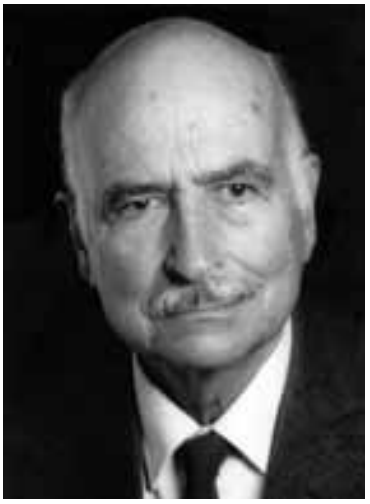
Silvio Weidmann

1921 – 2005



Despite having an almost pathological fascination with languages, and being of a generation that needed as a student in the 1950s to read German in order to keep up with the scientific literature (what is now the *European Journal of Physiology*, was *Pflügers Archiv für die gesamte Physiologie des Menschen und der Tiere* and was published entirely in German), I confess that I never found it congenial. I put it all down to a very bad experience at school with a teacher of the German language. But there is nevertheless a book in German that I know almost by heart: Silvio Weidmann's classic *Elektrophysiologie der Herzmuskelfaser* (Weidmann, 1956).

To a student of cardiac electrophysiology starting work at UCL in 1958 this was the gold standard. During the late 40s and early 50s Silvio had swept the board with a phenomenal set of microelectrode experiments on cardiac Purkinje fibres, partly based on his first use of microelectrodes with Edouard Coraboeuf and Morrell Draper, during his highly productive period at Cambridge. He worked on Purkinje fibres of the heart while Hodgkin and Huxley were pioneering their voltage clamp and mathematical analysis of the squid giant axon. Of course, you can find Silvio's original papers in English mostly in *The Journal of Physiology* during the 1950s, but his book, just 100 pages long, brought it all together and is still a mine of insights, not all of which are to be found in the papers.

Having first missed the action potential overshoot in his 1949 experiments with Coraboeuf (Coraboeuf & Weidmann, 1949), he not only found it later, but also demonstrated its behaviour as an almost perfect sodium electrode. The resting potential was also shown to behave more approximately as a potassium electrode at higher levels of $[K^+]o$. Significantly, he also observed the membrane depolarization at very low $[K^+]o$, a result that was eventually explained by the action of external potassium in controlling the inward rectifier current, iK1, and which has had major implications for pathological states in cardiac tissue at low potassium.

But the most tantalising results were those obtained on membrane conductance. The paradigm for this investigation was Cole and Curtis's (1939) demonstration of the large increase in conductance during the squid nerve action potential, a result fully explained by the Hodgkin-Huxley equations (Hodgkin & Huxley, 1952). Silvio used repetitive square current pulses injected through one microelectrode while recording the potential changes with the other (Weidmann, 1951). He found the large increase in conductance during the action potential upstroke. But then surprises were in store. The conductance rapidly falls at the beginning of the long plateau and falls even below the resting level towards the end of the plateau. He observed a gradual fall in conductance during the pacemaker depolarization. It was also by using this method that he found the phenomenon of propagated all-or-nothing repolarization. This was a rich haul indeed from a single technique.

These repetitive pulse experiments were to prove critical for the subsequent analysis of ionic current mechanisms. The fact that the plateau conductance is very low presaged the discovery of the inward rectifier current, iK1, (Hutter & Noble, 1960; Carmeliet, 1961), since Silvio had correctly surmised that there must be a large fall in ionic conductance on depolarization. In retrospect, this was the easiest of the results to explain. The others posed problems that took many decades to unravel.

The slow decline in conductance during the pacemaker depolarization is consistent with a pacemaker mechanism dependent on decay in the delayed potassium current, i_{Kr}, one of the mechanisms found later to be important in sino-atrial node pacemaker activity. But, paradoxically, the Purkinje fibre pacemaker depolarization is generated by an increasing conductance to the hyperpolarizing activated current, i_f. How this could generate a fall in net membrane conductance during the depolarization itself had to await computer modelling for a full explanation. Confusingly, the fall in conductance is a consequence of the depolarization in this case, not its cause (DiFrancesco & Noble, 1985).

The fall in net conductance during the plateau also required mathematical analysis to unravel fully. In fact it took 30 years before Silvio's square pulse experiments were fully explained quantitatively.

Interestingly, Silvio himself did not participate in this mathematical unravelling of his seminal experiments. As he said himself in his 1993 autobiographical article in *Annual Reviews of Physiology*, 'I still belong to a group of individuals who have reasonably good intuition but are unable to describe results in terms of equations' (Weidmann, 1993). In fact Silvio's unease with mathematical analysis went even further. In the same article he blames my initial success with computer modelling (Noble, 1960) for preventing people thinking of additional ionic current mechanisms. Of course, this is partly correct. We should indeed beware of

being blinded by our hypotheses, even quantitative ones, however successful. But the other side of the coin is that finding gaps or errors in mathematical models has also been the engine of further experimental discovery (Noble, 2002). We should see modelling and experimentation as an iterative interaction. They don't replace each other.

Interaction with Silvio after the 1960 modelling work was very important to me personally, even though we never actually discussed any equations. I met him in 1962 at the first IUPS Congress that I attended in Leiden, where he chaired a symposium on cardiac electrophysiology at which I was asked to present my work reconstructing his conductance experiments. He told me that he had read my thesis on the beach in a single day and that it gave him a headache! No matter, he kindly presented me with a signed copy of *Elektrophysiologie der Herzmuskelfaser* which I treasure to the present day.

As a further aside on languages, another recollection that I have of the 1962 Congress was its multilingual nature. I recall papers given in 5 different languages (English, French, German, Italian and Russian). By 1977 (the Paris Congress) we were down to two, and after that we arrived at the completely monoglot situation we find today. The reasons are obvious and necessary, but let us recognise also that something important has been lost. To return to Silvio, the ease with which Swiss people switch naturally between four languages, and sometimes even five (Rumansch being the fifth) is admirable. The name 'Silvio' betrays an Italian influence, though there was no family connection with the Italian-speaking region. Nevertheless, Silvio lived up to his name and appropriately spoke Italian. He also spoke Swedish, learnt from his days in Torsten Teorell's laboratory in Uppsala. He was fluent in six languages.

Silvio's pioneering experimental work stands the critical test of time. The experiments are still the touchstone for many aspects of current work. As an example, he showed that lowering external sodium greatly reduces the action potential duration – a result that also tended to blind us to the existence of other ionic currents, such as calcium currents, since it was so easily explained by the 1960 model. Well, we are still unravelling this process, as the roles of sodium-calcium exchange and of late persistent sodium currents become clearer.

He was not only accurate and insightful as an experimenter, he was exquisitely careful about his own interpretations. His elegant writing, both in German and in English, in fact mirrors the man – a refined, carefully spoken Swiss gentleman who impressed everyone with his beautiful English, spoken with a musical Bernese accent. My favourite recollection of him is a presentation he made at the Physiological Society on his work on intercellular connections. He had shown that the space constant of a ventricular trabecular muscle was much larger than the dimensions of single cells (Weidmann, 1970). He presented his results and finished with a slide fitting them with cable equations, together with a wide Weidmann smile and the comment 'Alan Hodgkin gave me the equations'.

True to himself, Silvio never gave us any equations. But he gave us more than enough to think about in his beautiful and highly quantitative experiments. It is hard to think about the beginnings of cardiac electrophysiology without recalling his monument. He was the one who first took us inside the cell.

Denis Noble

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David McKie Kerslake

1923 – 2005

With the death of David Kerslake from cancer at his home in Yateley, Hampshire on 9 June 2005, human physiology, and thermal physiology in particular, has suffered the loss of one of its most academically influential leaders. Most of his fundamental research was carried out at the Royal Air Force Institute of Aviation Medicine (IAM) at Farnborough with applications to aviation, but his work and contributions at the Institute have provided much deeper basic physiological understanding of human thermoregulation.

Both of David's parents were school teachers and in the early years he attended a school established by his