Wilfred F Widdas

1916–2008

Wilfred Widdas was a stalwart of The Physiological Society; a Member for over 50 years he was on the Editorial Board of *The Journal of Physiology*, and was its chairman (1970–72). He was assiduous in attending Society meetings even into old age, sitting near the front and always keen to contribute to discussion – sometimes in a blunt style that somewhat baffled those speakers who assumed the supremacy of textbook orthodoxy. Wilfred lived to see the atomic structures of molecules that underpinned processes that he had obtained theoretical insights into more than 50 years ago – this is discussed by Richard Naftalin. His willingness to think against the current grain, to embrace mathematical reasoning and to exploit quantitative prediction in cell physiology were characteristic of his personal, idiosyncratic style. Indeed his attempts to explain biological phenomena with physical mechanical analogues may have their Victorian roots via his own link to Faraday.

His more recent writings on muscle contraction (the most recent 'A reconsideration of the link between the energetics of water and of ATP hydrolysis energy in the power strokes of molecular motors in protein structures ' published only this autumn), and on the role of surface tension and water evaporation in protein conformation changes remain speculative, but are full of ideas that may yet challenge future experimentalists.

Much less abstruse but characteristically profound were his contributions to placental and fetal research. He started in this field in the late 1940s when as a young (medically trained) demonstrator at St Mary's Hospital Medical School in London he assisted his then Professor, A.S. Huggett, in work on a variety of experiments all related to fetal growth and its control. Following his move to his own department at Bedford College, University of London, he wrote in 1960 his last contribution to this area, a masterful yet brief review on 'Transport mechanisms in the foetus' for the British Medical Bulletin. His insights pithily summarized in this article remain incisive and relevant: thus, conceptually placental transport was seen to be distinct from transcapillary exchange with respect to mechanism; for the placenta, colloid osmotic forces were less important than those set by non-colloids, and it was the transport processes for these solutes, specifically for amino acids and for sugars that needed understanding. Widdas predicted that these processes would involve facilitated diffusion mechanisms – mechanisms of the type originally proposed by Widdas himself in his classic 1952 paper in *The Journal of Physiology*. That paper had appeared in the September issue of *The Journal*; the August issue had contained 'A quantitative description of membrane current' (all 44 pages) by two young physiologists working in Cambridge, individuals who set the scene for the heroic era of post-war UK physiology. It has to be relevant to the physiological community of today – scattered as it now is in the UK within many different academic communities – that both of these papers, that of Widdas as well as that of Hodgkin & Huxley, remain widely cited two generations later. Will the insights of articles in today's 'high impact factor' journals wear as well?

Wilfred Widdas (who died on 23 October) with Graham Baker (photo by Martin Rosenberg,1999).

Richard Boyd
Brasenose College, Oxford

Richard Naftalin writes:

To members of The Physiological Society Wilfred Widdas is synonymous with erythrocyte glucose carriers, GLUTs as they are now called. He was at the forefront of the twentieth century drive to bring the rigour of physical sciences to the description of biological processes. This reductionist approach to Biology has had its fair share of success over the past 60 years and Wilfred's work certainly has been very influential in shaping our current views on biological transport processes.

Despite a late start, delayed by World War II, during which he served as a doctor in the Royal Army Medical Corps retiring at the rank of Major in 1946, having qualified in Medicine at Newcastle in 1937, Wilfred had a long career in Physiology.

It started 2 years after being demobilized when he was awarded a studentship, for ex-service doctors to undertake PhD training in the Physiology department of St Mary's Hospital under the supervision of Prof A. Huggett FRS. His primary field of study was glucose transport across the sheep placenta. It was then thought that glucose crossed like oxygen from mother to fetus by passive diffusion down its concentration gradient i.e. glucose $\text{flux}_{mf} = k(S_m - S_f)$ where S_m and S_f refer to either glucose concentration in maternal or fetal blood. It became evident that although at low concentrations glucose could cross the placental barrier as a linear function of the glucose concentration gradient in either direction, at higher concentrations, the transport rates were consistent with a hyperbolic relationship between flux and glucose concentration. At high concentrations the glucose $\text{flux}_{mf} = k(1/S_f - 1/S_m)$.

Today, saturation kinetics is an everyday concept routinely taught as part of every first year biology course. But back in 1950 it was new departure. At the start the analysis of experimental data involved quite a lot of serious maths –well beyond the grasp of most physiologists at that time – or this. However, in addition to his medical degree, Wilfred

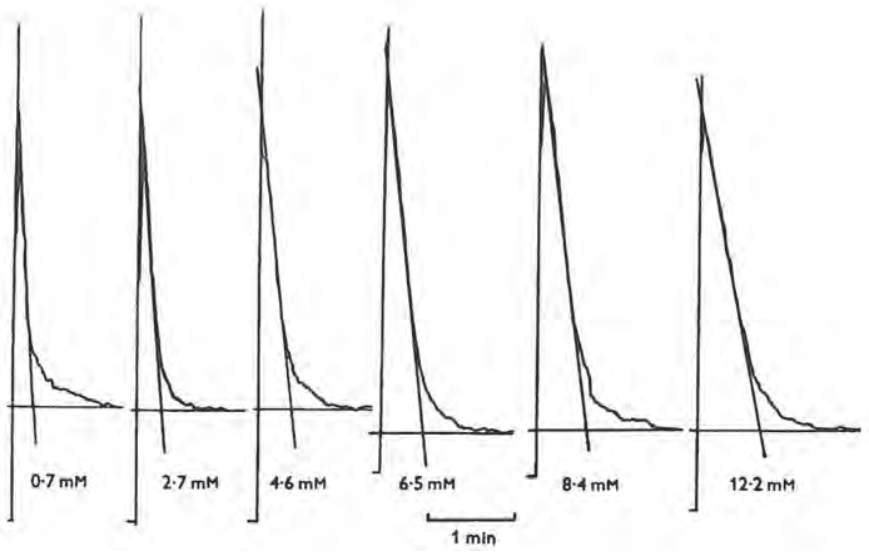

Figure 1. Tracings of a series of records from the photo-electric apparatus during 'exit' experiments at 37°C and pH 7.4. Cells equilibrated in 76 mM glucose were losing glucose into media containing glucose at the concentrations shown. The linear part of each record has been produced to cut the base line, and the time from injection of the cells to this intersection was measured for analysis of the results (from Sen & Widdas, 1962*a*).

had obtained an external London University degree in mathematics, so was well able to formulate the integral equations required to describe the time courses of net glucose movements across the placenta. In that far off age, when the slide rule was at the cutting edge of technology, even with his degree in maths, this was a considerable feat, which was under-appreciated by the majority of his contemporaries, who perhaps were more excited by descriptions of electrical transients in nerves and muscles coming from Cambridge and UCL than by the more sedate changes in blood sugar in fetal sheep reported from St Mary's Medical School.

We tend to think of Wilfred Widdas as an aloof establishment figure and he certainly became that: Foundation and only Professor of Physiology at Bedford College, London; Editor of *The Journal of Physiology*; member of the Senate of London University and Chairman of the Board of Studies in Physiology, London University.

However, it was not always so. In a rather bitter note to Physiology News (**65**, 10) Widdas describes how his theory of mediated diffusion of glucose was initially rejected by establishment figures at University College London (amongst whom was E. J. Harris, discoverer of ATP consumption during muscle contraction – and as a later claim to fame, supervisor to such worthies as Roger Thomas, my colleague Robert Hider and yours truly).

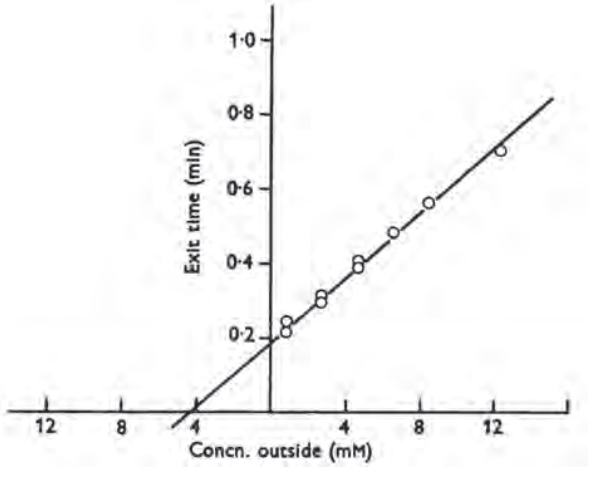

Figure 2. 'Exit' times obtained from the records described in Fig. 1 plotted against the concentration of glucose in the outside media. The line (drawn by eye) gives two intercepts; that on the ordinate represents the time (to) which would have been taken for exit into a glucose-free medium and that on the abscissa gives the concentration of glucose into which the exit time would be twice to (from Sen & Widdas, 1962*a*).

It was only after Fisher and Parsons working in Oxford had applied saturation kinetics to description of sugar flow across the intestine (Fisher & Parsons, 1953) that Widdas was permitted to publish what were to become his classical papers on analysis of glucose transport in placenta (Widdas, 1952, 1954).

These early studies are exemplary in their clarity, attention to detail and depth and breadth of understanding and prescience. These qualities apply to all Wilfred's work published in *The Journal of Physiology*. His papers that reached a wide following were those initiated in King's College London with A.K. Sen, but completed at Bedford College (Sen & Widdas, 1962*a*,*b*).

This work adopted the methodology of Orskov (1935) to monitor the volume changes of human erythrocytes suspended in isotonic solutions by change in light scattering. The method had also been used by Wilbrandt (1938) and LeFevre & LeFevre (1952) to monitor rates of hexose sugar inflow and exit from erythrocytes. They were one of the first direct means of recording an electrically silent phenomenon, which had been clouded both by laborious calculations using difficult maths needed to work out the rates and by tedious and imprecise chemical analysis of cytosolic sugar content.

Widdas's elegant and simple studies brought much needed precision to the ideas of how sugars move across the cell membrane.

The diagrams in Figs 1 and 2 show how Widdas used the Orskov method to obtain the infinite – cis K_m at 37ºC, later termed, the 'Sen–Widdas K_m' by W. D. Stein (Stein, 1989). Figures 1 and 2, taken from Sen & Widdas (1962*a*), show that increasing the glucose concentration in the external

bathing solution to 4 mM reduces the initial rate of glucose exit from cells containing 76 mM by half. If glucose were transported by diffusion then the concentration needed to reduce the initial rate by half would be 38 mM.

The hyperbolic relationship between the glucose concentration in the external bathing solution and the inhibition of glucose as illustrated in Fig. 2 suggests that glucose reversibly binds to an import site on the external surface of the cell membrane for glucose entry with a K_m of ≈ 4 mM. This glucose entry slows the rate of net glucose exit, which is the difference between exit and entry fluxes.

A conceptually simple way to explain saturation kinetics was in terms of a carrier which had the properties of ligand recognition and translocation from side to side. According to Widdas 'Lundegardh (1940) appears to have been the first to suggest that molecular components of the membrane may be involved in such transfers' (Widdas, 1952). This concept, first called the ferry boat model by Ussing (1952), was generally adopted in the 1950's to explain, first, the saturation kinetics and then selectivity of the transporter. The reason for preference for a mobile carrier over a fixed site transporter was the phenomenon predicted by Widdas in his 1952 paper on glucose transport by the placenta of uphill countertransport. This was first demonstrated elegantly by Rosenberg & Wilbrandt (1957). They argued that a fixed site model does not permit the possibility of uphill counterflow of a labelled by the downhill counterflow movement of an unlabelled ligand whereas a mobile carrier does. This argument together with the similar phenomenon now termed 'accelerated exchange' (LeFevre & McGinniss, 1960), where the rates of sugar exchange measured by isotope fluxes are observed to be much faster than the maximal rates of net flux, has been considered as crucial evidence in favour of mobile sites in the long running debate as to whether glucose transport is via a number of fixed sites occluding

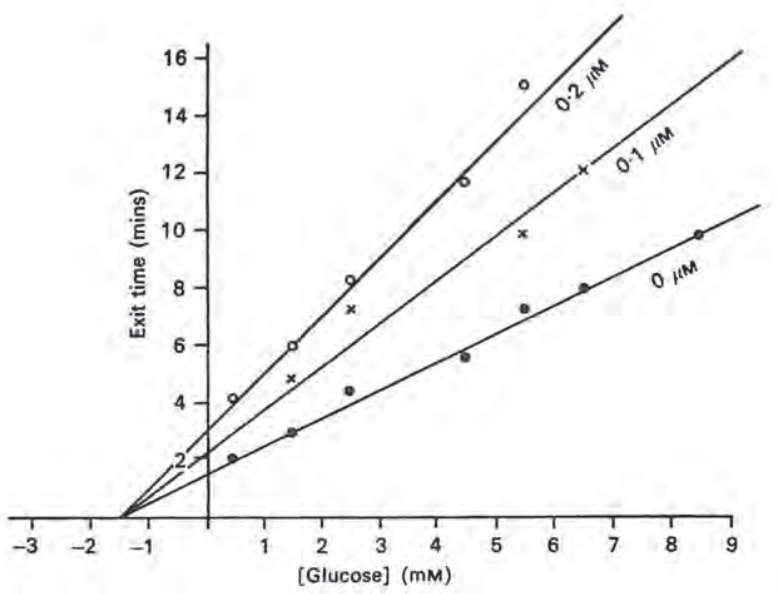

Figure 3. Effect of outside glucose concentration on glucose exit times in the absence and presence of Cytochalasin B at 16°C. Points • exits in control experiment, points x exits in the presence of 0·1 µM Cytochalasin B, points o exits in the presence of 0.2 µM Cytochalasin B (from Basketter & Widdas, 1978).

a channel or via a single site with alternating exposure to either side of the membrane.

The next important study Widdas undertook which combined the Orskov method with monitoring of isotopically labelled sugars was a demonstration by kinetics with David Basketter that cytochalasin B and phloretin, both known to be powerful inhibitors of glucose transport, act at different sides of the transporter. Cytochalasin B acts as a non-competitive inhibitor of external glucose exit (it does not affect the

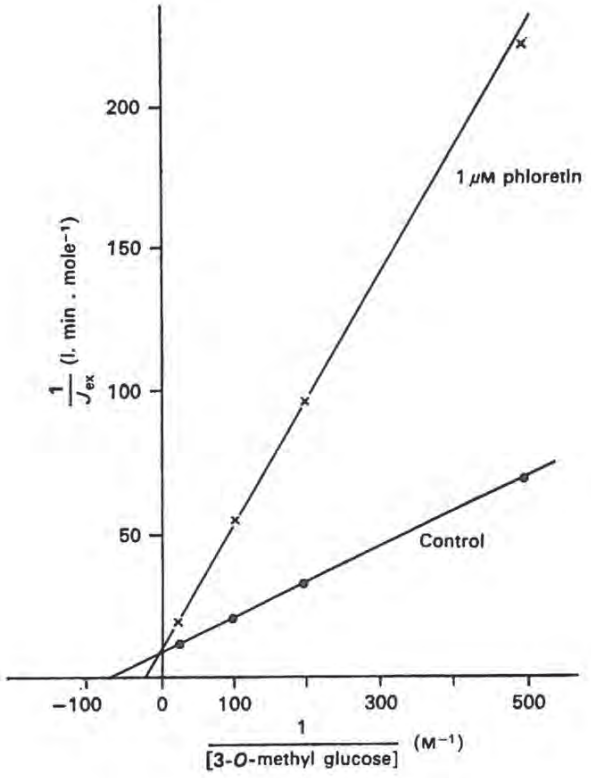

Figure 4. Lineweaver-Burk type plot of 3-*0*-methyl glucose exchange in the range 2-40 mM in the absence and presence of 1 µM phloretin. Points • control exchanges, points x exchanges in the presence of 1 µM phloretin. Points represent mean of two experiments (from Basketter & Widdas, 1978).

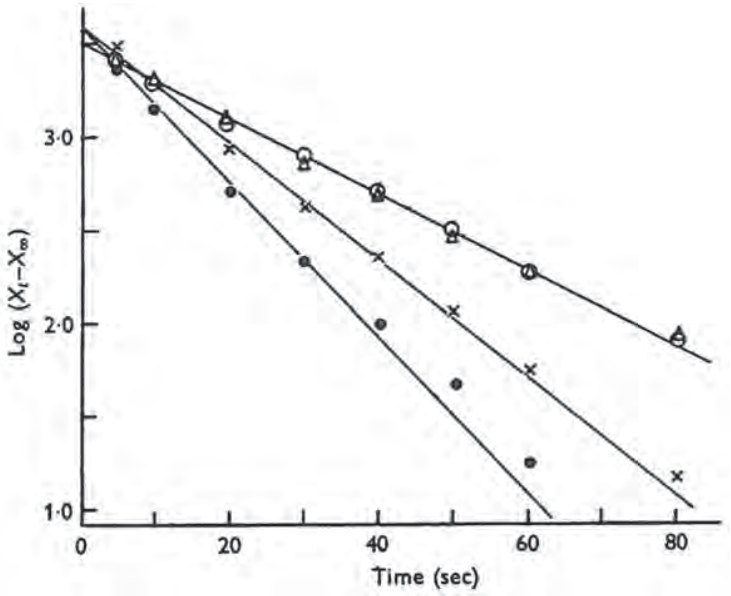

Figure 5. Effects of ethylidene glucose on the loss of intracellular radioactivity during glucose exchange at 20 mM (16ºC) plotted logarithmically. Points • control experiment: points x 50 mM inside: points o 200 mM inside: points Δ 25 mM outside. The slopes of such lines were used to derive the exchange flux as described in the text (from Baker & Widdas, 1973).

K_m at the external site (Fig. 3), but as a competitive inhibitor to glucose exchange flux, mainly controlled by glucose binding to the internal site. In contrast, phloretin and maltose, a non-penetrating dissacharide, act as competitive inhibitors at the external site, but as non-competitive inhibitors of exchange (Fig. 4) (Basketter & Widdas, 1978).

A key long-term collaboration Widdas had was with Graham F. Baker, who studied as an undergraduate, PhD student and then as post doctoral colleague. This collaboration with Graham continued after Graham moved to a lecturing post at Royal Holloway, Egham which amalgamated with Bedford College until Graham's untimely death in 2006.

The most important work of Baker and Widdas together, in my view, was their demonstration of the asymmetric affinities of the glucose transporter. This was first shown unequivocally using the non-transported, but permeant inhibitor 4-6-*O* ethylidene-D-glucose. The half-saturation concentration for ethylidene glucose inside the cell was estimated at *ca* 110 mM, whereas on the outside the value for exchange inhibition was ca 11 mM (Figs 5 & 6).

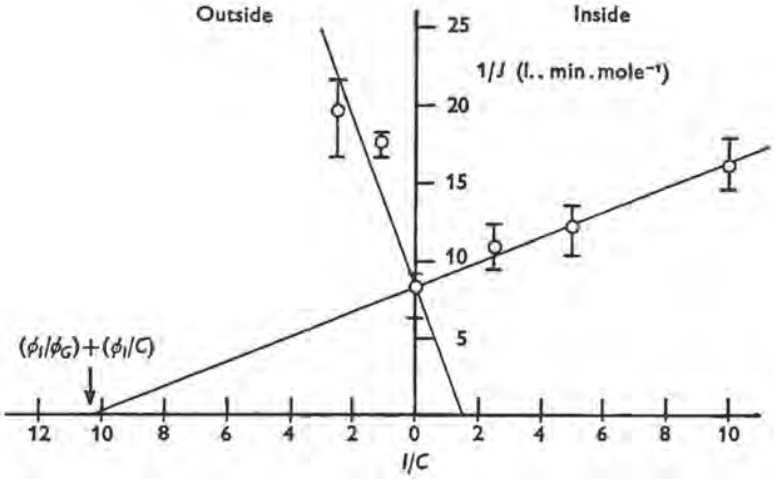

Figure 6. Reciprocals of glucose exchange fluxes (at 20 mM and 16ºC) at different concentrations of ethylidene glucose (relative to that for glucose). Points on the right were means (and range of 3 to 5 results) with the inhibitor inside the cells. Points on the left were means (and range of 3 results) with the inhibitor in the outside medium. Control point mean and range of ten results. Intercepts on the abscissa depend on the ratio of the half-saturation constants but also contain the term Φ_I/C (from Baker & Widdas, 1973).

The possibility of asymmetric transporters was first mooted by Widdas in his earliest papers (1952, 1954) The transport theories for carrier-mediated glucose transport formulated dialectically by Widdas and a few contemporaries quickly became the mainstays of the thin scaffold of evidence supporting the alternating site carrier theories of passive solute transport. It was also incorporated into symporter and antiporter theory. With very few dissenters, these models have become the dominant paradigm for biological transport mechanisms.

Although he dedicated most of his long and very distinguished academic career towards defining and refining how glucose crosses cell membranes, Widdas was very aware that kinetics is a remarkably ambiguous science which requires linkage to a firm structure to acquire credibility. Latterly, in his post-retirement years at Royal Holloway, Widdas attempted to rationalize the kinetic studies on glucose transport by projecting them onto the emergent 2- and 3-dimensional structures of transport proteins. Some of this later work has proved remarkably prescient, like his early kinetic studies.

Despite his widespread influence on transport theory Wilfred never had a large scientific budget or became part of the scientific nomenclatura, which now, more than ever before, decides on what and who will prosper. During most of his working life the bulk of his equipment was home-made or consisted of ex-military cast-off pen recorders, of which he was very proud. One wonders if he could have survived today.

As a man and physiologist Wilfred Widdas was indefatigable, continuing his work literally until the very last. He will be remembered, admired and respected by those who knew him for being both irrepressible and irreplaceable.

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Anthony Carruthers writes:

Wilfred Widdas and I met several times during my graduate study at King's College London. These meetings were occasioned by gatherings of the London membrane group and often found Wilfred, Graham Baker and Richard Naftalin engaged in discussions about their

Wilfred (at the back) with colleagues at Helmsley Hall, 1940–41.

recent findings or, if fortune smiled, discussing some of my data on sugar transport in squid giant axons. Listening to these three engaged in data interpretation opened new horizons for me by illustrating the cut and thrust of scientific discourse and by redirecting me to an evolving literature on the theory of protein-mediated solute transport across cell membranes.

Wilfred Widdas was a shy, modest man but possessed of deep insights into glucose transport. It was not surprising, therefore, to learn that Wilfred's contributions to the field of glucose transport were numerous and transformative. His work, along with that of Paul LeFevre and David Miller, forever changed the study of glucose transport from phenomenology to a quantitative science. He used the tools emerging from the simple but profound recognition that transporters are enzymes that translocate substrates between cellular compartments to develop and critically evaluate new hypotheses for sugar transport. More importantly, his contributions provided the foundation for others to build upon as the field grew and theories for transport multiplied. Wilfred's most important papers remain absolutely relevant to and revealing of the complexities of sugar transport. These include: (1) the defining 1952 opus describing saturable sugar transport and an alternating carrier transfer mechanism (Widdas, 1952); (2) the first consideration of a transport mechanism that simultaneously presents extra- and intracellular sugar binding sites (Baker & Widas, 1973); (3) demonstrations of asymmetric affinities for sugar transport inhibitors and techniques for determining inhibitor sidedness (Basketter & Widdas, 1978). These ideas coalesced into a 1980 review of sugar transport (Widdas, 1980) that remains both germane and a delightful read. Wilfred Widdas was a catalyst who legitimized the study of non-electrolyte transport, who offered the first description of the alternating carrier model for sugar transport that is so influential among today's biochemists and who remained true to the idea that theory must explain behaviour even at the cost of rejecting theory. Those of us who work in the field of non-electrolyte transport have lost a revered colleague who pioneered the foundations of our field.

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Gerald Elliott also writes:

Wilfred Widdas was the most charming and helpful of the people that I met after I arrived at King's College London as a very 'green' young Demonstrator in Physics in 1954. He was Reader in Physiology and a stalwart of the Mixed Common Room. Incidentally, contrary to some accounts of the Rosalind Franklin story, this facility existed happily alongside the male-only room and was very pleasant; the male one seemed rather less welcoming, being then dominated by a group of what we would nowadays call rather 'fogey-ish' young lawyers and historians

Wilfred taught me to order Dover sole on Fridays when available, and showed me how to dissect it. He told me he had been a Royal Army Medical Corps doctor during the war, perhaps because I had mentioned that I was completing my National Service in the Territorial Army. It was not until after his death that I learned that he had been plucked from the beaches of Dunkirk and returned to England by a minesweeper that had been sunk on a subsequent trip.

Wilfred described himself then as basically a simple medical man, a

Wilfred Widdas (1974) at the Delhi Congress, with AK Sen.

description he always reiterated whenever it was appropriate. Our meeting came just after the publication of his seminal *Journal of Physiology* paper mentioned elsewhere in these accounts. As a young physicist just starting in biology I am sure that I did not recognize his distinction at the time. However, I was very aware of his friendship, which meant a great deal to me, and of his encouragement and interest in all aspects of the science that went on at King's.

Though I was delighted for him, I was personally a little sad when Wilfred was appointed Foundation Professor of Physiology at Bedford College, since it meant we no longer saw him so often at King's. I greatly missed his company at lunch, though I continued to see him at Physiological Society meetings and enjoyed talking to him whenever we met. I recall that after Bedford merged with Royal Holloway we would sometime talk about the buildings of the merged College at Englefield Green, which I had visited in my childhood, and which were famously (and incongruously) modelled on a Loire Chateau.

The second phase of my interaction with Wilfred began 40 years on, when I wrote to congratulate him on being elected an Honorary Member of The Physiological Society in 1994. By this time I was well aware of his many distinctions. In particular, having come across his paper *Developments in sub-microscopic physiology* (*Biomedical Letters*, 1993, **48**, 15–27) I also knew that he was interested in biological machines. I sent him copies of some publications of my own on muscle contraction, and this initiated a 14-year correspondence between us about biological motors that was terminated only by his death on 23 October last year.

This correspondence had us agreeing on some things, but arguing about others. In retrospect, I am slightly sad that we tended to focus more on our disagreements – there was much that we did agree on, and it is a pity that we did not pursue these aspects further. As for the disagreements, as I understood it Wilfred was convinced that muscle contraction, and other biological phenomena, involved the interplay of two energy sources, these being the surface energy of water and the usual energy derived from ATP. I did not find his arguments on this point totally convincing – for me at present it is 'not proven' – although it is quite possible Wilfred may eventually turn out to have been correct. I am reluctant to try to summarize his ideas any further because in one of the last emails he sent me, about 2 weeks before his death, he wrote 'Here you go again, misquoting what I wrote and then arguing that the concept is unclear to you'. I was abashed because he went on to say that this was a technique that he had encountered from diverse referees, and that generally led to his papers being rejected – I too have often been on the wrong end of this phenomenon! Interested readers can find Wilfred's own account in the open access journal *Int J Mol Sci* (2008, **9**, 1730–1752), which is the paper we were currently discussing. Subsequently he developed what he called his 'wheelbarrow view of physiology' for me. This was related to a point that he made in his last letter to *Physiology News* (Winter 2008, **73**, 36) where he took issue with a rather sloppy shorthand statement on thermodynamics made by some crystallographers. As will be seen from that letter, Wilfred felt that earlier correct science (he cited Wallace Fenn's 1920s work on muscle) was too often subverted and misunderstood by subsequent workers.

Captain WF Widdas.

I spent the last part of October at my French holiday home for the cider-making season, and on the all-day ferry ride back to England I had a long think about a 'gedanken experiment' that I would put to Wilfred to take our discussion forward on the topic of the interaction and inter-conversion of biochemical energy sources. I intended to base this on the first electric motor invented by Michael Faraday, because I knew Wilfred was proud of his illustrious family forebear. Coming to my computer the next morning to write to him I was shocked and saddened to learn of his death. My last attempt to take Wilfred out to dinner a few years ago, in tribute to those long-ago King's College Dover soles, had been thwarted by his physical frailty and dietary regime. However, this frailty emphatically did not extend to his mental processes, as our email exchanges testified. In understanding, in intellectual capacity and in sheer energetic involvement Wilfred Widdas was at his best until the very end. For the second time in my life I shall miss him dearly.

The Society also notes with regret the deaths of:

Pavel Hnika, a Society Member since 1966.

Margarethe (Gretel) Holzbauer-Sharman, a Society Member from 1962.

Hans Friedrich Meves, a Society Member since 1965. He was a Member of *The Journal of Physiology* Editorial Board from 1977 to 1984.