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BRITTON CHANCE IN MEMORIAM

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This short note covers some of my favorite scientific accomplishments of Britton Chance.

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Britton Chance was a truly inspiring scientist, among the greatest. His long and vigorous career in biochemistry, biophysics, and biological instrumentation began with his now-classic kinetic and spectroscopic studies of the mechanisms of action of individual enzymes: catalases, peroxidases, and dehydrogenases. His rigorous detection of kinetically functional enzyme–substrate intermediates, *in vitro* and *in vivo*, disposed of vitalistic proposals of enzyme action, and established Chance as the founder of modern enzymology. His elucidation of the spectral properties of enzyme–substrate intermediates set the stage for their ultimate structural elucidation by X-ray diffraction and NMR, fields to which Chance had also made profound contributions.

Chance proceeded next to more complex multienzyme systems: the electron transport chains of respiration and photosynthesis. Mildred Cohn had shown that during mitochondrial oxidative phosphorylation, ^{18}O-labeled inorganic phosphate lost more than one ^{18}O atom, suggesting the reversibility of this process. Chance's spectroscopic studies of this process precisely located the chemical loci of energy conservation, and established the reversibility of such energy-coupled electron transport.

In the controversial field of energy coupling, crowded with leaders in biochemistry, the conventional wisdom was that this process occurred via an energy-rich chemical intermediate, analogous to 1,3-diphosphoglyceric acid in the glyceraldehyde-1,3-diphosphate dehydrogenase reaction. In 1961, Peter Mitchell proposed a very different mechanism of energy coupling, via a proton and electrochemical gradient across the mitochondrial membrane. This was strongly, but fairly criticized by Chance and others, requesting additional experiments. After years of experiments and arguments by Mitchell, Ephriam Racker, Albert Lehninger, Slater, and others, Mitchell's views became accepted, and Albert Lehninger (personal communication, 1977) successfully nominated Mitchell for the 1978 Nobel Prize in Chemistry. Subsequently, extending the ^{18}O exchange studies of Cohn and the transient kinetic studies of Harvey Penefsky; Paul Boyer, together with John Walker, a crystallographer, shared the 1997 Nobel Prize in Chemistry for "elucidating the enzymatic mechanism underlying the synthesis of ATP". Chance's studies of bacterial photosynthesis established the existence of electron tunneling and provided deep insight into the

mechanisms of outer-sphere electron transfer reactions in general.

Chance next proceeded to still more complicated systems, studying the oxygen requirements and energy metabolism of cell suspensions, perfused organs, and ultimately the entire organism, including man. In his work, he made use of his home-built ^{31}P NMR spectrometer. Chance's approach to a scientific problem was to design and build the best instrument, usually a spectrometer, with the highest resolution in timing, spectral frequency, and sensitivity to study the problem properly. His data were interpreted conservatively, using state-of-the-art mathematics and computation. When necessary, he also designed and built an appropriate computer.

Chance next became interested in medical imaging, expanding NMR imaging by extending it to phosphorus, and by developing near-infrared optical imaging for the detection of ischemia and cancers.

I had the privilege of collaborating with Chance in X-ray absorption studies of the enzyme glyoxalase I (1984), which revealed its essential Zn^{2+} to be in either a 7-coordinate or a distorted octahedral complex and to receive approximately two histidine ligands. Our collaborative studies of methemoproteins by NMR relaxation (1971) showed the 6th ligand of Fe^{3+} to be a water molecule at low pH and a hydroxyl ion at high pH, both in solution and in the crystalline state. Crystallization decreased the escape rate of water protons from the coordination sphere of Fe^{3+} via an entropy barrier. Working directly with Brit was a profound experience, for which I am very grateful.