

## S. Jonathan Singer: A man who loved ideas and detested walls

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S. Jonathan Singer, "Jon" to one and all, died February 2, 2017, at the age of 92. Educated as a physical chemist, he transitioned gracefully by way of protein and immunochemistry to become a cell and molecular biologist of huge renown. His initial bout with fame came in 1949 when Jon was a postdoctoral fellow with Linus Pauling at the California Institute of Technology and, together with Harvey Itano, showed that sickle cell hemoglobin differed from normal hemoglobin by Tiselius electrophoresis (1). The years at the California Institute of Technology also led Jon into the antibody field by way of a collaboration with the immunologist Dan Campbell, something that would stand him in good stead later. After his postdoctoral stint, Jon was appointed to the faculty at Yale in the Department of Chemistry, where he remained until 1961. At that point Jon joined the microbiologist David Bonner, who was leaving the Yale School of Medicine, to set up an innovative department of biology at a new branch of the University of California, La Jolla in San Diego (UCSD).



S. Jonathan Singer. Image courtesy of Nazneen Dewji (Cenna BioSciences, La Jolla, CA).

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Bonner had strong feelings about how molecular biology was changing the teaching of science in general and medicine in particular. His untimely death in May of 1964, forced Jon to take over as department chair. Fortunately, he and Bonner shared the same unbridled and idealistic views of science and education, and Jon set about ensuring that these views became an integral part of the new university. Theirs was the philosophy of the big tent: the Department of Biology would embrace all aspects of the subject; geneticists, biochemists, physiologists, all together; no separate departments to impede crossfertilization or the flow of knowledge. And, if there must be any boundaries at all, let them be

porous. At UCSD, the departments of Chemistry and Biology would not only be housed in the same building, they would have their laboratories alternately placed and would share general equipment as well as cold and warm rooms. Moreover, the undergraduate curriculum would be particularly fashioned to integrate principal fields of knowledge, and a planned school of medicine would have its first-year curriculum seamlessly rooted in the Biology and Chemistry departments.

I first met Jon in July 1964, when I arrived to take a research position in his laboratory at UCSD after 2 years of postdoctoral work in Sweden. The timing was inauspicious. The fledgling Biology Department was still located in temporary space at the Scripps Institution of Oceanography, a long distance from a not quite completed new building on the main campus up on the hill. Laboratories were in a halfpacked mode preparing for the move, and Jon was heavily involved in planning the curriculum for the first undergraduate students due in September. None of this seemed to me favorable for getting a new research project off the ground and I was nervous that I might be lost in the shuffle.

I needn't have worried. During that chaotic year, between long-distance phone calls recruiting new faculty, dictating letters, and attending countless committees involved in the launching of a new university, somehow Jon managed to find time for drinking coffee in the laboratory with his group and entertaining us at his home. He shepherded us into the new building, recruited a crop of talented young faculty, and wooed a luminary from Stanford (Clifford Grobstein) to be the new chair of Biology. By then, a faculty position had opened up for me in the Chemistry Department, undoubtedly with Jon's help.

Jon's seminal work on proteins, including the affinity-labeling of antibodies (2), had by 1969 earned his election to the National Academy of Sciences, but he is certainly best known today for the Fluid Mosaic Model of cell membranes, the most cited rendering of which appeared in a 1972 *Science* article (3). The model was the culmination of an extended series of experiments begun after Jon moved to La Jolla but

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depended heavily on techniques he had developed at Yale, particularly the use of ferritin-labeled antibodies to stain specific proteins in electron micrographs (4).

The standard membrane model at the time was a phospholipid bilayer sandwiched between two layers of globular proteins, presumed to be structural in nature, and held in place by simple electrostatic forces. The new model featured proteins in a completely different mode and role and was based on numerous experimental observations made in Jon's laboratory, including spectropolarimetric measurements on membrane proteins and, especially, their distribution as followed with ferritin-labeled antibodies and electron microscopy. Garth Nicolson, a graduate student in Jon's laboratory, generated a panorama of such electron micrographs of variously labeled membranes that showed, among other things, they were asymmetric, differing inside from outside. One of their most dramatic pictures was a red blood cell with its membrane torn and folded back on itself, the outside being heavily decorated with a ferritincoupled lectin and the inner surface totally bare.

The model itself made it clear that proteins were not passive, structural components of cell membranes; they were dynamic gate-keepers, transporters, signalers, and pumps. The proteins were embedded in the membranes, partially or spanning all of the way, in either case with hydrophilic portions remaining in the aqueous phase, either in or out or both. Moreover, proteins were able to diffuse laterally in a 2D lipid bilayer, as implied in recent experiments by others in light microscopy studies where immuno-fluorescent antibody-labeled cells showed surface proteins to be redistributed in hydridized cells.

Publication of the Fluid Mosaic Model was a turning point in cell biology, giving rise to a torrent of studies in the field. In the ensuing years a cavalcade of gifted graduate students and postdoctorates marched through Jon's laboratory, exploiting its many features. In 1994, at age 70, Jon moved to Emeritus status at UCSD, but he remained active both as a teacher and researcher. He began a collaboration with Nazneen Dewji in the Department of Medicine on a project dealing with the causes and genetics of Alzheimer's disease that was to keep both of them busy for the next 20 years (5). Jon also continued to teach a senior honors seminar course with his good friend Avrum Stroll, professor of philosophy, on the origins, nature, and future of Western science.

During this period, Jon became increasingly concerned about world problems. He turned to writing essays and opinion pieces, always with an acerbic wit and sardonic tone. In an article titled "Ideas are an endangered species," Jon railed against data-driven mega-science (6). Increasingly he came to lament the business model approach to universities. Still, Jon remained chauvinistic about UCSD, and especially the Biology Department, even as he fretted about the University expanding with its numerous internal and external walls. Jon worried publicly about a burgeoning administration and the diminished role of the faculty "who used to run the place but now only work here."

Many of these ideas were consolidated in his 2001 book, A Splendid Feast of Reason (7), a deep and serious work in which he offered his forthright views about biology, the human condition, and the world. Jon was gradually becoming reconciled to the fact that most of humankind is not given to rational thought. In the preface Jon wrote: "irrationality is a surpassing fact of life, an ineradicable and overriding compulsion of most human beings, a fateful genetic residue from our evolutionary past"; and then, quoting from King Lear: "The temper of the times/when madmen lead the blind" (7).

Jon's last months were blurred by a barrage of health problems and he was, perhaps mercifully, spared the special relevance of those words in the wake of our recent presidential election.

<sup>1</sup> Pauling L, Itano HA, Singer SJ, Wells IC (1949) Sickle cell anemia a molecular disease. Science 110(2865):543-548.

<sup>2</sup> Wofsy L, Metzger H, Singer SJ (1962) Affinity labeling-a general method for labeling the active sites of antibody and enzyme molecules. Biochemistry 1:1031–1039.

<sup>3</sup> Singer SJ, Nicolson GL (1972) The fluid mosaic model of the structure of cell membranes. Science 175(4023):720-731.

<sup>4</sup> Singer SJ (1959) Preparation of an electron-dense antibody conjugate. Nature 183(4674):1523–1524.

<sup>5</sup> Dewji NN, Singer SJ (1996) Genetic clues to Alzheimer's disease. Science 271:159–160.

<sup>6</sup> Singer SJ (1992) Ideas are becoming an endangered species. Mol Biol Cell 3(4):385-388.

<sup>7</sup> Singer SJ (2001) The Splendid Feast of Reason (Univ of California Press, Berkeley).