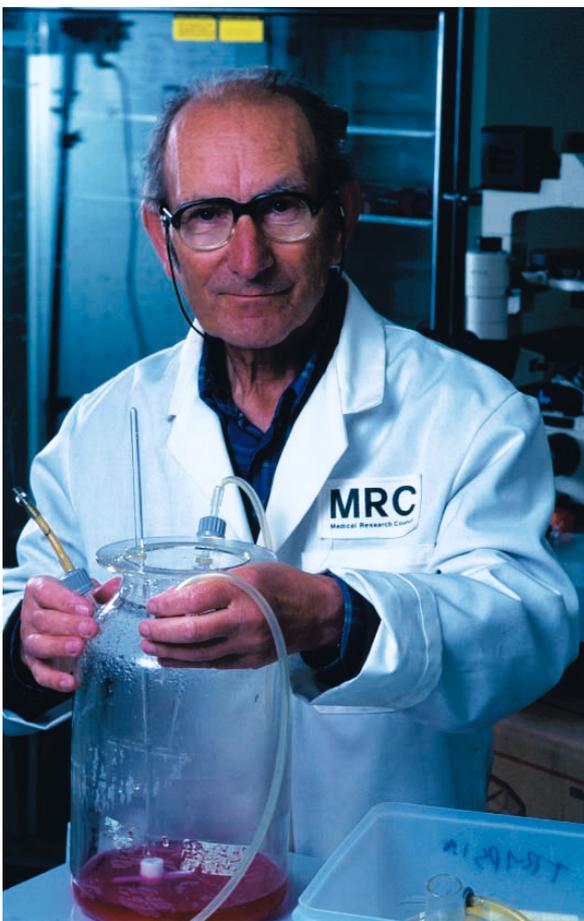


Obituary

César Milstein (1927–2002)

by Michael Clark



The sad news of the death of the Nobel Prize-winning scientist César Milstein was announced on Sunday 24 March 2002. Although he had officially ‘retired’ in 1995, César still actively and enthusiastically pursuing his research interests, had been working in his laboratory with John Jarvis, his long-term assistant of nearly 40 years, up until the Friday before his sudden death.

César was internationally famous for his work on monoclonal antibodies; his first seminal paper [co-authored with Georges Köhler (1946–1995), a postdoctoral fellow in his laboratory] was published in *Nature* in 1975. The paper described a method for the immortalization of B-cells through somatic cell fusion with a plasmacytoma cell line. This work was a progression from earlier studies in which Richard Cotton and César showed that the cell fusion of two established plasmacytoma cell lines resulted in the co-dominant expression of the individual immunoglobulin chains. In 1984, Köhler and César were awarded the Nobel Prize in Physiology or Medicine, along with Niels K. Jerne (1911–1994), for “theories concerning the specificity in development and control of the immune system and the discovery of the principle for production of monoclonal antibodies”.

Today, the applications of monoclonal antibodies are far reaching, particularly in research and diagnostics, and increasingly, in recent times, in therapeutics. Much of the credit for this progress can be given to César. He was notable for his open-door policy, was always keen to discuss new results, and was always ready and willing to offer advice. In the early years of monoclonal antibodies, there was always a steady stream of scientists visiting his laboratory seeking help and advice or wishing to collaborate with him. These collaborators were then

largely responsible for disseminating his ideas to a much wider field. The monoclonal antibody technology proved very easy to adopt and within a few years of the first description of the techniques, international workshops were held in which scientists exchanged monoclonal antibodies and compared data on their individual specificities. From this grew the widely accepted CD (cluster of differentiation) nomenclature, which is now used to define cell surface antigens that are recognized by collections of antibodies. Fittingly, the first group, designated as CD1, was applied to antibodies that included one from César’s own laboratory that was directed against an antigen they had called HTA1 (human thymocyte antigen 1).

There has been much public controversy over the years surrounding César’s failure to patent his early ideas, in particular with regard to whether this failure should be laid at César’s door or elsewhere. César always maintained that he had acted in good faith and had communicated his ideas first to senior officials in the Medical Research Council (MRC), and later to the National Research and Development Corporation (which been since privatized as BTG International plc), and that he had received no replies asking him to file patents or any requests for him to withhold publication. Not all the correspondence survives, but what does lends some support to César’s viewpoint. In July 2000, the MRC held a meeting in London to

celebrate 25 years of monoclonal antibodies, and César again raised this controversy in his address to the meeting (a video-recorded transcript of the meeting was made available via the Internet). Certainly, what is true is that the scientific culture in medicine and biology at the time was to publish and to make ideas readily available through the traditional scientific literature. Few scientific institutions had an established mechanism for the rapid assessment of commercial potential. In contrast, nowadays the field of monoclonal and recombinant antibodies is one of the most complicated legal areas for biotechnology patents, with many litigation battles recently taking place throughout the world.

César was born in 1927 in Bahía Blanca, Argentina, the middle of three brothers; his father was a salesman and his mother a school teacher. César received his secondary education in Buenos Aires and studied for his BSc in chemistry at the University of Buenos Aires before proceeding to a PhD. His early research career was as an enzymologist working on aldehyde dehydrogenase with Professor A. Stoppanni at the University of Buenos Aires.

“Today, the applications of monoclonal antibodies are far reaching, particularly in research and diagnostics, and increasingly, in recent times, in therapeutics.”

In 1958, he was awarded a scholarship by the British Council and travelled to Cambridge to work with Malcolm Dixon in the Department of Biochemistry, where he studied for a second PhD on the mechanism of activation of phosphoglucomutase.

He returned to the University of Buenos Aires as Head of the Division of Molecular Biology in 1961, but after 2 years, as a result of the political climate, César resigned and travelled back to Cambridge, where he joined Fred Sanger in the newly formed MRC Laboratory of Molecular Biology. Prompted by Sanger, César then made the key decision to change from studying enzymology to looking at antibody structure, function, and in particular, the mechanisms for generation of antibody diversity. Nevertheless, although mainly recognized for his work on monoclonal antibodies, César participated in several other significant areas. He and George Brownlee worked on mRNA and they published one of the first descriptions of the signal peptide sequence of secreted proteins.

César's early work on antibodies helped to define differences in disulphide bonding of the heavy and light chains of different antibody classes and subclasses. However, before 1975 and again in recent years, his main interest was in the mechanisms for generation of antibody diversity. Much of this more recent work was in collaboration with his colleague Michael Neuberger of the MRC Laboratory of Molecular Biology, and provides evidence of the enzymic mechanisms and the specificity for somatic hypermutation in B-cells.

César was elected a Fellow of the Royal Society in 1975 and in addition to his Nobel Prize in 1984, he received many other significant prizes, awards and honours. He was made a Companion of Honour in 1995, served as a Fellow of Darwin College Cambridge from 1981 to 1995 (Emeritus), and was made an Honorary Fellow of Fitzwilliam College Cambridge, where he had

been a student while studying for his PhD between 1958 and 1961.

Outside work, César enjoyed cooking and eating, the arts, sailing, cycling, skiing and walking. After diagnosis of cardiovascular problems and surgery in the 1970s, César adopted a strictly controlled diet and a regular pattern of exercise.

“in addition to his Nobel Prize in 1984, he received many other significant prizes, awards and honours.”

He could be seen on a regular daily basis taking one of his constitutional walks around Cambridge. He would either take along a portable radio and listen to the news, or he would dictate letters into a tape recorder. Often, colleagues would be invited along to discuss their work with him, but some complained that it was a challenge to even keep pace with him, let alone hold a complex discussion! César also took an interest in international politics, and he gave much of his time and used his international fame, recognition and influence to help young scientists from less developed countries. He was a supporter of charitable causes such as Amnesty International and Shelter.

César is survived by his wife Celia Prillelensky, whom he married in 1953. She too was an immunologist and worked on the structure of antibodies for many years in the laboratory of Arnold Feinstein. César and Celia collaborated together and co-published several pieces of work.

After a first degree in Biochemistry at University College London, Michael Clark studied for his PhD, from 1978–1981, with César Milstein at the MRC Laboratory of Molecular Biology. He is now a senior lecturer at the University of Cambridge, Department of Pathology, and his main research interests are in antibody structure and function, and the therapeutic applications of antibodies.