JGP Journal of General Physiology

IN MEMORIAM

# In Memoriam: David C. Gadsby, PhD

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David C. Gadsby, PhD, passed away in New York City on March 9, 2019. David was an internationally renowned physiologist and a major figure in the history of the *Journal of General Physiology* (*JGP*). David was appointed to *JGP*'s Editorial Board by Paul Cranefield in 1982. He became Associate Editor in 1984 and served as such until 2008, when he joined the Editorial Advisory Board and served until his death. David contributed immensely to *JGP*, both as an author of 23 research papers and 2 other publications, and as a reviewer and editor of an immeasurable number of manuscripts.

David was born in Cardiff, Wales. He was proud of his Welsh roots, as was evident from a banner with one of the impossible polysyllabic Welsh words above the door to his office at The Rockefeller University. He received his undergraduate training in physiology and biophysics at Trinity College, Cambridge University, where he studied with Alan Hodgkin. For his doctoral training, David went to University College London to work with Rolf Niedergerke in the Department of Biophysics on questions relating to cardiac contractility (Gadsby et al., 1971) and the contribution of the $Na^+$,$K^+$-ATPase to skeletal muscle membrane potential (Gadsby et al., 1977). These early articles were already typical of David's scientific style: impeccable logic, rigorous design, impressive data quality, and systematic examination of the possible outcomes. According to David, the joint influences of Hodgkin and Niedergerke combined to make him a foe of sloppy thinking.

For his postdoctoral training, David came to Paul F. Cranefield's Laboratory of Cardiac Physiology at The Rockefeller University in 1975. He was promoted to Assistant Professor in 1978, Associate Professor in 1984, and Full Professor and Head of the Laboratory of Cardiac and Membrane Physiology in 1991. The focus of David's early studies at Rockefeller was the $Na^+$,$K^+$-ATPase in cardiac cells. He developed increasingly sophisticated electrophysiological protocols that permitted vivid demonstrations of the pump's electrogenicity (Gadsby and Cranefield, 1979) and detailed kinetic studies of pump activity, a topic that continued to fascinate him for the next 40 yr. David's early studies (Gadsby, 1980) focused on ionic currents and resulted in an elegant, compelling description of the kinetics of pump-mediated $Na^+$ extrusion. Soon after, David and his colleagues established protocols, which now are classics in the field, to record the transient currents associated with individual steps in the reaction cycle. This allowed them to show that the outward movement of $Na^+$ includes a voltage-dependent transition that is consistent with the movement of one positive charge across the membrane (Nakao and Gadsby, 1986).

Photo courtesy of Angus C. Nairn.

David's interest in the $Na^+$,$K^+$-ATPase reaction cycle and the transient currents associated with the individual steps led him in the late 1970s to study the squid giant axon, which permits exquisite time resolution. He established a 30+-yr-long collaboration with Francesco Bezanilla, Paul De Weer, Robert F. Rakowski, and others (De Weer et al., 1988; Gadsby et al., 2012) at the Marine Biological Laboratory (MBL) in Woods Hole, MA. The advantages conferred by the squid giant axon also allowed David and his colleagues to demonstrate the presence of an extracellular access channel for $Na^+$ in the $Na^+$,$K^+$-ATPase (Gadsby et al., 1993). This was an observation that David, together with Pablo Artigas, later expanded upon by showing that the $Na^+$,$K^+$-ATPase may legitimately be considered an ion channel, albeit a special kind of channel with two gates that are never open at the same time (Artigas and Gadsby, 2003).

David loved the scientific environment at the MBL and the physical environment around Woods Hole. He and his wife Patricia decided in the mid-1980s that they would like to spend significant time in Woods Hole and bought a house, which they rented out for the first 10 yr before beginning to spend a significant part of their summers in Woods Hole. This allowed David to divide his time between the laboratory and his favorite pastime, fishing (see photos).

In the late 1980s, David and his colleagues discovered that β-adrenergic stimulation of cardiac myocytes activated a

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PKA-regulated $Cl^-$ conductance (Bahinski et al., 1989). A few years later (Nagel et al., 1992), David and his colleagues were able to show that this novel PKA-activated $Cl^-$ current was indistinguishable from that of the epithelial CFTR, the ATP-binding cassette (ABC) transporter that evolved into a chloride channel. These discoveries led to a long-standing collaboration with one of us (A.C. Nairn), which enabled David and his colleagues to develop an in-depth description of the CFTR reaction cycle. David's last published article was a magisterial review of CFTR's structure, gating, and regulation (Csanády et al., 2019).

The studies on CFTR may have appeared to be a departure from the very successful line of research that David had been pursuing for nearly 20 yr and that would continue throughout his scientific career; his last article on (a disease-causing mutant of) the $Na^+$,$K^+$-ATPase appeared in 2017 (Isaksen et al., 2017). However, David had long been pondering the distinction between channels and pumps, building on the ideas of Peter Läuger (1979) and others. This led David to formulate a "one gate versus two gates" principle, in which channels need have only one gate to regulate channel activity, whereas pumps need to have (at least) two gates to be capable of thermodynamically uphill transport. As David noted, the key distinction between channels and pumps "boils down to the requirement of strict coordination between a pump's two gates (whatever their physicochemical form)" such that they cannot be open at the same time (Gadsby, 2009).

As David and Paul Cranefield explored the electrogenicity of the $Na^+$,$K^+$-ATPase, they also discussed *JGP*, where David published more than 25% of his scientific output. By that time (1981), Cranefield had been the Editor of *JGP* for ∼15 yr, a period in which *JGP* had become the premier venue for publishing the in-depth mechanistic studies of ion channel function that it is famous for. To acknowledge David's growing importance for *JGP*, Cranefield appointed him to the Editorial Board in 1982. At about the same time, Cranefield and David began planning a new structure for how *JGP* should be edited. The new structure was implemented in January 1984, when David and two of us (O.S. Andersen and R.M. Shapley) became Associate Editors. In short order, we established the editorial model that has been in place for the past 35 yr, involving a weekly meeting at which manuscripts were discussed, reviews were evaluated, and decisions were made. To ensure that we were in a good mood, Cranefield would bring Eastern European delicacies (sausages, bread, and cheese) from downtown New York City that we ate while we deliberated. Cranefield went through the manuscripts before we met and often discussed difficult cases with David beforehand. Initially, Cranefield drafted most of the decision letters before we met, which we then would revise based on our own reading of the manuscripts and reviews. Because Cranefield usually traveled through Africa for 4–6 wk every summer, the three Associate Editors took on more responsibility before long. In practice, this meant that David Gadsby went through many of the manuscripts before we met.

The weekly *JGP* meetings not only became the decision meetings but also became an amazing forum for discussing science and world affairs. The four of us had different, yet overlapping, interests and personalities, and we left every meeting having learned something new from each other. David's

Photo courtesy of Angus C. Nairn.

office and his electrophysiology rig were next to where we met, and David would tell us about his recent results with great enthusiasm. This was where we learned about the $Cl^-$ current that β-adrenergic stimulation activated, which David and his colleagues identified as CFTR a few years later.

David was a logical person to succeed Paul Cranefield as Editor of *JGP*, but he did not wish to assume the associated administrative responsibilities. Fortunately, however, he was willing to continue as Associate Editor when O.S. Andersen accepted the editorial responsibility for *JGP* in the summer of 1995. By that time, R.M. Shapley had become less involved and relinquished his remaining responsibilities to *JGP*, which meant that for a brief time there was just an Editor (O.S. Andersen) and one Associate Editor (David), and David was in Woods Hole each summer. David suggested that A.C. Nairn be invited to become Associate Editor, which he accepted. L.G. Palmer also accepted an invitation to be an Associate Editor, and these four became the core of *JGP* for the next 13 yr. During this time, most of *JGP*'s business was performed during weekly meetings in a small office at The Rockefeller University, whose main charm was a view across the East River. Each spring, David was usually the first to spot the blossoms on the cherry trees on Roosevelt Island.

When O.S. Andersen decided to step down as Editor of *JGP* in 2008, David decided that he wanted to focus his efforts on his laboratory at The Rockefeller University and also in Woods Hole, where he and Patricia, by then, had established deep roots. Though this was a loss for *JGP*, it brought other benefits; David and Patricia decided to get a shellfishing license, and every year they hosted an amazing oyster fest in David's laboratory at The Rockefeller University during the week after Thanksgiving. Reflecting David's outgoing character and stature among his colleagues, this was where everybody who was involved in membrane research on the tri-institutional campus (The Rockefeller University, Memorial Sloan-Kettering Cancer Center, and Weill Cornell Medical College), plus many others, got together for an extravaganza featuring local Falmouth, Massachusetts oysters, various kinds of "bubbly," and other delicacies, in addition to stimulating discussions.

For many years, David had said that he would retire at 70 and then move to Woods Hole, where over the years he served the MBL as Trustee and Chairman of the Science Council and as faculty in the Neurobiology course. He did indeed close his

laboratory in 2017 as planned, just after the structure of human CFTR was published (Liu et al., 2017)—as David put it, "70 years old, and my first article in *Cell*." But soon after, he became ill, and the years that he and Patricia had looked forward to did not materialize. However, he continued to be involved in science, and his last major effort was the CFTR review he wrote with László Csanády and Paola Vergani (Csanády et al., 2019). He left a rich legacy of friends, alumni from his laboratory, and authors of articles in *JGP* that he had mentored over the years.

As befitting his many scientific contributions, David received numerous awards, including the K.S. Cole Award from the Biophysical Society (1995) and a National Institutes of Health MERIT Award (1998–2007). In 2005, he became an elected Fellow of the Royal Society, and in 2018 he was elected a Fellow of the American Association for the Advancement of Science.

We will remember David's energy, enthusiasm for science, and emphasis on rigorous logic and careful writing—also his dry humor and infectious smile.


Artigas, P., and D.C. Gadsby. 2003. $Na^+/K^+$-pump ligands modulate gating of palytoxin-induced ion channels. *Proc. Natl. Acad. Sci. USA.* 100:501–505. https://doi.org/10.1073/pnas.0135849100

Bahinski, A., A.C. Nairn, P. Greengard, and D.C. Gadsby. 1989. Chloride conductance regulated by cyclic AMP-dependent protein kinase in cardiac myocytes. *Nature.* 340:718–721. https://doi.org/10.1038/340718a0

Csanády, L., P. Vergani, and D.C. Gadsby. 2019. Structure, gating, and regulation of the CFTR anion channel. *Physiol. Rev.* 99:707–738. https://doi.org/10.1152/physrev.00007.2018

De Weer, P., D.C. Gadsby, and R.F. Rakowski. 1988. Voltage dependence of the Na-K pump. *Annu. Rev. Physiol.* 50:225–241. https://doi.org/10.1146/annurev.ph.50.030188.001301

Gadsby, D.C. 1980. Activation of electrogenic $Na^+/K^+$ exchange by extracellular $K^+$ in canine cardiac Purkinje fibers. *Proc. Natl. Acad. Sci. USA.* 77:4035–4039. https://doi.org/10.1073/pnas.77.7.4035

Gadsby, D.C. 2009. Ion channels versus ion pumps: the principal difference, in principle. *Nat. Rev. Mol. Cell Biol.* 10:344–352. https://doi.org/10.1038/nrm2668

Gadsby, D.C., and P.F. Cranefield. 1979. Electrogenic sodium extrusion in cardiac Purkinje fibers. *J. Gen. Physiol.* 73:819–837. https://doi.org/10.1085/jgp.73.6.819

Gadsby, D.C., R. Niedergerke, and S. Page. 1971. Do intracellular concentrations of potassium or sodium regulate the strength of the heart beat? *Nature.* 232:651–653. https://doi.org/10.1038/232651a0

Gadsby, D.C., R. Niedergerke, and D.C. Ogden. 1977. The dual nature of the membrane potential increase associated with the activity of the sodium/potassium exchange pump in skeletal muscle fibres. *Proc. R. Soc. Lond. B Biol. Sci.* 198:463–472. https://doi.org/10.1098/rspb.1977.0110

Gadsby, D.C., R.F. Rakowski, and P. De Weer. 1993. Extracellular access to the Na,K pump: pathway similar to ion channel. *Science.* 260:100–103. https://doi.org/10.1126/science.7682009

Gadsby, D.C., F. Bezanilla, R.F. Rakowski, P. De Weer, and M. Holmgren. 2012. The dynamic relationships between the three events that release individual $Na^+$ ions from the $Na^+/K^+$-ATPase. *Nat. Commun.* 3:669. https://doi.org/10.1038/ncomms1673

Isaksen, T.J., L. Kros, N. Vedovato, T.H. Holm, A. Vitenzon, D.C. Gadsby, K. Khodakhah, and K. Lykke-Hartmann. 2017. Hypothermia-induced dystonia and abnormal cerebellar activity in a mouse model with a single disease-mutation in the sodium-potassium pump. *PLoS Genet.* 13:e1006763. https://doi.org/10.1371/journal.pgen.1006763

Läuger, P. 1979. A channel mechanism for electrogenic ion pumps. *Biochim. Biophys. Acta.* 552:143–161. https://doi.org/10.1016/0005-2736(79)90253-0

Liu, F., Z. Zhang, L. Csanády, D.C. Gadsby, and J. Chen. 2017. Molecular structure of the human CFTR ion channel. *Cell.* 169:85–95.e8. https://doi.org/10.1016/j.cell.2017.02.024

Nagel, G., T.C. Hwang, K.L. Nastiuk, A.C. Nairn, and D.C. Gadsby. 1992. The protein kinase A-regulated cardiac $Cl^-$ channel resembles the cystic fibrosis transmembrane conductance regulator. *Nature.* 360:81–84. https://doi.org/10.1038/360081a0

Nakao, M., and D.C. Gadsby. 1986. Voltage dependence of Na translocation by the Na/K pump. *Nature.* 323:628–630. https://doi.org/10.1038/323628a0