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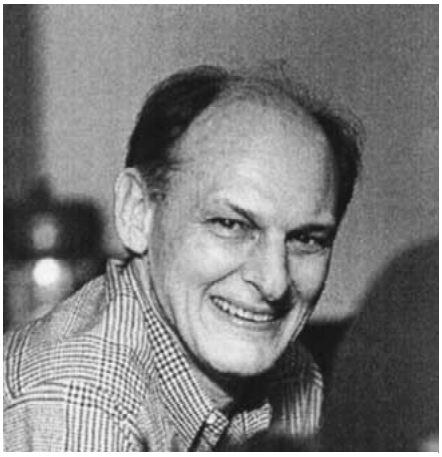
Obituary



Gerald T. Babcock (1946–2000)

Dr Gerald T. Babcock, University Distinguished Professor of Chemistry at Michigan State University, passed away December 23, 2000 following a heroic, year-long battle with cancer. Jerry was born to Frank and Emelda (Mel) Babcock on February 9, 1946, in Minneapolis, Minnesota, where he received his primary and secondary school education. As an undergraduate, he attended Creighton University in Omaha, Nebraska, where he received his BS degree with honors in Chemistry, and where he was also a member of the varsity basketball team, playing on an National Collegiate Athletic Association scholarship. After graduation from Creighton, Jerry joined Kenneth Sauer's group at Berkeley as a PhD student in 1968. Berkeley was then, as now, a center for the application of biophysical techniques to problems in photosynthesis. These were exciting years for progress in understanding the mechanism of photosynthetic oxygen evolution, with the flashing light experiments of Pierre Joliot and Bessel Kok that established the period four pattern of oxygen release. Jerry took this area as his thesis topic and continued researching it for his entire scientific career. Along with Charles Weiss, a postdoc in the Sauer group, he built a Joliot-style oxygen electrode that was a complex marvel of pumps, hoses and a hodge-podge of electronics salvaged from other uses. It was not pretty but it worked remarkably well. This 'make it work' philosophy was characteristic of Jerry and his approach to science. Soon Jerry supplemented his work with the oxygen electrode with studies on EPR signals associated with photosynthesis. These signals had first been observed by Barry Commoner some years earlier and the laboratory of Melvin Calvin had done some work on them in photosynthetic bacteria, but Jerry was the first at Berkeley to study Signal II, which was associated with Photosystem II (PS II). Its sluggish kinetics initially suggested that it was not a mainstream electron carrier and therefore did not receive much attention. Under Ken's guidance, Jerry undertook a systematic investigation of the 'Signal II' species, and showed that there was, in fact, more than one contributing radical component in the signal (Babcock and Sauer 1975). By a variety of treatments that affected O_2 evolution, Jerry was able to show that the kinetic behaviors of these signals coincided with the presence or absence of a functional O_2-evolving reaction. Out of these investigations emerged the first systematic nomenclature for these important PS II redox intermediates: Signal IIs, the dark-stable form of the signal, Signal IIf, the EPR signal from a second species detected upon inhibition of water oxidation, and lastly, Signal IIvf, a

very rapidly decaying species associated with the fully functional O_2-evolving reaction. It was on the basis of work by Jerry and one of us (RB) that Ken Sauer's group was able to position the Signal IIf/IIvf species as a redox intermediate between the O_2-evolving reaction and the primary donor, P680, of Photosystem II (Blankenship et al. 1975). But the molecular identity of Signal II (later renamed 'Z') was still elusive. Some experiments indicated that it might be a quinone, but the data were not very convincing. Jerry would return to this question later in his independent scientific career.

Jerry received his PhD in 1973, and spent a year as a post-doctoral fellow in the Sauer group. In 1974, he joined Graham Palmer's laboratory at Rice University where he began research on cytochrome oxidase that was to later become a major part of his independent scientific career. His weekdays were spent learning about cytochrome oxidase, with fellow postdoc Larry Vickery, resulting in several ground breaking (and still often quoted) papers on the electronic properties of the heme centers of cytochrome oxidase (Babcock et al. 1976, 1978; Tweedle et al. 1978). During this time, he augmented his experimental expertise with techniques such as resonance Raman, that would be critical to the success of his later research. It is less widely known that many weekends (when Graham was out of town) were spent flashing thylakoid membrane suspensions that were quickly transferred into an EPR cryostat in search of paramagnetic signals that Jerry believed would be associated with the S_2 state of the Kok-Joliot Cycle. It remained for G.C. Dismukes to find this elusive signal (Dismukes and Siderer 1980), the well-known S_2 multiline signal of Photosystem II.

Canoeing was a favorite mode of relaxation for Jerry, as many of his former students and post-docs will testify. At Rice, Jerry organized several memorable outings. However, in one case he neglected to call ahead to check on the water level in the east fork of the San Jacinto River, and members of the Palmer group ended up carrying their canoes some distance down a dry river bed to the point where they were to be picked up.

Jerry was recruited by the Chemistry Department at Michigan State University (MSU), where he joined the faculty as an assistant professor in 1976, and where he spent the rest of his career. He was promoted to associate professor with tenure in 1980 and to full professor in 1984; from 1990 to 1998, he was chair of the Chemistry Department. In 1997, he received the highest honor his university can bestow, the title of University Distinguished Professor. When he arrived at Michigan State, Jerry set about establishing a first-rate facility for the application of physical methods to the characterization of cytochrome oxidase and photosynthetic systems. He began the process of recruiting a research group of enthusiastic graduate students and initiated a number of innovative research projects that continued to the end of his career. In his first work on cytochrome oxidase, he collaborated with Irving Salmeen (Ford Motor Company) and Chris Chang (at MSU) to carry out a series of resonance Raman studies on oxidase and model heme compounds (Salmeen et al. 1978; Babcock and Chang 1979; Babcock and Salmeen 1979). These and subsequent studies were critical to defining the complex vibrational spectrum of the enzyme, knowledge that would be key to later incisive investigations of the mechanism of oxygen reduction and the nature of the metal ligands. A particularly important contribution from model studies (Ward et al. 1983) and spectral analysis of oxidase (Callahan and Babcock 1983) was one of the first explicit molecular models of how a redox reaction could be linked to proton pumping in cytochrome oxidase (Babcock and Callahan 1983). During a sabbatical with Bill Woodruff in Austin, the first time-resolved resonance Raman studies on cytochrome oxidase were carried out (Babcock et al. 1984, 1985). This began a 15-year intensive effort to pin down the elusive oxygen intermediates of the cytochrome oxidase reaction, an effort that would require pushing resonance Raman spectroscopy to its limits.

With the oxidase experiments up and running, Jerry returned to investigations of the Signal II species associated with Photosystem II that involved his first graduate students in this area (ChristineYerkes, Demetrios Ghanotakis) and a post-doctoral fellow, Patrick O'Malley. The focus of this research was to extend the characterization of the EPR signal (Yerkes and Babcock 1981; Ghanotakis et al. 1982), and to discover its molecular origins. In the first of these experiments, a search was made for model compounds that would simulate the EPR spectrum of Signal II, by now called 'Z'. This approach identified quinone radicals as promising candidates (O'Malley and Babcock 1984a), but the spectroscopic data from these compounds was never entirely satisfactory, and the plastoquinone content of Photosystem II preparations was insufficient to account for the presence of Q_A, Q_B, and the two additional quinones needed for the two EPR signals comprising the difference Signal II species. The alternate approach was to apply isotopic

labeling techniques and assess the results using EPR. The first experiments by Bridgette Barry, who was a joint post-doc with Jerry and Lee McIntosh, explored incorporation of deuterated tyrosine into cells of *Synechocystis* PCC 6803; the EPR properties of 'Z' were dramatically modified (altered lineshape, narrowed linewidth), a result showing that 'Z' was in fact a tyrosine radical (Barry and Babcock 1987). This key result was quickly followed by the site-directed mutagenesis experiments, in collaboration with Rick Debus and Lee McIntosh, that identified the redox active tyrosines of Photosystem II as Tyr161 of D1 and Tyr160 of D2 (Debus et al. 1988a, b). These seminal findings prompted one last revision of the nomenclature for these important redox constituents of Photosystem II, to Y_Z and Y_D.

Other work on Photosystem II derived from a collaboration with one of the authors (CY), who spent a sabbatical year in the Babcock lab. Jerry's complaints about the difficulties of making EPR measurements on $Y_D^\bullet$ and $Y_Z^\bullet$ in the presence of a very large signal from $P700^+$ accelerated the publication of a method for purification of Photosystem II in its active form (Berthold et al. 1981). Quantification of the Mn content of PS II and a characterization of its inhibitor sensitivity (Yocum et al. 1981) also resulted from this collaboration. Longer term interactions between the Babcock and Yocum groups were central to the discovery that Ca^{2+} was an essential cofactor for water oxidation (Ghanotakis et al. 1984a, b) and to the isolation of stable Photosystem II reaction center preparations that resulted in a reevaluation of the pigment content of the reaction center (Ghanotakis et al. 1989).

Other research by Jerry's group in this period examined the spectroscopic properties of Photosystem I. Prior research had established that the reaction center was comprised of a chlorophyll a dimer, but that in $P700^+$ the unpaired spin was localized predominantly on a single chlorophyll molecule (O'Malley and Babcock 1984b). A sabbatical visit to Leiden University in 1983 brought Jerry to the Biophysics Department of the Huygens Laboratory, where he worked with Arnold Hoff to apply electron spin echo techniques to a study of signal II (De Groot et al., 1986), and with Hans van Gorkom's group (Dekker et al. 1984) on UV absorbance changes associated with the S-states.

The oxidase research evolved to a point where Jerry and his graduate student, Costas Varotsis, had refined the technology to detect the oxygen intermediates in the energy transducing oxygen reduction reaction of cytochrome oxidase (Varotsis et al. 1989). Time-resolved resonance Raman was a powerful but challenging methodology demanding large quantities of enzyme and yielding very low signal to noise. Nevertheless, Jerry and Costas were able to resolve and identify the transient vibrational modes for oxygen bound to reduced heme a_3 and the ferryl-oxo intermediate after the oxygen was cleaved (Varotsis et al. 1990, 1993; Varotsis and Babcock 1990). A predicted peroxy intermediate was frustratingly undetectable, a fact that became more understandable in terms of the theory that Jerry and his collaborators developed in the last few years before his death, suggesting a concerted, four electron reduction of the oxygen (Proshlyakov et al. 1998, 2000) involving formation of a tyrosine radical at the active site. The power of resonance Raman and all of the groundwork done by Jerry and coworkers in identifying many of the vibrational modes in oxidase, allowed him to play a key role in the analysis of mutant forms of a bacterial oxidase from *Rhodobacter sphaeroides*, in collaboration with one of us (S.F.-M.), Robert Gennis and colleagues. These studies identified the ligands of the metal centers in the enzyme (Shapleigh et al. 1992), and gave an amazingly accurate model of their arrangement in the active site (Hosler et al. 1993; Calhoun et al. 1993) several years before the crystal structure was obtained.

Jerry's continuing interest in the chemistry and function of tyrosine radicals gradually evolved into a rethinking of the possible roles of these species in the mechanism of photosynthetic oxygen evolution. A difficulty with conventional models for cycling of the S-states is that if one assumes that the mechanism involves sequential oxidations of the Mn cluster, two problems are encountered. First, metal-centered oxidations would, in theory, produce a potentially damaging accumulation of positive charges within the water-oxidizing site, and second, the final step of the cycle ($S_3 \rightarrow S_4 \rightarrow S_0$) might require formation of an Mn^{5+} species; generation of this oxidation state is generally believed to be beyond the capabilities of biological redox systems. As Jerry viewed this problem, the latter issue could be resolved if the S_4 state involved the combination of S_3 and the neutral tyrosine radical, $Y_Z^\bullet$. If this were so, it would involve $Y_Z^\bullet$ directly in H_2O oxidation chemistry. The former difficulty, ameliorating possible damage to PS II stability from the accumulation of excessive positive charge, could be accomplished if the chemical mechanism for H_2O oxidation were reformulated to avoid charge buildup on the Mn cluster. Jerry, his post-docs (Curt Hoganson, Kurt Warnecke), and his

collaborators (Bruce Diner, John McCracken, Cecelia Tommos) devised a theoretical mechanism (Babcock 1995; Hoganson et al. 1995; Hoganson and Babcock1997; Babcock et al. 1997; Blomberg et al. 1997; Lydakis-Simantiris et al. 1997; Tommos et al. 1998; Tommos and Babcock 2000) for oxygen evolution in which Mn-bound H_2O was oxidized by $Y_Z^{\bullet}$ via an H-atom abstraction reaction. This reformulation of electron transfer on the oxidizing side of PS II would require that the Mn cluster and Y_Z be in relatively close proximity to one another to facilitate the H-atom transfer reaction. Pulsed magnetic resonance measurements on modified forms of PS II that accumulate the S_2 $Y_Z^{\bullet}$ state (Lakshmi et al. 1998) have placed the tyrosine within 7–8 Å of the Mn cluster, as would be required for a functioning H-atom abstraction mechanism. This distance is supported by the recent solution of the PS II crystal structure to a resolution of ca. 4 Å (Zouni et al. 2001), where a Mn–Y_Z separation of about 7 Å is proposed. The 'charge-neutral' model has stimulated new debates about the mechanism of H_2O oxidation, and is now being tested in a number of laboratories around the world.

The neutral radical proposal illustrates how Jerry's wide-ranging interests meshed with his ability to draw together information from a number of fields in order to synthesize new ideas and models for fundamental processes in electron transfer systems. In addition to his research on reaction centers and cytochrome oxidase, Jerry also collaborated on a number of problems in related systems, such as myeloperoxidase, green heme protein, ribonucleotide reductase, hydroxylamine oxidoreductase, galactose oxidase, DNA Photolyase and guanylate cyclase. His collaborators in this work included R. Wever, J. Stubbe, A. Ehrenberg, B.-M. Sjöberg, A. Hooper, J. Whittaker, A. Sancar and M. Marletta. Members of the Babcock group who worked on these and closely related projects include Guert Deinum, Rene Floris, Matt Gardner, Yvonne Gindt, Tony Oertling, Hans Schelvis, Steve Siebold and Esther Vollenbroek, among others. Near the end of his life, he began another new research initiative which employed Fourier transform infrared spectroscopy to characterize the PS II S-states (Hillier and Babcock 2001).

Jerry received a number of awards and honors in the course of his career. Among them was a Distinguished Faculty Award from Michigan State University (1989), a visiting professorship at the College de France (1990), the Philips Lecture at Haverford College (1990), a Sigma Xi Senior Research Award (1995), a Michigan Academic Governing Board Award (1999), and the Charles F. Kettering Award for excellence in photosynthesis research, presented by the American Society of Plant Physiologists in 2000. He was sought after as a member of federal advisory panels, and served in this capacity for a number of agencies, including USDA (United States Department of Agriculture), NIH (National Institutes of Health, USA), and DOE (Department of Energy, USA). He was a member of several editorial boards, including Photochemistry and Photobiology, Annual Reviews of Physical Chemistry, Biochimica Biophysica Acta – Reviews on Bioenergetics, Biochemistry, and Journal of Biological Chemistry. He chaired the 1985 Gordon Research Conference on Physicochemical Aspects of Photosynthesis and was chair-elect of a forthcoming Gordon Conference on Radicals. He was an invited speaker at numerous regional, national and international meetings. It was not uncommon for Jerry to prepare the overheads for these talks the night before, in longhand, and many of us remember his posters at various meetings, which were often hand written, on brown paper that was in many instances derived from grocery bags.

Although these professional activities consumed an enormous amount of time, Jerry was able to mentor 33 graduate students, and 33 post-doctoral fellows. The research expertise of these students was divided about equally between photosynthetic and cytochrome oxidase research projects. He was also a gifted teacher in the classroom, something that was easily deduced from listening to one of Jerry's symposium presentations. It is significant that even when he had been promoted to the top faculty ranks he continued to teach a course in introductory chemistry.

Jerry Babcock's life now seems like a 'brief candle' to those of us who had the privilege to interact closely with him. Death has interrupted a career that was at one and the same time in a mature phase, allowing us all to benefit from his wisdom, keen insight and broad-based knowledge, and yet still moving in exciting new directions that were only beginning to bear fruit. In this obituary, we have cited only a small portion of Jerry's publications. At the time of his death, he had already authored or co-authored 253 papers and reviews on his research, and we will never know how much further Jerry's ever-inquiring mind and innovation would have taken him. What we do know is that our fields of research profited immensely from Jerry's exceptional gifts, and that we are all far richer for the time that we had with him. We extend

our sympathies to Jerry's sons, Lee and Andrew, and to his mother Mel, his brother Frank and his sisters, Mary Jo Hollinger and Therese Corfits.

Acknowledgements

A special debt of gratitude is due Ms Vada O'Donnell, Jerry's last secretary, for her unstinting efforts to keep us apprised of the status of Jerry's illness, and for her work in collecting material that will be used for a longer forthcoming perspective on Jerry's career. We are grateful to Jim Siedow (Duke University) for his recollections and assistance in writing this article. It is inevitable, given both space limitations and the wide range of Jerry's interests and collaborations, that we have not been able to mention everyone who was part of his scientific career. We apologize for these omissions.

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