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The Evolution of Protein Structure and Function

Edited by
DAVID S. SIGMAN
and
MARY A. B. BRAZIER

UCLA FORUM IN MEDICAL SCIENCES

NUMBER 21

The Evolution of Protein Structure and Function

A SYMPOSIUM IN HONOR OF PROFESSOR EMIL L. SMITH

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Preface

The symposium "Evolution of Protein Structure and Function" was held June 28–29, 1979, in the Dickson Art Auditorium, University of California Los Angeles (UCLA). Its objective was to honor Professor Emil L. Smith on the occasion of his retirement as Professor and Chairman, Department of Biological Chemistry, School of Medicine, UCLA. The papers presented by Emil's colleagues, friends, and students from all phases of his long and varied scientific career provided a valuable review of enzymology, protein chemistry, and biochemical evolution, and prompted the publication of these proceedings as a volume in the UCLA Forum in Medical Sciences series.

The warm personal reminiscences interwoven into the contributions and some others reproduced in Appendix I obviate the need for a formal biographical sketch. These remarks, as well as the enthusiasm and interest of all those participating or attending the symposium, clearly convey the high esteem and regard felt toward Emil. Representative publications, reflective of the broad range of his research interests, are listed in Appendix II.

The symposium was made possible by the generous financial support of the UCLA School of Medicine and the Calbiochem–Behring Corporation. Dean Sherman Mellinkoff and Associate Dean A. Fred Rasmussen, Jr., provided immediate support and warm encouragement for the entire project.

Special thanks are due Douglas Brown and Katherine Kanamori for assistance in conducting the symposium. Assistant Dean Byron Backlar was instrumental in arranging for the publication of the proceedings in the present form. Melody Horner, Assistant Editor of the UCLA Forum series, played a central role in the editing and organization of the manuscripts.

DAVID S. SIGMAN
MARY A. B. BRAZIER

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Introductory Review to a Symposium Concerned with Forty Years of Research on Proteins

STANFORD MOORE

The Rockefeller University
New York, New York

The contributors to this symposium spoke of advances in protein chemistry during four decades in the career of one of the most productive contemporary investigators of the subject. This occasion, in honor of Emil L. Smith, took my thoughts back to when I first met him when he joined Max Bergmann's laboratory at The Rockefeller Institute for Medical Research in 1940. I respected him as an experienced scientist who had already written an impressive series of papers on photosynthesis and chlorophyll–protein complexes (e.g., refs. 1–3) from the laboratory of Selig Hecht at Columbia University and in cooperation with David Keilin at the Molteno Institute in Cambridge. He had publications on seed globulins (e.g., ref. 4) with Hubert Vickery of the Connecticut Agricultural Experiment Station and proceeded to publish with Bergmann a pioneering paper (5) on the peptidases of intestinal mucosa (Fig. 1), a communication that marked the beginning of his experimental concern with enzymes; the bibliography of the 1944 article provides a glimpse into the European heritage of the chemistry of peptides and peptidases in that epoch; it began with the name of K. Linderstrøm-Lang and closed with that of E. Abderhalden. The staff of The Rockefeller Institute in 1940 reflected the same tradition; we recall lunching on occasion with Karl Landsteiner, Leonor Michaelis, or P. A. Levene. Today the bibliographies of current papers in our field reflect the truly worldwide growth of biochemistry in the intervening years, an enterprise in which Emil Smith has been a major contributor as an experimentor and educator and through his concern for science at the international level. The breadth of participation in this symposium warmly illustrated the scope of his scientific missions.

THE EVOLUTION OF PROTEIN STRUCTURE AND FUNCTION

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THE PEPTIDASES OF INTESTINAL MUCOSA

BY EMIL L. SMITH AND MAX BERGMANN

(From the Laboratories of The Rockefeller Institute for Medical Research, New York)

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Etc.

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Fig. 1. From Emil Smith's first paper on enzymes (5) in 1944. (By permission.)

During these four decades Emil Smith and his associates have explored a remarkable number of aspects of protein chemistry; the list of proteins studied in depth includes aminopeptidases, carboxypeptidases, γ-globulins, cytochromes, papains, subtilisins, histones, and glutamic dehydrogenases. Through direct participation, and through the influence of example, Emil is appreciated by protein chemists working on a very wide variety of researches.

John Pierce has asked me, in the spirit of the following addresses, to focus this essay in considerable part on current experiments from our laboratory, with a measure of history as to how our researches have evolved since Emil and I were among the apprentices in the Bergmann laboratory; that is the limited theme of the following paragraphs. The breadth of this symposium rests on the sum of its contributions.

AMINO ACID ANALYSIS

In a report with Vickery on the amino acid composition of seed globulins in 1941 (4), Emil Smith and his co-authors undertook to determine three amino acids, arginine, tyrosine, and tryptophan; the methods used were gravimetric or colorimetric. The state of the analytical art at that time was not encouraging. For example, in those years, William H. Stein and I had been assigned by Bergmann the task of seeing whether we could develop new methods for determining several amino acids, including glycine and leucine, that did not have unique functional groups. We were struggling with the design of a new approach to gravimetric analysis (6, 7), with precipitating agents pioneered by Bergmann. The aim, in the tradition of organic chemistry, was to be able to express the complete composition of a protein in terms of the constituent amino acids, but the goal seemed far away. Erwin Brand, at Columbia, was

making a major effort to do this for β-lactoglobulin by the combined use of chemical, microbiological, and gravimetric methods (8). When Stein and I returned to amino acid analysis after the war, the renaissance in chromatography stimulated by Martin and Synge (9) in England was under way. Their concept of partition chromatography, with starch or cellulose as the stationary phase, was rendering the chromatographic method applicable to many classes of water-soluble compounds. Also, Lyman Craig, who was our neighbor on the fifth floor of Flexner Hall, had introduced countercurrent liquid–liquid distribution (10) as a separation method that further evidenced the potential resolving power of multiplate systems. Stein and I decided to see whether we could develop quantitative chromatographic methods for amino acids. We were very happy in those days, when, after considerable developmental work, which included the design of a drop-counting fraction collector (11) and a quantitative photometric ninhydrin method for analysis of the effluent (12), we were able to analyze an acid hydrolysate of serum albumin or β-lactoglobulin in 2 weeks by running three starch columns, with alcohol–water eluents, to resolve all overlaps (13,14). The first user of our starch column procedure, outside of our laboratory, was John Pierce, then working across the street with Vincent du Vigneaud at Cornell University Medical College (15); they thus determined the composition of a hydrolysate of purified beef oxytocin (Fig. 2). At about this time synthetic ion exchange resins came on the market and the time for a complete amino acid analysis was reduced to one week by developing aqueous buffer systems for the elution of amino acids from sulfonated polystyrene columns (16). Emil Smith's laboratory at the University of Utah was one of the first users of the ion exchange, fraction-collector procedure; it was Joe Kimmel who assumed primary responsibility for placing the method in operation for the determination of the amino acid composition of crystalline papain (Fig. 3) in 1954 (17). I recall one special feature of the early analyses in Salt Lake City. It was

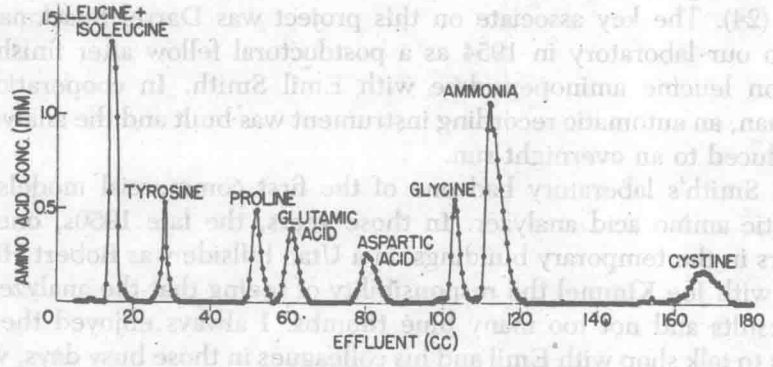

Fig. 2. Separation of the amino acids from a hydrolysate of bovine oxytocin on a starch column [Pierce and du Vigneaud (15), by permission]. A second column was run to separate leucine and isoleucine.