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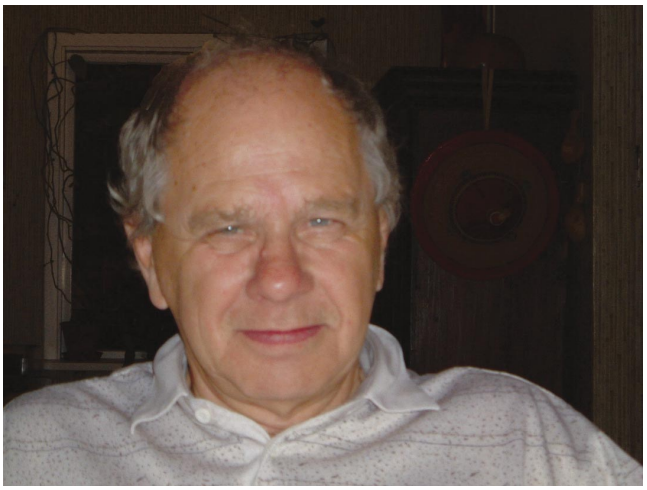
Carl-Ivar Brändén (1934–2004)



Science lost a valued citizen on 28 April 2004 when Carl-Ivar Brändén succumbed to lung cancer following an 18-month battle. Brändén was a prominent member of the structural biology community.

Carl grew up in Lapland in northern Sweden, where his father was the teacher in a one-room schoolhouse. His active and free childhood instilled a life-long love of exploration and nature. At the same time he developed a strong desire to expand his horizons beyond the frozen north, and decided that a good education was his ticket to rest of the world. This led him, from age 13 onward, to schooling away from his family and eventually to Uppsala University.

Carl's higher education in science was characterized by an ability to take opportunities where and when he found them and by an intellect that was restless unless challenged with an important problem. He began studying mathematics and physics at Uppsala University, but, bored by the undergraduate physics curriculum and inspired by Linus Pauling's texts, he switched to chemistry. An early and important mentor was Professor Ingvar Lindqvist, who invited Carl into his laboratory for PhD studies in chemical crystallography. During his studies with Lindqvist, Carl co-authored a least-squares refinement program for the first Swedish electronic computer and used it to refine the structures of several metal coordination complexes he had solved. Again bored and on the verge of leaving both crystallography and chemistry, Carl was enticed to the new field of protein crystallography by a lecture course in biochemistry. Thus, he leapt at a post-doctoral opportunity to develop refinement methods for myoglobin with John Kendrew at the MRC laboratory in Cambridge, UK, where in 1962 joined the first generation of protein crystallographers. In the company of Max Perutz, John Kendrew, Francis Crick, Fred Sanger, Michael Rossmann, David Blow, Sydney Brenner, Aaron Klug, Lubert Stryer, Richard Henderson and many others, Carl experienced the heady early days of molecular and structural biology and celebrated the Nobel prizes to Crick, Watson and Wilkins, and to Perutz and Kendrew.

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Carl returned to Sweden in 1963 with great enthusiasm for establishing a new research program in protein crystallography. This was not easy, given the resources then available to young scientists starting careers in new (and expensive!) fields. After nearly a decade of work in difficult conditions, Carl had established a group and solved the structure of the enzyme alcohol dehydrogenase. As for all protein crystal structures at the time, the structure determination was a stunning technical achievement, in which X-rays were produced by sealed-tube generators, diffraction was recorded on photographic film and diffracted intensities were measured manually. All crystallographers remember the thrill of their first solved structure. I imagine that Carl's thrill upon completing the polypeptide chain trace of alcohol dehydrogenase was many-fold greater than what we experience today, because of the years of hard work and struggle that preceded it. Alcohol dehydrogenase was followed by many other crystal structures from Carl's group, notably ribulose bisphosphate carboxylase and thioredoxin. However, alcohol dehydrogenase stood apart because Carl's interpretation of his new structure led to concepts of fundamental importance to biology.

Carl tackled the alcohol dehydrogenase structure at the same time that Michael Rossmann and his group were working on the crystal structure of lactate dehydrogenase. From comparison of low-resolution electron-density maps, Carl and Rossmann predicted that these apparently unrelated dehydrogenases use a common fold to bind their common co-factor (NAD). It was another four years before both structures were solved in sufficient detail to prove the hypothesis. This also proved to be one of the great 'Aha!' moments of molecular biology, in which new information fundamentally changes our thinking about an important problem. The crystal structures showed that although the dehydrogenases had no obvious sequence similarity, they employed the same architecture to perform the same function. Carl and Rossmann concluded immediately that the dehydrogenases had diverged from a common ancestor, and realized that protein structure is more conserved than amino-acid sequence. Their excitement about this discovery fairly leaps from the pages of their 1973 correspondence. Eventually light bulbs went on in heads around the world, and a new era of protein structure analysis was born. This discovery, and others that soon followed, led to the sequence-structure analysis that is enormously important to biology today, and to new scientific directions for Carl at the time.

Given the importance of the dehydrogenase discovery, what other fundamentals may lie hidden in the detail of protein structures? Here was an intellectual challenge that fascinated Carl for the remainder of his life. Here was an important problem in which Carl's clear vision, evident in so many areas of his working life, was especially valuable. And herein lies, arguably, his greatest scientific legacy. Protein molecules are treasure troves of interesting detail, interesting to structuralists but not to most biologists. Carl distilled the essence of the detail and presented a clear summary of the most relevant big-picture items. He is credited with recognizing that the active sites of enzymes occur in common locations on their folds: the 'top' of the familiar $(\beta/\alpha)_8$ barrel, the commonest enzyme fold, and the topological crossover point of open, parallel β-sheet folds. His ability to communicate essential structural details to a general audience is most evident in his highly successful text *Introduction to Protein Structure*, co-authored with John Tooze. Each drawing in the text, touched by Carl's own hand, illustrates an important point, stripped of distracting detail. This is exactly what biologists need to apply structural information to biological problems. This interpretation of crystal structures helped turn 'protein crystallography' into

'structural biology'. As the rate of structure determination accelerated and with the advent of protein engineering and genomics, Carl was among the first to understand that protein structure was critical to the progress of basic biology, medicine and agriculture. So convinced was Carl of the importance of structure to biology, that in 1993 he joined Wayne Hendrickson in founding the journal *Structure*, which has become a premier structural biology forum.

Clear vision was also a hallmark of Carl's work in science administration. As he became a senior member of the Swedish scientific community, Carl felt a special responsibility towards younger scientists. He never forgot the importance to his own advancement of his mentor Ingvar Lindqvist, and took great delight in helping younger scientists he thought were able to contribute in important areas. Help came in the form of positions, laboratories, funding and encouragement. Carl did this through his work with Swedish funding agencies, at the European Molecular Biology Organization and on various national and international advisory groups. The vibrant Swedish structural biology community has many outstanding members who were trained, recruited or promoted by Carl. He worked for several years as a member of the Nobel Committee for Chemistry. Always with an eye to the bigger picture, his many science policy activities consistently advanced good science and scientists. Much of his administrative and policy work was done behind the scenes by quietly but persistently promoting projects and people he felt were beneficial to the advancement of biology. His work at the European Synchrotron Radiation Facility (ESRF) is a good example. Near the end of his career, he spent five years in Grenoble in order to give structural biology a solid foundation at the new European synchrotron. Today the ESRF leads the world in providing experimental facilities for macromolecular crystallography.

Carl, known as Calle to family and friends, had a great love of life, and of bright and lively people. I knew him best during his years at the ESRF, which I believe were typical of his approach to life. While in Grenoble, Calle assuaged his homesickness with frequent outings in the mountains, followed whenever possible by a good meal. Together with his wife Malin Åkerblom, he searched out good art in small places in the South of France. He made a research project of stocking a wine cellar for his return to Sweden. He provided a warm welcome to many interesting visitors to Grenoble, and he continuously supported and advanced the best ideas and the best people in structural biology. I last saw Calle at the Advanced Photon Source less than eight months before his death, and was impressed with his courage in the face of illness, his determination to fight cancer, his will to live and work fully for as long as possible, and his peacefulness. He told me how fortunate he felt to have had a long working life without a single boring day, and to have shared his life with his wife, two sons and grandchildren. What a lesson for us all.

We shall miss him, his clear vision, and his love of good science, good living and good people.

Janet L. Smith
Department of Biological Sciences
Purdue University
West Lafayette
Indiana
USA
E-mail: smithj@purdue.edu