Obituary
Recollections of Sidney Bernhard
(1927-1988)

Friends and former students of Sidney Bernhard met at the Heceta Head Lighthouse on the Oregon Coast last July (1989) to honor his contributions to science. Those present took this occasion (one year after his sudden death on 24 July 1988) to reflect on the many facets of his scientific and human legacy.

The ***Lighthouse Conferences in Molecular Biology*** were initiated by Sidney in 1975 to provide a stimulating environment where established scientists and young investigators could share scientific knowledge and provocative ideas, while enjoying the beauty of the Oregon Coast and the very special homemade seafood dinners that Sidney arranged. The atmosphere was always very friendly and a true reflection of Sidney's many abilities in science, music and art. This same excitement was there in July, the sorrow for Sidney's absence being overcome by the feeling of his lively presence in our thoughts, our scientific sessions and in every activity we engaged in during the Conference. Sidney was a truly great scientist, a man whose humanity strongly influenced many of those who became acquainted with him and, for many of us, our best friend.

Conference participants included colleagues who had worked with Sidney either as graduate students, post-doctoral fellows or faculty in the Institute of Molecular Biology at the University of Oregon and their students. Colleagues from other universities, artists from the Eugene area, and members of Sidney's family were also present. During a rainy afternoon, these close friends and loved ones gathered to tell stories of their experiences with Sidney. In keeping with traditions established at earlier Lighthouse Conferences, we viewed the works of filmmaker Ron Fenne about the Pacific Northwest.

The meeting

The subject of our 1989 Lighthouse Conference was 'Interactions in Molecular Biology'. Peter von Hippel and Gian L. Rossi opened the Conference with tributes to Sidney Bernhard's contributions to science, and recollections about his life. The topics presented in the scientific sessions included chemical bonding in enzyme catalysis and enzyme regulation, protein-nucleic acid interactions, the role of direct metabolite transfer between enzymes in metabolism, protein folding, protein conformation change and peptide structure-function relationships. Of the many interesting individual contributions presented, some of the highlights included the evidence presented by the Rossi and Dunn laboratories that allosteric interactions in the E. coli and S. typhimurium tryptophan synthases modulate chemical bonding interactions during catalysis. The von Hippel and Matthews laboratories presented new chemical, spectroscopic and structural evidence about the nature of the interactions involved in protein-nucleic acid recognition. The Dunn laboratory demonstrated that the large, phenol-induced conformation change in the Zn(II) or Co(II)-substituted insulin hexamers is an allosteric transition. Will Bloch (Cetus Corporation) discussed the enzymology of the polymerase chain reaction. David Anderson (NEO-RX Corporation) presented his work on the role of peptide structure in cell surface antigen recognition for the major histocompatibility complex. The MacQuarrie and Rosenberry laboratories presented their recent findings in the areas of lysophospholipids and neural membrane structure and function. The most lively session involved discussion of the evidence for ***direct*** **transfer** ***of metabolite between enzyme pairs***. The Bernhard and Dunn laboratories reviewed evidence for the significance of the direct-transfer mechanism in dehydrogenases, glycolytic enzymes and the tryptophan synthases from enteric bacteria in vitro. The Keizer and Bernhard laboratories presented computer models of direct transfer in metabolic cycles simulated for in vivo conditions.

The man

Sidney A. Bernhard, Professor of Chemistry and member of the Institute of Molecular Biology at the University of Oregon, grew up in Brooklyn, graduated in chemistry from ***Brooklyn College*** in 1948, and completed a Masters degree at ***Pennsylvania State University*** in 1949. His PhD studies (1949-1951) were under the direction of Louis P. Hammett in physical-organic chemistry at ***Columbia University***. As a National Research Council Fellow, he took up a post-doctoral position with Linus Pauling at the ***California Institute of Technology*** (1951-1953), and then spent part of a year (1953) in England at the ***University of Cambridge***. Upon returning to the States, Sid took a position in the Division of Physical Biochemistry at the ***Naval Medical Research Institute (Bethesda)*** as a Research Chemist (1954-1958), from where he moved to ***NIH*** as Chief of the Section of Physical Chemistry (1958-1961). During this period, Sid also spent a year

(1959) in residence at the ***Weizmann Institute*** as an NSF Senior Post-doctoral Fellow. In 1961, he joined the Chemistry Department and the newly formed ***Institute of Molecular Biology at the University of Oregon*** as an Associate Professor.

Sid began his research career as a physical chemist working on such prob-lems as the composition of the Grignard reagent, the acid catalytic properties of ion exchange resins and the ionization constants and heats of ionization of phosphate buffers. His interests rapidly expanded to include a wide range of topics in physical biochemistry and molecular biology. ***Enzyme kinetics, reaction mechanisms and regulation*** became the major focus of his research at the University of Oregon. He was one of the leaders in the use of ***rapid-mixing techniques*** for the study of fast reactions, and (perhaps more than anyone else) Sid showed how ***chromophoric substrate analogs*** could be exploited as probes to characterize the physical and chemical interactions involved in enzyme catalysis. His first book, "The Structure and Function of Enzymes"[1], was published in 1969 at a time when the structures of only a few proteins were known. This book was considered a very timely and innovative contribution to the field and remains a very valuable reference source. At the time of his death, Sid and Dr. D. K. Srivastava were in the final stages of preparing a completely revised and expanded edition for publication, including their recent work on the role of enzyme-enzyme interactions in the regulation of metabolic pathways[2].

The authors of this tribute became acquainted with Sid as post-doctoral fellows in the period 1965-1969 at a time when he was deeply engaged in studies of the ***serine protease*** catalytic mechanism to which he contributed new evidence and ideas about the roles played by the protein in activating chemical intermediates along the catalytic path. He was then just beginning to extend his efforts to the investigation of the oligomeric enzyme systems, ***acetylcholine esterase, glyceraldehyde-3-phosphate dehydrogenase (GPDH), alcohol dehydrogenase, and the ATPases***. When reflecting on these years, we recall many images of Sid's life in Eugene - some of which we share here: Sid and Myron Bender paddling about on Fern Ridge Reservoir in Sid's rubber raft while discussing mysteries of the chymotrypsin catalytic mechanism in the summer of 1966; the synthesis of ***P-(2-furyl)-acryloyl phosphate***, the analog of 1,3-diphosphoglycerate which then was used to trap and identify the GPDH acyl-enzyme intermediate; the first measurements of the UV-visible spectrum of a crystalline acyl-enzyme intermediate; and the first evidence of ***half-of-the-sites reactivity in GPDH***. There were stimulating group discussions of Sid's ideas about half-site reactivity, ***negative cooperativity*** and the recently published models for allostery of Monod el al.[3] and Koshland et al.[4]. We remember Sid playing the recorder and jazz piano at parties, and there were 4th of July picnics at Sid's house where the war in Vietnam occupied much of our thoughts and discussions.

His early work on oligomeric enzymes developed into major research themes in the 1970s which explored the relationship between subunit organization and function[5,6]. His studies of chromophoric GPDH acyl-enzyme intermediates provided new insight into the roles played by subunit and coenzyme interactions in the regulation of catalytic function. During the period 1969-1988, Sid spent considerable time periods lecturing and doing research in Europe and on the East Coast. He developed and taught an honors college course entitled the ***'Origins of Life'***, a subject of considerable interest to him. In 1976, he was a Visiting Professor both at the ***University of Parma*** and at the ***University of Paris***. He spent an academic year (1978-1979) in residence at NIH as a Fogarty Research Scholar. Between 1971 and 1988, Sid traveled all over the world to visit friends and give lectures. In 1986, Sid was a featured speaker at the 621st Meeting of the Biochemical Society in London. In the fall of that year, he visited Professor Om Malhotra in Varanasi, India, where he was the key speaker at the International Seminar on 'Structure and Function of Enzymes' at Hindu University. He thoroughly enjoyed this opportunity to meet young Indian scientists and to explore India..

Whether it was San Francisco's China Town or Positano on the Amalfi Coast of Italy, Sid was always highly valued by his friends as a source of information about the location of the most interesting places to stay and to dine. His opinions about these matters were certain and strongly held. Sid's ideas and views about structure-function relationships in biological phenomena were equally certain and strongly held, they were also insightful and provocative. He believed that ***taking a position on issues was an obligatory part of doing good science***, a way to stimulate his students, co-workers and colleagues to carry out incisive experiments. His views added considerably to the ongoing debates about such subjects as the serine protease catalytic mechanism, negative cooperativity and half-of-the-sites reactivity, the role of protein conformation change in catalysis and the importance of direct transfer of metabolite between enzyme pairs in metabolic pathways; his research efforts also made substantial contributions to all of these areas. It is certain that he played a critical role in shaping the thinking of many of his students and colleagues about the relationships between biological function and the physical, chemical, and structural properties of the components of the macro-molecular systems of living organisms.

References

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