin, who had joined the faculty before Emil's arrival and remained throughout Emil's tenure as chairman, commented, "He led the department by example, by consultation, by encouragement, and by persuasion when necessary." Early in 1965, together with Paul Boyer, Emil co-founded UCLA's Molecular Biology Institute.

At UCLA, Emil resumed with minimum of delay the research projects he had initiated in Utah. He devoted the rest of his career to the determination of the sequences of thoughtfully chosen proteins. Initially, the focus was on cytochromes c from diverse species, the sequences of which, collectively, enabled the insights into protein evolution discussed above.

In parallel, Emil launched a project to determine the amino acid sequences of subtilisins BPN' and Carlsberg, the secreted proteolytic enzymes of *Bacillus subtilis* var. amylosachariticus and *Bacillus licheniformis*, respectively. These enzymes were known to be serine proteases, inactivated by reaction with diisopropylfluorophosphate, just like the mammalian proteases of the trypsin family. The amino acid sequences, along with later crystal structure determinations by others, led to unexpected results. Even though their catalytic activities and specificity were very similar, these two highly homologous proteins differed in the residues at 82 (30%) of 275 positions. The three-dimensional structures of the two subtilisins were remarkably similar, but bore no resemblance to those of the trypsin family proteases. Surprisingly, the active sites of the subtilisins and of the trypsin family proteases all possessed the "catalytic triad" of active site aspartate, histidine, and serine residues; a common catalytic mechanism; and a conserved arrangement and nature

of binding sites for the polypeptide substrate. This remains an astounding early example of convergent evolution at the molecular level.

In 1967, James Bonner suggested that he and Emil collaborate on determining the sequence of histone IV from calf thymus and from buds of pea seedlings. Douglas Fambrough in his laboratory had shown that the corresponding pea bud and calf thymus fractions of histones III–IV, obtained by polyacrylamide gel electrophoresis, are closely similar in amino acid compositions and have identical N-terminal groups (Fambrough and Bonner, 1966). Emil readily agreed and a postdoctoral fellow, Bob DeLange, a talented protein chemist, undertook the sequence determination. The project proceeded expeditiously and the complete sequences of the two histones were published in 1969. The results were dramatic. The sequences of calf thymus and the pea histones IV were identical in 100 of the 102 positions, with two conservative substitutions: Val/Ile and Lys/Arg. These were the most highly conserved sequences known in such widely diverged organisms. Notably, there were differences in the pattern of posttranslational modification in the amount and distribution of ε-N-acetyllysine.

The sequence of calf thymus histone III revealed an even more complex pattern of posttranslational modification: with ε-N-methylation at particular lysine residues with ε-N-monomethyl-, ε-N-dimethyl, and ε-N-trimethyllysine present at each modified site, and partially ε-N-acetylated lysine residues at other positions. Moreover the histone III preparation consisted of molecules with either one or two cysteine residues. The outcomes of these studies contributed significantly to the development of the idea of the nucleosome (Kornberg and Thomas 1974).

Next, Emil embarked on an ambitious project to compare the sequences of glutamate dehydrogenases that have different modes of regulation, in terms of their expression. *Escherichia coli* NAPD-specific glutamate dehydrogenase is regulated by induction-repression, and the amino acid sequence of this protein was already known. Emil began to sequence vertebrate liver NADP- and NAD-glutamate dehydrogenases, which are regulated in expression by purine nucleoside phosphates. He also sequenced *Neurospora crassa* NADP- and NAD-glutamate dehydrogenases, which are regulated by coordinate induction/repression. This multiyear project was brought to a successful conclusion and provided valuable new insights on the structure and evolution of this class of enzymes (Smith 1979).

Other activities

The textbook *Principles of Biochemistry*, first published in 1954 and co-authored with Abraham White, Philip Handler, and De Witt Stetten, was a lifelong source of satisfaction and pride for Emil. Over twenty-nine years, the book went through seven editions and a steady dedication of hundreds of hours of work. The reward was commensurately high. "These efforts made me a better and more knowledgeable teacher," he wrote (Smith 1982).

Smith with Chinese Prime Minister Chou En-lai and translator in Beijing, 1973.

Emil was particularly respected for his many years of effort to promote international scientific cooperation, particularly with Russia and China. In 1973, as co-chairman of the Committee for Scholarly Communication with Peoples' Republic of China, he led a delegation to negotiate in Beijing the first exchange agreements between the National Academy of Sciences and the Chinese Academy of Sciences, a breakthrough ending a long period when there were no contacts between scientists in the two countries. During that visit he met one-on-one with Prime Minister Chou En-lai, Communist China's first Premier and its longest-serving leader. A picture of the two at that meeting was displayed in Emil's UCLA office on the wall facing his desk.

Emil was elected to the National Academy of Sciences in 1962. He was also a member of the American Academy of Arts and Sciences (1965) and the American Philosophical Society (1973). He was the recipient of the CIBA Foundation Gold Medal (1968) and Stein and Moore Award of the Protein Society (1987). On his retirement in 1979, his colleagues from four continents came to UCLA to participate in a memorable symposium in his honor and to share warm personal reminiscences (Sigman and Brazier 1980).

Epilogue

In an autobiographical essay (Smith 1982) and in his oral histories (Smith 1991; Smith 1994), Emil emphasized that he "owes much to the efforts of many individuals who contributed their talents both to the ideas and to the experimental work," and he recognized individually more than eighty people—PhD students, postdoctoral and senior collaborators, as well as assistants—with whom he had collaborated and many of whom he had trained at the University of Utah and at UCLA.

He expressed his gratitude for the many decades of happiness and support he had received from Esther: "without her *joie de vivre* and optimism it would not have been such fun and might not have been possible." He was very proud of his sons, Donald and Jeffrey, and particularly delighted that both had chosen academic careers, one in biochemistry, the other in medicine.

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