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Introduction

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In Denmark, protein chemistry had never had a stronger position than during the twenty years Kaj Linderstrøm-Lang was head of the Department of Chemistry of the Carlsberg Laboratory. He was born in 1896, and came as a young chemical engineer to the laboratory in 1919 to work as assistant to Professor S. P. L. Sørensen. The laboratory was already well known internationally through Sørensen's studies of hydrogen ion concentrations and osmotic pressures of protein solutions, and from him Lang learned to crystallize proteins, to make Kjeldahl analyses and to measure pH with the utmost precision.

He soon became deeply interested in physical chemistry and in 1923, one year after Debye and Hückel had formulated their theory of ionic interactions, Lang demonstrated his profound knowledge of mathematics and thermodynamics, by extending their work to include ionization of proteins and polyvalent electrolytes. For his thesis he studied casein, and resolved a long dispute by demonstrating that this protein was not a homogeneous substance but a complex mixture of related components. In 1926 he went to Munich to study with Professor Willstätter, who was engaged in major work on the proteolytic enzymes, and upon his return to Copenhagen, he developed an improved method for determination of the free amino groups released by proteolysis, the so-called acetone titration.

In several of these early investigations Lang had collaborated with foreign guests who visited the laboratory for short periods. A lifelong collaboration however was started in 1930, when the young Austrian scientist, Heinz Holter, arrived at the laboratory. The two started upon an ambitious project to develop methods of such high sensitivity that they could determine the localization of enzymes within single cells or fragments of cells. They realized this would require much better enzyme determination methods than the ones which were known at that time, and with great ingenuity and a lot of hard work they first created a complete set of micro tools, such as capillary pipettes and capillary burettes, which increased the sensitivity of the enzyme methods about 1000-fold. However, to complete their project they needed even more sensitive methods, and in the following years Lang developed two, elegantly based on simple physical principles: the Cartesian diver for microgasometric measurements, and the density gradient column for determining the specific gravity of very small droplets of liquid.

With the gradient column he could follow enzymatic reactions which were accompanied by an increase in the number of ionized groups, since the resulting electrostriction would slightly increase the specific gravity of the reaction mixtures. By measuring the movements of small drops of the reaction mixture in a density gradient column, Lang demonstrated that he could follow the enzymatic hydrolysis of peptide bonds. Both the Cartesian diver and the density gradient method were about 100 000-fold more sensitive than the methods known when they started their project, and thus it finally became possible for them to work with single cells or fragments of cells rather than with whole tissues. The ultramicromethods were received with much interest and Lang was invited to give lectures in many places, with the result that the laboratory soon was crowded by a large number of enthusiastic young visitors who desired to learn the new techniques.

When Sørensen retired in 1938, Lang became head of the Department of Chemistry and returned to his protein studies, while the further development of the micromethods was left to Heinz Holter. In his new position, one of Lang's first works dealt with the volume changes accompanying the hydrolysis of peptide bonds by proteolytic enzymes. He observed that in addition to the normal contraction due to the number

of peptide bonds being hydrolysed, there was a large initial contraction by globular proteins, which he was able to correlate with the denaturation of the proteins.

In 1946 when I arrived at the laboratory, Lang was interested in measuring the amount of water bound to protein molecules. While we developed a micromethod for this purpose with ovalbumin as a model protein, we saw that the ovalbumin we regenerated had changed crystal form. Lang was so excited about this unexpected result that the hydration studies for the time being were put aside – actually they were never completed. After a few months of hectic work we could prove that the ovalbumin had been changed to another protein, plakalbumin, through a limited proteolysis, caused by a novel bacterial enzyme, subtilisin.

Under Lang's inspiring guidance, limited proteolysis became a major topic in the laboratory, with assistants and visiting scientists investigating the action of subtilisin on a variety of proteins, using modern equipment like spectrophotometers, electrophoresis apparatus, analytical ultracentrifuge and column chromatography, which all came to the laboratory in the 1950s.

Lang never wrote a book, but in 1952 he delivered a series of lectures at Stanford University, the Lane Medical Lectures, in which he summarized his work with micromethods, his ideas on the biological synthesis of proteins and his studies of both deep and limited proteolysis.

After Pauling and Corey had formulated the concept in 1950 that hydrogen bonded helical structures might be important parts of globular proteins, Lang wanted to find a probe of such structures. Optical rotation was first used and although it made a clear distinction between native, globularly folded proteins and denatured proteins, so many factors influenced optical rotation that it was not possible to obtain from these experiments a quantitative measure of the hydrogen bonded structures. Looking for a more direct method, Lang reasoned that peptide hydrogens involved in helical structures might be less reactive than free peptide hydrogens. He hoped such decreased reactivity would be reflected in a measurably slower hydrogen exchange rate with the surrounding water for hydrogen bonded peptide hydrogens than the exchange rates for free peptide hydrogens.

In the first half of the 1950s Lang used all his experimental skill in designing micromethods to determine peptide hydrogen exchange rates, and in his final method he dried a small protein sample by lyophilization in a closed system, or cryosublimation as Lang called it. The dry protein sample was then incubated with deuterium oxide to exchange all labile hydrogens, surplus deuterium oxide was removed by a second cryosublimation, and ordinary water was added. The back exchange of deuterium to the solvent water was then followed by taking samples of the mixture at appropriate intervals, cryosublimating the samples and determining the deuterium content in the isolated water samples in the gradient tubes.

With this method Lang confirmed the rapid exchange of N- and O-bound protons in small peptides, and the dramatic slowing of the exchange rates produced by the formation of hydrogen bonded structures in globular proteins, and he could even begin to make quantitative estimates of the number of protons in various exchange classes. These results strengthened Lang's idea that proteins were flexible structures, that they had motility, as Lang said.

The scientific achievements of Linderstrøm-Lang made the Carlsberg Laboratory of the 1950s an international centre for protein research. Practically everybody in biophysics came to visit him at one time or another, and to the young scientists working in his laboratory he became not only an inspiring leader, but also a good friend who always had time to listen to their problems. It should be added that Lang was far more than a gifted scientist. He had outstanding artistic talents and if his scientific career had not diverted him, I am convinced he could have had a professional life as a writer, a painter or perhaps as a musician. Many of his coworkers remember him from parties, where in the company of friends he revealed his happy spirit, and unfolded his talent for entertaining. At the famous Christmas parties he demonstrated his pronounced ability for making caricature drawings, and it was a tradition that everybody working in the lab should be portrayed by him in this fashion. Lang also liked to travel to meet friends and colleagues, and his trips were usually loaded with meetings, official and informal, lectures and entertainment, in a whole series of different cities.

As a natural consequence of Lang's understanding and insight into the problems of science he was given many administrative tasks, such as President of the Danish Academy of Technical Sciences, and President of the Council of Technical-Scientific Research. His foreign colleagues also showered him with honours. To mention just a few: Fellowship of the Royal Society, London; foreign associate of the U.S. National Academy of Sciences; visiting professorship at Rockefeller University, New York; and honorary doctors degrees at many universities. Through his many personal contacts, Lang also came to play an important role in the creation of the International Union of Biochemistry. This organization elected him President in 1958, but unfortunately his illness and death in 1959 prevented him from ever taking up this post. It was only natural that a large group of his friends and colleagues should want to honour his memory by creating a Kaj Linderstrøm-Lang endowment fund to reward scientists for outstanding achievements within those fields in which Lang had worked.

So far the Kaj Linderstrøm-Lang prize has been awarded to 12 outstanding scientists:

1966 Prof. Walter Kauzmann, Princeton Univ., USA
1969 Prof. E. Katchalski-Katzir, The Weizmann Institute, Rehovot, Israel
1972 Drs Stanford Moore and W. H. Stein, The Rockefeller University, New York, USA
1976 Prof. Pehr Edman, Max-Planck-Institut für Biochemie, München, Germany
1978 Prof. Frederic M. Richards, Yale Univ., USA
1980 Prof. Bert L. Vallee, Harvard Medical School, Boston, USA
1982 Prof. Harold A. Scheraga, Cornell Univ., Ithaca, USA
1986 Prof. R. J. P. Williams, Univ. of Oxford, England
1989 Prof. Louise N. Johnson, Univ. of Oxford, England
1992 Prof. Harry B. Gray, California Inst. of Technology, USA
1996 Prof. Kurt Wüthrich, ETH, Zürich, Switzerland

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