Paul F. Cranefield Award to Daniel H. Cox

The late Paul F. Cranefield, M.D., Ph.D. was the Editor of the *Journal of General Physiology* for 30 yr, from 1966 to 1995. During this time he worked incessantly to further the mission of the *Journal*: to promote and publish studies at the interface between biology, chemistry, and physics in order to obtain insights into fundamental mechanisms that underlie biological function at all levels.

When Dr. Cranefield stepped down as Editor, the Council of the Society of General Physiologists acknowledged his numerous contributions to the *Journal*, and thus to the Society, by instituting the Paul F. Cranefield Award, which should go to a young investigator who in the preceding year had published an article of exceptional quality in the *Journal*. The award would be given at the Annual Meeting and Symposium of the Society, which takes place in Woods Hole, MA, and the criteria for selecting the awardee should be so stringent that the award might not be given every year.

Despite these high standards, there were many outstanding candidates. One stood out, namely Daniel H. Cox from the Department of Neuroscience at Tufts University School of Medicine, who has made many important contributions toward understanding the regulation of Ca^{2+}-activated potassium channels. Dr. Cox accepted the Award at the September, 2003, meeting of the Society.

Dr. Cox received his Ph.D. from Tufts University, where he worked in the laboratory of Kathleen Dunlap and studied calcium channel function. He received his postdoctoral training with Richard W. Aldrich at Stanford University, where he began his studies on Ca^{2+}-activated potassium channels. This was an exciting time in the Aldrich lab, as evidenced by a long series of distinguished articles—published in the *Journal of General Physiology*—having various combinations of D.H. Cox, J. Cui, and F.T. Horrigan in the author list. The aim of these studies was to understand the allosteric linkage between the Ca^{2+}-dependent and the voltage-dependent channel gating. In these studies Dr. Cox also demonstrated his impressive quantitative capability to develop a powerful analytical model for dissecting the influence of Ca^{2+} and voltage on channel gating. This work led to the by now famous—or infamous, depending on your point of view—50-state model of channel gating. Given the model's complexity, it is impressive that different laboratories deduced it using rather different experimental strategies—and sobering that they concurred that the model most likely is oversimplified, as was suggested already in Dr. Cox's early contributions to the field.

The kinetic studies define a channel of tantalizing beauty. But what are the molecular identities of the voltage and Ca^{2+} sensors, and how are they coupled? These questions, and in particular the Ca^{2+} sensors, have been the focus of Dr. Cox's recent work. By analogy with other voltage-dependent cation channels, the voltage sensors most likely are the S4 segments; the Ca^{2+} sensors have proven more elusive. A number of studies have implicated a large intracellular COOH-terminal domain as being involved in Ca^{2+} sensing—and identified a so-called Ca^{2+} bowl in a conserved sequence motif with 10 acidic residues—but structure-function studies could not define the precise role of the Ca^{2+} bowl for normal channel function. The puzzle was resolved in large part by studies in Dr. Cox's laboratory, which were published in the August 2002 issue of the *Journal* (with L. Bao, A.M. Rapin, and E.C. Holmstrand). The premise of the work was that though the Ca^{2+} bowl is involved in Ca^{2+} sensing, there are likely to be additional (high-affinity) Ca^{2+} binding sites outside the bowl. The challenge thus became to identify the Ca^{2+} binding sites inside and outside the bowl—and further to define their Ca^{2+} binding characteristics and interactions. Indeed, mutating charged sequence segments in the bowl disrupt the channels Ca^{2+} sensitivity, and implicate a DDDPD segment as forming a high-affinity Ca^{2+} binding site. But, as noted in previous studies, mutations in the Ca^{2+} bowl could not account for all high-affinity Ca^{2+} sensing. Searching for additional binding sites, a methionine residue at position 513 far (in sequence space) from the Ca^{2+} bowl was found to alter the channels' Ca^{2+} sensitivity. When both the DDDPD segment and M513 is mutated (the latter to I) all high-affinity Ca^{2+}-dependent gating is abolished; but the channels maintain a further low-affinity, Mg^{2+}-sensitive gating. Further, comparing the Ca^{2+} sensitivity of the DDDPD→AAAAA and M513I mutants and the double DDDPD→AAAAA + M513I mutant, the mutations have almost independent effects on the channels Ca^{2+} sensitivity, which could suggest that there are two independent high-affinity Ca^{2+} binding sites.

This was the first time that all high-affinity Ca^{2+}-dependent gating was abolished, which establishes an important mile-stone. Together with Dr. Cox's previous work on Ca^{2+}-dependent potassium channels, this work further confirms his well-deserved reputation as an up-and-coming leader in this field—just four years into his independent career.