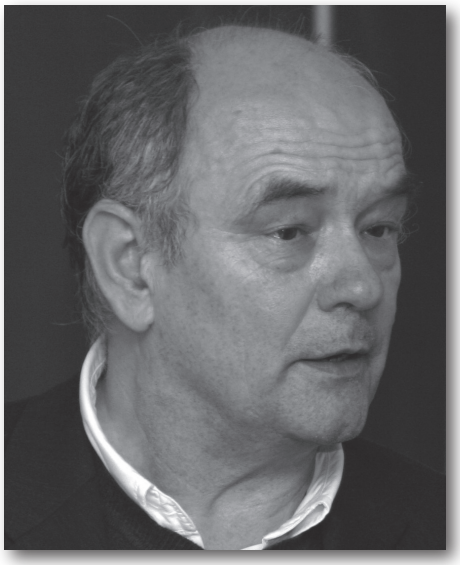
Reinhart Heinrich (1946–2006)



by Athel Cornish-Bowden (CNRS, Marseilles)

It falls to few of us to found a new subject of research, and to fewer still to do so on the basis of work done at the beginning of a career. Reinhart Heinrich, whose sudden death on 23 October 2006 deprived biochemistry of one of its most original thinkers, was one of these few: metabolic control analysis derives in part from work that he did with Tom Rapoport while working in the group of Samuel Rapoport in Berlin, and in part from studies carried out independently at about the same time by Henrik Kacser and Jim Burns in Edinburgh. He was thus one of the founding fathers of systems biology, a subject that has grown in the past few years from almost nothing to become a major sub-discipline of biochemistry. He remained fully active as one of the leaders in this field right up until the end of his life. This description may give the impression of someone who devoted the whole of his research career to a single topic, but that would be very misleading.

It is a measure of the originality of the revolution brought about by the Berlin and Edinburgh groups that for the first decade it had essentially no impact on biochemistry. Reinhart's first papers were published in 1974, at the height of the enthusiasm for the classical picture of metabolic regulation, and his ideas seemed (wrongly, as we now realize) to contradict everything that had been learned in the previous 10 years about cooperativity, allosteric interactions, feedback inhibition at the first committed step and so forth. Biochemists were not ready for Reinhart's ideas, and the simplest response seemed to be to ignore them. The citation record makes it very clear that that is what happened: in the first 8 years after publication his principal paper was cited about ten times, a total that would be substantially lower if it were not for references from others in East Germany. In the 3 years from 1978 to 1980 it was cited just once, and seemed well on the way to oblivion; yet in 2006 alone it was cited about 30 times, and it has been consistently cited around 20 or more times in every year from 1985 onwards. There can be few papers that are cited 20 times as often after 30 years as they were in their early years. For those who think that the 'impact factor' is the only thing that matters this would appear to be a failed piece of research, but for those with a less simple-minded view of the impact of research the interpretation must very different.

Reinhart's investigation of the quantitative nature of metabolic control was part of a broader project studied in the Berlin group, the efforts to understand erythrocyte metabolism in sufficient detail to permit computer models to predict its behaviour accurately. This was far from being a purely academic project, as it sprang directly from efforts to lengthen the usable life of blood for transfusion; it required a great deal of experimental work to characterize the kinetics of all the enzymes in sufficient detail, but it also required careful analysis of how to integrate all the information to understand how they would behave as a system, and not just as individual purified enzymes in a spectrophotometer. The simple-minded idea of the rate-limiting step was almost universally accepted at the time, but it was not enough, and in his paper with Tom Rapoport he showed how to deal with the whole matter quantitatively. At the same time, in another paper that has become less well known, but which also represented an important step in our understanding, they discussed how the cross-over theorem, useful and valid when used properly, was coming to be widely misused. Thanks in large part to the efforts of the Berlin group, the erythrocyte has become one of the systems in biochemistry that is most thoroughly understood in quantitative detail.

Reinhart's PhD studies in solid-state physics at Dresden served him well when he later came to apply the ideas of physics and mathematics to biochemical systems. He was interested not only in whole systems, but also in dissecting the kinetic properties of individual enzymes in great detail and in understanding the thermodynamic profiles of pathways: why, for example, do we find two ATP-consuming steps near the beginning of the glycolytic pathway, and the ATP-producing steps near the end? Would it work just as well if the different kinds of chemical steps occurred in a different order? Is there an optimizing principle involved, and if so, what is it?

Biochemists know Reinhart Heinrich for his brilliant research career, and for his book *The Regulation of Cellular Processes*, which he wrote with Stefan Schuster. However, this is to know only half of the story: he also published a novel, *Jenseits von Babel*; he was fluent in Russian (as well, of course, as English and German) and spoke a passable Georgian; he was also an accomplished musician. Just two weeks before his sudden death he was participating in the Systems Biology congress in Japan, as full of life as always, and discussing his plans for future research. His current studies of the chemical logic of metabolic networks, their modular structure, their robustness and potential for expansion during evolution, were far from complete, and leave much for his colleagues to develop.

He is survived by his wife Nana, his daughter Lisa and his son Lukas. ■