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CHOH HAO LI

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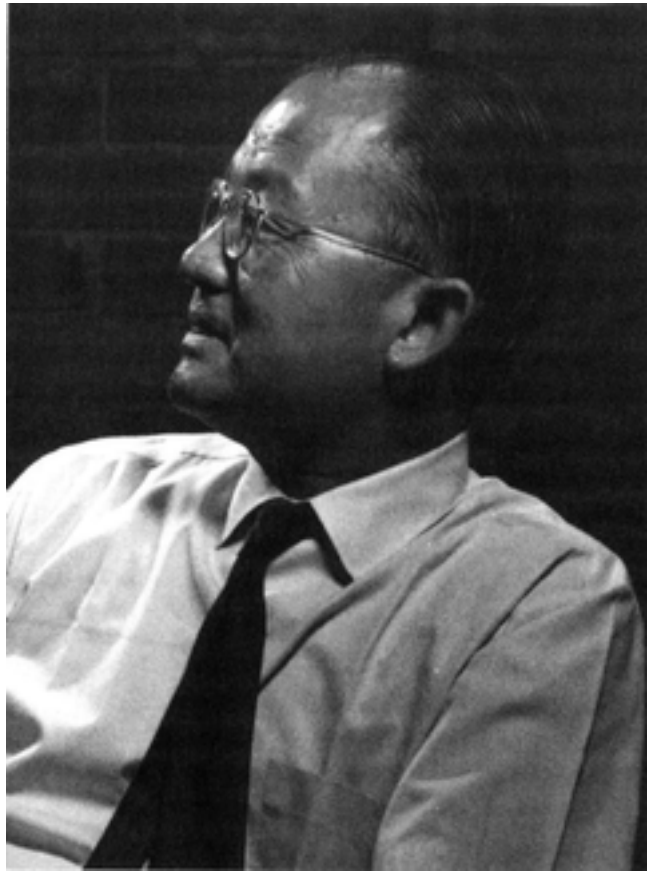
A Biographical Memoir by

R. DAVID COLE

Biographical Memoir



C. W. I.

CHOH HAO LI

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BY R. DAVID COLE

FOR A HALF CENTURY Choh Hao Li studied peptide and protein hormones, especially those of the anterior pituitary gland and for much of that time dominated the biochemistry of the field. He was first, or among the first, to purify and determine the molecular structure of adrenocorticotropin, lutropin, follitropin, growth hormone, lipotropin, prolactin, endorphin, and melanotropin. The biological properties and clinical applications of these hormones were also extensively studied in his laboratory. Li was a pioneer in the synthesis of biologically active peptides and proteins and analogs of the natural species and accomplished the chemical synthesis of melanotropins, corticotropins, endorphins, lipotropin, and growth hormone. Since peptide and protein chemistry was in its infancy when Li began his studies, he also contributed heavily to the development of techniques and methods for protein chemists.

Recognition of Li and his work was extensive abroad, as well as in the United States. Among his ten honorary doctorates were ones from the Catholic University of Chile, the Chinese University of Hong Kong, and the University of Uppsala. Li was an honorary member or fellow in fourteen societies and academies, including ones in Argentina, the

Republic of China, Chile, Israel, and India. He was elected to the American Academy of Arts and Sciences in 1963 and to the National Academy of Sciences in 1973.

An international scope also is evident in Li's twenty-six awards and medals which include the Gold Medal of the City of Milan; the University Medal, Liege; the Science Award, Academia Santa Chiara, Genoa; and the Heyrovsky Gold Plaque of Honor for Achievement in Chemistry, Czechoslovak Academy of Sciences. His major American awards are the Lasker Award, the Lewis Prize of the American Philosophical Society, and the Nichols Medal of the American Chemical Society. In 1947 the Endocrine Society gave Li his first award, the Ciba Award, to acknowledge his outstanding promise as a young researcher and then in 1981 recognized his vast record of accomplishments with the society's senior honor, the Koch Award. Li was particularly gratified by the Scientific Achievement Award of the American Medical Association in 1970 because it marked the far-ranging ramifications of his basic research—throughout medical research and practice.

Even in a brief sketch of the accomplishments that lie behind Li's honors it can be seen that a salient characteristic of his was an alertness to opportunity, even when opportunity was at the very periphery of his field of activity and even when it was risky. This might have made him ineffective by scattering his efforts were it not that once he decided to grasp a new opportunity he creatively wove it into the fabric of previous work. He had the capacity to envision what was actually possible long before most of us saw it. Therefore, Li had a knack for gambling on winners and he backed his bets with unstinting commitment of resources and personal energy.

His resourcefulness and a capacity to concentrate his effort may have been necessary for intellectual survival as

Choh Hao (C. H. to his friends) grew up in Guangzhou, China, with ten siblings, all of whom became successful scholars. One brother, Choh Ming Li, played a key role in determining where C.H.'s career would be lived out. After earning a B.S. degree in chemistry at the University of Nanking in 1933, C. H. stayed on as instructor. He took the opportunity to do research with F. H. Lee, who had just returned from the United States with a newly earned Ph.D. The research completed a project begun by Lee with W. V. Evans at Northwestern University and led to a publication in the *Journal of the American Chemical Society*, authored by the three men. This publication was another factor that determined the place where C. H. would live the rest of his life and develop his career.

His application rejected by the University of California at Berkeley, C. H. was on his way in 1935 to the University of Michigan, where his application for doctoral studies had been accepted. When C. H. stopped in Berkeley to visit his brother, a graduate student in business administration, Choh Ming advised C. H. to show the paper from the *Journal of the American Chemical Society* to Gilbert Lewis, who ruled the College of Chemistry at the university. The college had rejected C. H.'s application because they knew nothing of the University of Nanking, and had not had any graduate students from China. Lewis knew Evans, and was impressed by C. H.'s scientific paper, and admitted him to the doctoral program provisionally. Financing this opportunity was a challenge because there was severe competition for the few jobs available during the depression. Generally in the competition being from China was a disadvantage, but C. H. found an opportunity to turn it to advantage by teaching Chinese at the Chung-Mei Home for boys, about 5 miles from campus. To do this $30-per-month job C. H. invested in a jalopy and learned to drive. He took to the streets after a one-

hour driving lesson with characteristic determination and concentration, but with uncharacteristic fear. Fortunately, he did survive and by 1938 had earned a Ph.D. studying chemical kinetics with Thomas Dale Stewart.

Academic and industrial positions were extremely scarce in 1938 for chemists with fresh Ph.D. degrees, and Li felt himself very lucky to secure a position, even though it was an unusual one. It was an opening on the Berkeley campus for a chemist in the Institute for Experimental Biology, headed by Herbert Evans, a professor of anatomy and a preeminent endocrinologist. This was a high risk opportunity because it had almost nothing to do with the kind of chemistry for which C. H. had been trained. The members of the institute used various biological approaches to study endocrinology of the pituitary gland. Evans's vision of a chemical approach to endocrinology was novel, so much so that the nature of such chemistry was unclear at Berkeley and even elsewhere. As foreign as this sort of research was, Li poured himself into it wholeheartedly, grateful for the opportunity. The hormones to be studied were proteins, and protein chemistry was in its infancy. The state of the art was crystallization, centrifugation, and moving-boundary electrophoresis. Amino acid analysis, amino acid sequencing, and X-ray crystallography were only dreams, and chromatography, gel electrophoresis, and circular dichroism were not even dreamt. To make matters more bleak, hormones occurred in tissues in minute amounts and had very crude assays, whereas the little protein chemistry being practiced in 1938 was done with abundant proteins and usually with enzymes that had fairly precise assays. Only one of the pituitary protein hormones, prolactin, seemed to be pure at the time, and it was not even clear how many other pituitary hormones there were. C. H. came to see the potential of a field he might have somewhat to himself if he was

lucky, smart, and hardworking. In any case he took the gamble and won because he was lucky, smart, and hard-working.

Although Li collaborated some with another chemist who joined the group, Heinz Fraenkel-Conrat, for the most part during the first decade he worked alone in a basement lab. For the biological aspects of his research he had strong support from the institute's biologists such as Evans, Miriam Simpson, William Lyons, William Reinhardt, Willet Asling, and Leslie Bennett. In the first decade Li published 126 papers, including announcements of the preparation of highly enriched extracts of corticotropin (ACTH), lutropin (LTH or ICSH), and follitropin (FSH), and the purification of somatotropin (STH or growth hormone). He also served on the faculty of the university as lecturer in chemical morphology (1942-44), and as assistant professor (1944-47) and then associate professor (1947-49) of experimental biology.

In 1949, as a new generation of techniques for protein chemistry was aborning, Li took advantage of a Guggenheim fellowship to study peptide chromatography with Arne Tiselius in Uppsala. He arrived in Europe at an opportune moment. In conversation at a conference C. H. heard of promising experiments on the determination of amino acid sequences in insulin, and so he changed his plans to spend a month with Fred Sanger and Rodney Porter at the University of Cambridge. These experiences in Sweden and England set the research approach of Li's lab for years to come.

Returning to Berkeley in 1950, Li established the Hormone Research Laboratory and was appointed its director and professor of biochemistry and experimental endocrinology. The establishment of the Hormone Research Laboratory separate from the Institute of Experimental Biology was instigated by Robert Sproul, president of the University

of California, who was always eager to forestall the loss of rising stars to other institutions. The chance to build a large research team was rare in those days and to do so would severely reduce Li's time at the lab bench, as well as turn him to the unfamiliar tasks of administration, political maneuvering, and raising financial support. C. H. was an instant master of those unfamiliar tasks. Initially the university provided all the support for the laboratory, but the need for major outside support arose almost at once. The extensive array of sources for financial support that we know today was not available in 1950, but C. H. was quite effective, and before he retired he had tapped thirty-two public and private sources. Of extraordinary help to C. H. was Mary Lasker, who not only gave generously from her own foundation, but introduced Li to productive contacts in government agencies and to Maxwell Geffen and Charles Allen, Jr., who became major, long-term benefactors of the laboratory. Mrs. Lasker made annual visits to the lab with her scientific advisor. On those occasions, one by one, those of us in the lab joined C. H. in his office with the visitors. I clearly recall nervously taking my turn, chatting over a cup of especially delicious jasmine tea, and then presenting my most exciting recent findings. After being in the lab somewhat longer it dawned on me that this choice tea was not served on any occasion other than Mary Lasker's visit–that jasmine tea was her favorite. C. H. was attentive to detail in all phases of his work.

In 1952 when I joined the Hormone Research Laboratory (HRL) as a graduate student it was already thriving in rooms scattered from the basement to the fourth floor of the Life Sciences Building on the Berkeley campus. The research staff consisted of David Chung, Peter Condliffe, Jonathan Dixon, Irving Geschwind, Ieuan Harris, George Hess, Anthony Levy, Harold Papkoff, Ning Pon, and Jerker

Porath. Through the years many famous researchers visited and many worked for a while in the lab. Li made a point of generously sharing the time of the famous ones with all of us; it was a heady experience for a graduate student. By 1983 when C. H. retired the HRL had moved (in 1967) into contiguous space that C. H. designed at the San Francisco campus of the university, and it had been the training ground for more than 300 visiting scholars, postdoctoral associates, and graduate students. C. H. never gave up experimenting with his own hands, and his unbounded enthusiasm for working at the lab bench infected us all. Li was a good mentor with a style that used modeling and encouraging rather than explicit instructing. Indeed, C. H. was especially effective as an encourager and he consistently took pains to enhance morale in other ways as well. The HRL in San Francisco was even well decorated. When I visited there Li proudly showed me the paintings he had hung in the lab as well as in his office. Although my recollection might be colored by nostalgia for the sweet simplicity of graduate years I recall a lot of laughter and excited discussion; it was fun and hard, driving work. My impression is that C. H. was successful in maintaining an ambience of joy, excitement, and strong friendship within the HRL throughout its history. The family-like affection of the large numbers who were associated with C. H. in the HRL was evident in enthusiastic reunions on the twentieth and thirtieth anniversaries of the founding of the HRL and on the celebration of C. H.'s sixtieth birthday. Many who attended came from the far ends of the world; the HRL was a markedly cosmopolitan (and democratic) community. The HRL had a personality—in many ways the personality of C. H. himself.

The research productivity of Li and his HRL was so vast and multifaceted that severe selectivity is needed to fit a discussion of it into this memoir. Such a selective story could

be told from many different angles, but I choose to tell it along lines that C. H. himself used on occasion. This traces the trail from corticotropin to lipotropin to endorphin and it has the advantage of showing the progression in Li's research program over the whole history of the HRL. Moreover, the story illustrates Li's alertness to opportunity.

Although an extract had been greatly enriched in adrenal stimulating activity while C. H. still worked with Herbert Evans, by 1950 C. H. was in a race with three pharmaceutical firms for the complete purification of corticotropin (ACTH). Two of the pharmaceutical firms published the purification of a large active fragment of pig corticotropin (Armour) and intact pig corticotropin (American Cyanamid) before the HRL published its isolation of intact sheep corticotropin in 1953. Actually, pure corticotropin had been obtained by the HRL well before the publications of the pharmaceutical firms, but Li's team delayed publication while they attempted the replication of their initial success. Unfortunately, replication was delayed because the sheep pituitaries used in the first several months of frustrated attempts had been previously stored by the supplier in a warehouse next to one that burned down, evidently allowing the frozen pituitaries to thaw and refreeze. When a new batch of starting material was used the initial results were replicated. While C. H. was disappointed to be late in publishing he took this bad luck stoically. Since C. H.'s competitiveness is commonly recognized, I note to his credit that he never publicized the spoiling of the starting material as an excuse for failing to purify corticotropin before the others.

In 1955 the amino acid sequence of corticotropin was published by Li's lab. C. H. saw in it an opportunity to test two notions that had fascinated him for several years despite their unpopularity with most other protein chemists. One of these notions was derived from the observation that

even the purest lab preparations of hormones generally had biological activities overlapping those of other hormones. Although most workers explained this by cross-contamination, C. H. felt that the activities overlapped because portions of the structures were homologous from one hormone to the next. The second notion that fascinated C. H. was that biologically active fragments could be derived from hormones because qualitatively the basis for activity resided in a limited region of the molecule, while other regions modulated the basic activity. Many of us in the lab in the early 1950s, myself included, looked at this notion askance, but this notion and the first one became major themes in the program of the HRL. It can be seen that Li's position was vindicated as a generality for peptide/protein hormones. The first notion was confirmed in 1956 when Ieuan Harris in Cambridge and Li's lab in Berkeley learned the amino acid sequence of the melanocyte-stimulating hormone, melanotropin (MSH). Corticotropin preparations also stimulated melanocytes to some extent and it became evident that the MSH-like activity of ACTH preparations was inherent because the 18-residue sequence of MSH was found within the 39-residue sequence of corticotropin.

The notion that biological activity could exist in a fragment of a hormone had been tested for several years by attempting the isolation of active fragments from enzymic digests of hormones. The results, however, were vulnerable to the criticism that the isolated fragments were contaminated with minor amounts of intact hormone—such was the reliability of peptide separations then. Li saw that a rigorous proof could be obtained by chemical synthesis of peptide fragments. Moreover, he innovatively envisioned that the synthesis of analogs would permit correlations of structure with biological activity that could reveal general principles and that some might be useful in drug design. Work-

ing out the vision, however, would be a high-risk commitment. Nobody in the HRL knew about peptide synthesis and the best that was done anywhere else produced meager yields of relatively short peptides. Nevertheless, C. H. gambled and took a sabbatical leave in 1957 to learn peptide synthesis with Robert Schwyzer in Basle. In 1958 with Schwyzer's help Li established a synthesis team in the HRL at Berkeley, a team consisting of Eugen Schnabel, Tung-Bin Lo, Johannes Meienhofer, Janakiraman Ramachandran, and David Chung. By 1960 this team had synthesized longer and longer peptides until they made one containing the first 19 residues of corticotropin and were delighted to find that this peptide had adrenal-stimulating and melanocyte-stimulating activity, just as did the intact hormone of 39 residues. Peptides shorter than 19 had MSH activity, but no ACTH activity. Many 19-residue analogs were studied and detailed correlations were made between structure and activity.

Immediately after Bruce Merrifield introduced solid-phase peptide synthesis in 1963 James Blake and Donald Yamashiro put it to work in the HRL. After making some significant modifications in the method they were able to synthesize corticotropin-related peptides and ultimately to accomplish in 1973 the synthesis of the entire hormone. One of the things that was learned as this work progressed was that the addition of residues between 19 and 26 increased the ACTH potency of the peptide progressively up to the natural level. The experience gained in synthesis of ACTH was valuable in subsequent syntheses of other protein hormones—lipotropin, endorphin, and a growth hormone.

Attempting to improve yields of naturally occurring ACTH, Yehudith Birk and C. H. made a minor change in the purification procedure and, among other things, this resulted in the appearance of a new peak in one of their chromatograms. The peptide represented by the new peak was iso-

lated and found to be chemically different from all the known hormones. Since analogs of ACTH fragments were then being assayed for lipolytic activity the new component was also tested. It proved to be much more potent in lipolysis than corticotropin and so it was named β-lipotropin (β-LPH). It lacked ACTH activity but had an MSH activity equivalent to that of corticotropin. Normally the discovery of the activity of a protein precedes its purification and characterization, but Birk and Li, with some combination of luck and intuition, had reversed that order. It will be seen shortly that luck and intuition continued to play a role as research on lipotropin progressed.

When the amino acid sequence of lipotropin was deciphered in 1965 it was clear why β-LTH had MSH activity. The 18-residue sequence of MSH was contained within the 91 residues of β-LTH and, therefore, lipotropin can be viewed as a prohormone from which MSH is derived by protein processing. Always alert for active fragments and intrigued with the implications of protein processing, Chrétien and Li studied a side fraction from β-LTH preparation and in 1967 found a new lipotropin, which they labeled γ-LTH. It consisted of the first 58 residues of β-LTH and contained the MSH sequence as its carboxyl terminal region. When David Chung and C. H. were searching for LTH in extracts of camel pituitaries they failed to find intact LTH, but they did find a 31-residue peptide that consisted of residues 61-91 of β-LTH. It represented the carboxyl region of β-LTH and accounted for nearly the whole difference between β-LTH and γ-LTH. This peptide was named β-endorphin (β-EP). Avram Goldstein recognized a 5-residue sequence in β-LTH that matched Met-enkephalin and wrote to C. H. for related peptides to be assayed for morphine-like activity. Li sent him β-EP, which C. H. knew had the five amino acids of Met-enkephalin at its amino terminus. The opioid activ-

ity of endorphin was thus discovered in early 1976. Once again a peptide hormone had been discovered from its chemical properties before it was identified biologically. One conclusion to be drawn from this work is that β-LTH in addition to being a lipotropic hormone in its own right is a prohormone for not just one, but three hormones, γ-LTH, β-MSH, and β-EP. As C. H. typically did following the initial purification of a hormone, he and his colleagues went on to study the biological properties of β-EP and synthetic analogs of it. In this case the potential for clinical applications to drug addiction and psychiatric problems added extra drive as Li followed up the chemical studies with many biologists and clinicians as collaborators. Undoubtedly, the follow-up work will now be continued by others.

In summary, I told a story that sketches out a lasting legacy that C. H. left to basic science. This legacy includes an understanding of the structural bases for the activities of five pituitary hormones of the anterior and intermediate pituitary. Additionally, Li's elucidation of an unusually rich example of the protein processing of a prohormone, β-lipotropin, was part of the story. Hopefully this story illustrates both Li's genius and the general nature of the stream of consciousness as the research program developed in the HRL.

Unfortunately, the story bypassed parallel research done by C. H. and the HRL on prolactin, lutropin, follitropin, growth hormone, and chorionic gonadotropins. It has not covered the extensive comparisons of amino acid sequences in most of these hormones across a very wide range of animal species, comparisons that were a rich source of data on evolution, and on structure/function relationships. Neither has it even sketched the far-ranging biological studies on all these hormones. The story was told, after all, by a protein chemist under the pressure of severe space limita-

tion. No doubt one of C. H.'s more biologically or medically oriented colleagues would have written with profoundly different emphases. They might have described a legacy that includes a vast store of information on metabolic and other biological effects of several of the pituitary hormones and on their evolutionary relationships. Li left a body of knowledge which will surely be a foundation that future biology will inevitably build on.

One part of Li's legacy to medical practice must not be passed over–the availability and knowledge of human growth hormone. The production of genetically engineered growth hormone and its widespread clinical use are direct extensions of Li's research program and critically dependent on it. Probably some of the deleterious effects of the overzealous use of growth hormone in the clinic might have been avoided if more physicians had paid more attention to Li's biological studies. The legacy of biological and clinical research by Li includes studies of most of the pituitary hormones, not just growth hormone. Furthermore, the legacy extends far beyond the publications that bear Li's name because he contributed substantially to clinical research by responding to requests for samples of the hormones handled in the HRL. C. H. was well known for his generosity in sharing his preparations without obligation.

Another part of Li's legacy to the clinic must be added even though it is somewhat tangential to the general line of his work. There was another of those side products that Li was alert enough to purify, characterize by amino acid sequence, and synthesize. Perhaps C. H. did it searching for active fragments of growth hormone, but in any case the side product turned out to be a growth factor active in cell cultures, and so it was named insulin-like growth factor-I. The significance of the factor for the public became clear while this memoir was being composed. The newspapers

announced that insulin-like growth factor-I is effective in substantially slowing the progress of amyolateral sclerosis (Lou Gehrig's disease), and that the stock of the companies producing it by genetically engineered processes had risen abruptly. Even if the factor does not have further application to other diseases of nerve degeneration, it appears it will be a boon for many.

The legacy C. H. left to the profession of science can be outlined in terms of his service at the policy level. He was on many advisory boards, but special mention must be made of his contributions to the founding of biochemistry programs as he served on the Scientific Advisory Board of the Institute of Biological Chemistry, Academia Sinica, Taiwan, and the Academic Advisory Board of the Chinese University of Hong Kong. The editorial work C. H. did was prodigious, having included membership on numerous editorial boards, advisory boards of journals, and editorships of individual volumes. Two of his most outstanding editorial contributions were as editor of the series *Hormonal Proteins and Peptides* from its beginning in 1973 until his death in 1987 and as one of the executive editors of *Archives of Biochemistry and Biophysics* (1979-87). Perhaps Li's most lasting legacy to scientific publication is in the *International Journal of Peptide and Protein Research*, which he served as co-associate editor from 1969 to 1976 and as editor in chief from 1977 until his death. During his tenure the circulation increased and the journal established itself as a major vehicle for publication in its field.

To those of us who had the privilege of direct contact with C. H. he left a more personal legacy—the memory of his character and style. Although this could be expressed in the context of the laboratory it can also be typified by the social gatherings we used to have at the Li's in Berkeley. As a host C.H. did not dominate the group with his ego as

other public stars sometimes do. Instead, he contrived to catalyze amicable interactions among all those present. He was more like a symphony conductor than a concerto performer. He had gracious and quite subtle ways of encouraging participation by those who would otherwise tend to stay on the periphery. Annie's graces complemented his so that these house parties hold a warm place in my memory. C. H. had a carefully acquired American sense of humor that added to our fun, and it was the more charming because we could sometimes detect that it did not come to him naturally. In any case, his kind concern that we all enjoy each other was manifest in the lab and outside and it remains a bond of spirit among those who worked in the Hormone Research Lab at one time or another.

An appreciation of art was conspicuous in C. H., and the Li home showed it. C. H. never missed a chance to brag about the art of his wife Annie, pointing out the art objects that she had created and reminding us that Annie had designed their house. He was pleased to tell how his daughter Eva designed the covers for two books published on anniversaries of the HRL's founding. In addition to his pride in Annie's art C. H. had a profound respect for her judgement. He commonly laid out his writings for her to read, expecting to discuss her reactions over the dinner table. Even though Annie was not trained in science C. H. valued her opinions about the significance of the reported research and particularly about how effectively he had communicated it. Li's twin interests in science and art may well be reflected in the lives of his children. The children were frequently included in lab parties and C. H. was very vocal about his pride in them. His son Dr. Wei-i Li is a surgeon in Bellevue, Washington; his artist daughter, Mrs. Eva Li Hill, lives in Toronto; and his veterinarian daughter, Dr. Ann-si Li, is in Berkeley. His family has made clear their pride in

C. H. by endowing a professorship in his name at the University of California in Berkeley. Professional colleagues have also sought to make clear the honor with which they remember C. H. by establishing memorial lectureships at the university in Berkeley and also at the Academia Sinica and National University of Taiwan.

It seems lame to close with the cliche that Choh Hao Li ought not to be forgotten and certainly won't be, but after all, that is the plain truth.

TO ANNIE LI I am deeply indebted for a wonderful visit during which she spoke from a warm and loving heart of experiences that illuminated her husband's feelings as well as his actions. I am grateful to Professor Howard Bern for his personal reflections, which he gave at the dedication of the Choh Hao Li Professorial Chair in Biochemistry and Molecular Biology at the University of California, Berkeley. Much of the story on corticotropin/lipotropin/endorphin was based on an article written by Li as chapter 10 in *Selected Topics in the History of Biochemistry: Personal Recollections*, ed. G. Semenza. Amsterdam: Elsevier Science Publishers (*Compr. Biochem.* 35[1983]:333-52). Other information came from two books edited by Li entitled *Hormone Research Laboratory 1950-1970* and *Hormone Research Laboratory 1950-1980*, which were published as limited editions by the University of California Press to commemorate the twentieth and thirtieth anniversaries, respectively, of the founding of the laboratory. It was helpful to read the preface by Jerker Porath and the forward by the editors in *Proceedings of the International Workshop on Hormones and Proteins (1974)*, eds. T. A. Bewley, L. Ma, and J. Ramachandran, published by the Chinese University of Hong Kong; and to read the dedication by J. Ramachandran and J. Meienhofer in *Archives of Biochemistry and Biophysics*, vol. 225, 1983. The last two books commemorated Professor Li's sixtieth and seventieth birthdays, respectively.

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