Colin McClare (1937–1977): a tribute

Luca Turin

Received: 14 January 2008 / Accepted: 20 August 2008 /
Published online: 3 February 2009
© Springer Science + Business Media B.V. 2009

Colin McClare was the first scientist to envision the potential importance of long-lived vibrational excitations in proteins. He did so at a time when there was no experimental evidence for their existence, no plausible mechanism to make them happen, and no interest in the possibility among his peers. He came to the idea by a process worthy of Sherlock Holmes' famous dictum "When you have eliminated the impossible, whatever remains, however improbable, must be the truth."¹ His brief career was a 12-round fight against muddled thinking, both his own and others'. It was also a fight against depression. After a

---

¹He used this very phrase in some notes he wrote (box D13 in the archive).

L. Turin (✉)
Department of Biomedical Engineering, Massachusetts Institute of Technology,
500 Technology Square, Cambridge, MA 02139, USA
e-mail: turin@mit.edu

first breakdown in 1967 from which he recovered, McClare took his own life on the night of January 4, 1977 by drinking cyanide in his King's College London office. He stood defiantly at death's door: he wrote his wife a note telling her he loved her; then, after taking the poison, in her words "a scientist to the last," he recorded his sensations until he lost consciousness.

Alwyn Scott planned to write an article about McClare for a special issue of *JOBP* he was editing. Al is now gone, and that special issue is now, alas, about him as well as about the area of science he did so much to foster. His wish to give McClare due credit was passed on to me. I should stress that, though he has been a hero to me since my student days, I never met Colin McClare. All that follows comes from reading his published works, speaking to his wife Jill, friends, detractors, and former students and reading the papers in the archive that his Head of Department, Nobel Prizewinner Maurice Wilkins, presciently created soon after his tragic death.

McClare's CV covers barely half a neatly typed page. Born 1937, he won a scholarship to Emmanuel College, Cambridge in 1955, graduated in Natural Sciences in 1958, worked for 3 years at the Medical Research Council's laboratories, won a prestigious Beit Memorial Fellowship in 1961, got his Ph.D. from Cambridge in 1962. His doctoral work was a study of hypochromism in DNA bases. Hypochromism is a lowering of the UV absorption by the purine and pyrimidine bases when stacked above one another. McClare's work showed that this was not the only source of hypochromism: another was the "horizontal" hydrogen bond interactions that prevent DNA from unzipping. This was a solid piece of physical chemistry work, published in the prestigious *JACS* in 1967 [1]. The source of the delay in publication is unclear.

After his Ph.D., McClare applied to work with Rothen at the Rockefeller University. Rothen had become first famous, then infamous in the 1940s for having published experiments in which he purportedly showed that an enzyme, trypsin, could exert its proteolytic action across a Formvar membrane 5–20 nm thick, i.e., without contact with its substrate. This was later shown to be due to holes in the Formvar [2]. McClare did not know or did not believe this, wanted to work with Rothen, and had in fact been thinking since his undergraduate days about the possibility of energy somehow being concentrated in particular degrees of freedom of a molecule, even radiated from place to place. A handwritten note entitled "Growth" written over a period of years between 1964 and 1974 records McClare's focus on this. The first entry reads: "1958 [He was 21] Sugden's lecture. Monochromatic IR inhibits reaction." The next paragraph, for 1959, reads: "Begin to follow up. Enzymes work by IR. Discover Rothen. [...] Few silly experiments. Begin to talk with people. First excitement." Then "59–67. Lasers and enzymes. (v. vague indeed) [...] Discouragement. Szent-Gyorgyi. Made chemicals for experiment. Talked to Perutz. [...] Thought of going to Rothen. Fell thru. Discouragement." The last sentence refers to the fact that Jill fell ill just as everything had been arranged and the move to New York was abandoned.

McClare applied instead for a King's College lectureship position "to get some interview experience." He was pleasantly surprised when they wrote back on the very day of the interview to let him know he'd got the job. Once settled at Kings, McClare embarked on an experimental study of *Halobacterium halobium* membranes. This archaean microorganism was then beginning to attract attention because its membranes, built for high salt (halobacteria live in hypersaline lakes, drying seawater pools, and alarmingly, salted fish and meats), readily fell apart into proteolipid components when placed in low-salt environments. One of the big debates at the time was the relationship between membrane proteins and lipids.

The prevailing view of membrane was then the Davson–Danielli model. I do not recall what evidence was in its favor, but I do recall the textbook drawing with a neat lipid bilayer with protein zigzag patterns adsorbed on either side. Such a model seemed no more likely than teleportation to account for ion transport across membranes.

McClare's *Halobacterium* paper is no doubt a worthy contribution but makes dull reading today, and its chief conclusions are not particularly illuminating: the “envelopes” of *H. halobium* are held together by both hydrophobic interactions and electrostatic ones, the latter likely involving magnesium chelates between phosphate groups. Nevertheless, the paper includes a considerable amount of painstaking experimental work, which McClare undertook alone (he acknowledges some technical help late in the project). This is a testimony to McClare's industry, considering the pressures of teaching and administration, which must even then have been piling up on him. Five years later, Singer and Nicolson's landmark 1973 review proposing the fluid mosaic idea of lipid membranes put paid to the Davson–Danielli model.

Remarkably, McClare's *Halobacterium* work was published as a full article in *Nature* [3], and one must wonder how it got so lucky. No doubt the answer is partly that the world was a smaller place then and King's Biophysics was prominent since Franklin and Wilkins' famous DNA experiments and Wilkins' Nobel Prize. But beyond that, one must look to the near-regal powers of *Nature* in those days, powers which lasted until the late 1980s. *Nature* Editor John Maddox, arguably the last man to have a working knowledge of all of science, decided what went into his journal and saw *Nature's* role as that of the king in a feudal world, capable of going over the heads of the barons to single out a promising commoner for ennoblement and elevation to service.

Aside from a short methods paper on a phosphate assay published in *Analytical Biochemistry* in 1972, the *Halobacterium* paper was McClare's last experimental publication. McClare then suffered a mental breakdown (depression, as it would be called today) after his *Halobacterium* work and was silent for 4 years. From his recovery on, he only worked on theory. His last four refereed publications were published, in *Journal of Theoretical Biology* and *Nature* [4–7], where this early connection probably helped. A few words are in order about *Journal of Theoretical Biology*. In the 1970s, those, like myself, who had a passion for biophysics had only a few places to go to: *Biofizika* (translated from the Russian as *Soviet Biophysics*), *Journal of Theoretical Biology*, whose editor was then the Danielli of the membrane model, and a couple of more specialized journals such as *Biosystems* (origin of life) and *Medical Hypotheses*. All were frowned upon by mainstream biologists for whom “theoretical biology” was an oxymoron. To be fair, the proportion of zany dross in all these journals was high, but had it not been they would have been considerably duller. We undergraduates used to poke gentle fun at *Journal of Theoretical Biology*, and would, around noon, make gnomonic statements such as “Lunch: a unifying hypothesis.”

McClare's first venture in bioenergetics proper, the subject which had exercised his mind from the first and which would keep him obsessively busy for the rest of his professional life, was a paper in *Journal of Theoretical Biology* entitled “In defence of the high-energy phosphate bond.” But, one may ask, what is the high-energy phosphate bond and why would it need defending? The great biochemist Fritz Lippman had, in a 1941 review, first propounded the view that ATP was the energy currency of cells and that the hydrolysis of the terminal phosphate group was the key reaction in bioenergetics. Lippman was of the opinion that, insofar as the hydrolysis energy of ATP to ADP was larger than that of ADP to AMP, there was something special about being the third phosphate in line, and coined

the phrase “high-energy bond.” By the time I got to college in 1970, this was enshrined in textbooks as a special tilde-like squiggle $\text{ADP} \sim \text{P}$.

This sort of sloppy biochemistry-speak was a red rag to physical chemists, and it duly goaded some of them into publishing a critique in *Nature* in 1953. The senior author was Charles Vernon, a distinguished chemist at University College London. He made the point that no bond in ATP could be said to be high-energy, that in a hydrolysis reaction only the difference between energies of reactants and products mattered, and that the term “high-energy bond” was misleading. All true. However, Vernon went on to say something which we now know to be manifestly false: “It is impossible for any simple bond-dissociation process to be energy producing and the concept of energy-rich bonds and the storage of energy in bonds are physically meaningless.” Counterexamples are the high energies involved in bond breakage of strained hydrocarbons like cubane, and the storage of large amounts of energy in vibrational excited states of stretch modes, as in the HF laser. Much of McClare’s future struggles hinged on the fact that Vernon, in clarifying one thing, had obscured another. By the time I got to UCL, Charles Vernon was teaching chemistry to first year undergraduates. On the first lecture of the first day, Vernon held up a copy of Lehninger’s *Bioenergetics*, replete with $\sim$ squiggles and said “I want every one of you to buy and read this book: it is utter rubbish from beginning to end.” We had no idea what this was about but were suitably cowed. I found out much later that Vernon had been cheated of due credit on a fundamental discovery of biological chemistry, the chemical mechanism of lysozyme action, which may have accounted for his dislike of biologists.

McClare’s main point in his defense of the squiggle was this: there may be no high-energy bond in ATP, but its hydrolysis must somehow create one. He points out (as Brillouin and Szilard had done before him) that, as machines get smaller, the interference of fluctuations with their operation must get correspondingly larger, as must the relative cost of control. McClare argues that, at the single-protein level, the assumption of thermal equilibrium inevitably leads to loss of most of the energy which is to be converted, say from ATP hydrolysis into a force. McClare deduces that nonthermal storage of energy in an excited state, vibrational or electronic, is essential to energy conversion. In his view, enzymes may have been selected by evolution not to be at thermal equilibrium at all times with their environment and that this may be the key to their function. Most readers found his papers obscure in concept despite being written in clear English. Those who understood them well enough to disagree argued variously (a) that microscopic thermal disequilibrium in a condensed phase has never been seen and (b) that it is impossible. McClare countered that it is not impossible and had been seen in lasers, etc.

At that point, McClare was in a position similar to that of Boltzmann in 1906: Boltzmann needed evidence for the existence of atoms, McClare needed evidence for long-lived vibrational excited states in proteins. Had the 1954 results of Fermi, Pata, Ulam, and Tsingou been known to him, McClare could have used this precious ammunition in his defense, at least until the Davydov soliton came along in 1973. McClare curiously did not appear to view Davydov’s *Journal of Theoretical Biology* article as momentous, though he mentions it soon after publication in a letter. I suspect that, owing to Davydov’s rather unclear writing, McClare was (as I was for years) under the impression that what vibrates are the hydrogen bonds between peptide groups, and unaware that what Davydov was in fact proposing Amide I vibration propagating by dipole–dipole coupling. But this was later: all McClare could offer in 1971–1972 were subtle arguments for the necessity of such excited states, and a modified form of the second law: “The only forms of energy which can be used to drive a particular cyclic isothermal machine which takes a time τ to operate are those

forms which remain unavailable to non-specific exchanges for a time longer than tau.” This did not help him with most biologists, whose fear of thermodynamics is in exact proportion to their ignorance of the subject. An odd story pieced together from his correspondence illustrates this. *New Scientist* editor Roger Lewin wrote to him in May 71 “confirm[ing] the invitation to write an article for us on the second law in biology,” and added graciously “If you can do it you will be doing a great service to the scientific world; From what I’ve seen I’m sure you can.” The length was 2,000 words, the fee £25. McClare wrote it forthwith. Nine months later, having heard nothing, McClare asked what had happened to it. Two weeks later, Lewin replies that it “simply failed to generate enthusiasm in the other members of editorial staff who read it.” This does not ring true: the article was concise and brilliant, and in any event, Lewin could have asked for changes. It is hard to resist the impression that McClare’s views had been declared “unsound” in high places.

In the early 1970s, McClare began to focus on muscle as a possible system in which to study biological energy conversion. In part, this was due to the proximity of the distinguished muscle physiologist Jean Hanson, also at King’s Biophysics. Two miles away, University College London’s Physiology Department was also prominent in this field. There, in addition to A. F. Huxley’s group, R. C. Woledge and D. R. Wilkie (then chair of the department) were studying thermal phenomena occurring during contraction and publishing on the subject of the energetics of muscle contraction. To put all this in perspective, between 1969 and 1973, UCL Physiology staff had published papers with the following titles (in no particular order): Reassessment of the role of ATP in vivo; Thermodynamics and biology; Energetics of muscular contraction; Chemical change and energy output during muscular contraction; Energy balance during muscular contraction; Heat production and energy liberation in the early part of a muscular contraction; An examination of absolute values in myothermic measurements; Proposed mechanism of force generation in striated muscle. Many of these papers disagreed with each other.

UCL Physiology also counted among its staff the organic chemist Barbara Banks, wife of Charles Vernon, and equally vitriolic in combating sloppy thinking among biologists. Banks and Vernon had revived the old ATP controversy with a 1970 paper in *Journal of Theoretical Biology* that essentially described as meaningless all free-energy measurements of ATP hydrolysis. Barbara Banks also wrote an article in *Chemistry in Britain* ridiculing the naive thermodynamics notions entertained by her biologist colleagues. This led to a series of replies by Linus Pauling, Douglas Wilkie (her Department chairman), and Andrew Huxley (ex-chairman, Nobel Prizewinner, and Royal Society Research Professor). Banks and Vernon clearly lost the debate.

McClare blundered into this argument with his 1972 *Nature* paper [7] entitled “A Quantum-Mechanical Muscle Model.” *Nature*, astonishingly, had taken fully 3 years to publish it after acceptance, and one suspects that the decision of when to go to press may have once again rested entirely with John Maddox, who waited for a suitable moment to toss a burning rag on the pyre. McClare’s abstract is innocently incendiary: “Phenomena well known in chemical spectroscopy are used to explain muscular contraction; fundamental reasons for excluding alternative explanations are outlined.” Figure 1 depicted an energy conversion scheme involving, heaven forbid, both vibrationally and electronically excited states. Contrast this with the low-key tone of Huxley and Simmons, also in *Nature* a year earlier: “Recordings of the change in tension in striated muscle [...] have made it possible to suggest how the force between thick and thin filaments may be generated.” Huxley’s closest collaborator, R. M. Simmons, was my tutor. My first

assignment as a tutee had been to use the then-awesome IBM 360 recently installed at UCL to obtain numerical results of Huxley's model for muscle contraction.

I remember reading the article in *Nature* and rushing up excitedly to Bob Simmons' office to ask him what he thought. He puffed on his cigarette and languidly let drop "complete rubbish" but would not elaborate. The reaction was not long in coming, unsurprisingly from Banks and Vernon, still spoiling for a fight, in the correspondence pages of *Nature*. It was extraordinarily violent: its last sentence reads "The [model] put forward by McClare has nothing particularly to do with quantum mechanics or thermodynamics or muscle contraction." Barbara Banks told me 30 years later that she deeply regretted the contemptuous slap across the face and felt partly responsible for McClare's death. To be sure, the tone of Banks and Vernon's letters to McClare is gratuitously sarcastic and makes a stark contrast to the letters exchanged between McClare and very eminent scientists like A. F. Huxley and T. L. Hill who, while in complete disagreement, were unfailingly courteous.

In truth, the impact of all this on McClare is hard to assess. On one hand, when I met his wife in the late 1990s and mentioned Barbara Banks, she vividly remembered Colin endlessly, angrily talking about her and Charles Vernon. On the other hand, McClare's own papers suggest that he felt he had won the argument with Banks and Vernon. This did not mean that everyone agreed with him, though McClare's supporters, Karl Popper, David Bohm, and Maurice Wilkins among them, were every bit as eminent and scientifically respectable as his enemies. Popper's support was not merely that of a friend: Popper had been interested in the foundations of statistical mechanics and had written a paper in 1957 [8] on equipartition. Nevertheless, the stress must have taken its toll. McClare published a longer and more detailed version of the muscle model in *Journal of Theoretical Biology*, but his private musings reveal the rise of a groundswell of despondency that heralds his second, final depression. We are now in the endgame of McClare's tragic career: his ideas were maturing rapidly, and he was given two more chances to make them known.

The first was in a symposium organized by David Green at the New York Academy of Sciences, whose proceedings were published in the *Annals* [9]. Green's gracious letter of invitation to McClare expressed "confidence that the conference is destined to make scientific history by setting the future directions of bioenergetics." McClare replies wistfully that he had "expected the future to begin in 1983, not 1973." He wrote amusing notes of his impressions of other speakers at the New York congress, showing that he too could be caustic in private. David Green was "very imaginative but undisciplined," others "waffle on," are "totally incomprehensible," say "nothing new at all," are "Crap" or "even worse. Irreversible bullshit," "how can anyone talk such utter nonsense?," "a cluttered mind." Only Hartley finds favor: "Really beautiful exposition." Each speaker gets at least half a page of notes full of questions, arguments, exclamation marks. Clearly, McClare was in his element at last, enjoying himself, surrounded by scientists who agreed with him on what the problems were, though they might differ on the nature of the solution. His own paper is, as always, elegantly written, free of all jargon, almost nakedly devoid of mathematical equations. On the last page (and this before Davydov's solitons), he suggests prophetically that the energy of ATP hydrolysis might be carried by an overtone of the Amide I band of the alpha-helix. He was clearly unwell: soon after (May 73) he wrote to Green "for some reason I do not understand I get very low in spirit after an experience like your meeting."

His last publication was an invited paper and lecture at a Ciba Symposium on Energy Transformation in Biological Systems held in 1975 in London [10]. This was a completely different affair from the New York one, and the lineup of speakers pitted him as the lone heretic against a formidable array of biophysicists and biochemists, almost without

exception representing the “conventional” view. The exception was Fritz Lippmann, who in his opening lecture unrepentantly stated: “In the phosphoanhydride bond of ATP metabolic energy apparently collects before it is transmitted for functional use.” McClare talk came immediately after A.F. Huxley’s, a formidable act to follow. McClare started his talk by saying that he felt “as if [he’d] been thrown to the lions.” What makes this last publication fascinating is that the subsequent discussion, as was customary for lavishly funded Ciba Symposia, is recorded verbatim. The hostility is palpable, particularly given the usual politeness of British scientific discussions. His questioners take careful aim and are clearly irritated to see him dodge lethal bolts time after time. Two pages into the discussion, rapid-fire one-liners are being exchanged “McGlashan: “No it does not. Nobody ever said it did”; McClare: “Einstein (1917) did [...]”. His last words in print are emblematic. To a pedantic comment to the effect that he had got one excited state wrong, McClare replies: “I accept that the details are also important and that I may have got them wrong. But this error would make no difference to the argument about the energetics, which is all I used the analogy for.”

Thirty years later, we can see that McClare had got one fundamental thing right: vibrational energy can be stored and transmitted in proteins. Two other questions he asked remain complete enigmas: how are these excitations generated and how are they used at the receiving end? Had more recognition or better medication stayed his hand on January 4, 1977, Colin McClare would be 71 today and would no doubt have some ideas on the matter.

References

1. Gratzner, W.B., McClare, C.W.F.: A hypochromic effect from pairing of purine and pyrimidine bases. *J. Am. Chem. Soc.* **89**, 4224–4225 (1967)
2. Kauzmann, W.: Reminiscences from a life in protein physical chemistry. *Protein Sci.* **2**, 671–691 (1993)
3. McClare, C.W.F.: Bonding between proteins and lipids in the envelopes of *Halobacterium halobium*. *Nature* **216**, 766–771 (1967)
4. McClare, C.W.F.: Chemical machines, Maxwell’s demon and living organisms. *J. Theor. Biol.* **30**, 1–34 (1971)
5. McClare, C.W.F.: In defence of the high energy phosphate bond. *J. Theor. Biol.* **35**, 233–246 (1972)
6. McClare, C.W.F.: A “molecular energy” muscle model. *J. Theor. Biol.* **35**, 569–595 (1972)
7. McClare, C.W.F.: A quantum mechanical muscle model. *Nature* **240**, 88–90 (1972)
8. Popper, K.R.: Irreversibility; or entropy since 1905. *Br. J. Philos. Sci.* **8**, 151 (1957)
9. McClare, C.W.F.: Resonance in bioenergetics. *Ann. N. Y. Acad. Sci.* **227**, 74–97 (1974)
10. McClare, C.W.F.: How does ATP act as an energy source? In: *Energy Transformation in Biological Systems Ciba Foundation Symposium 31 (New Series)*, pp. 301–325 (1975)