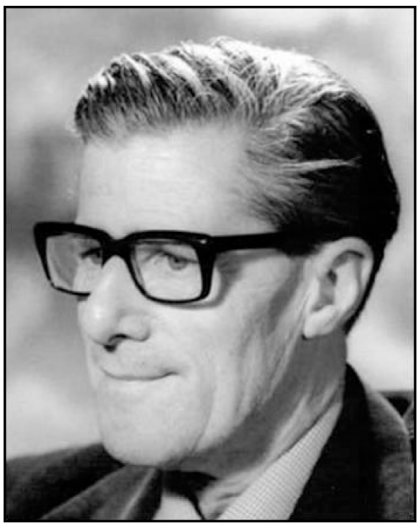
Cell

Michael Stoker 1918–2013

Sir Michael Stoker, a pioneer of virology and the cell biology of cancer cells, died on 13 August at the age of 95. Viruses have always been useful tools for probing the workings of cells, and Michael exploited tumor-causing viruses to gain a better understanding of oncogenic mechanisms at the dawn of the molecular biology of animal cells. During a long career, Michael not only made groundbreaking discoveries himself, such as immortal nontransformed cell lines and scatter factor, but he also had an extraordinary influence on generations of cell biologists.

Michael George Parke Stoker was born on 4 July, 1918 in Taunton, England, where his Irish-born father was a physician. After school at Oakham, he studied medicine at Cambridge and gained clinical training at St Thomas's Hospital at the beginning of World War II. He then enlisted in the Royal Army Medical Corps and was posted to India working in Lucknow and Hyderabad until, by a stroke of luck, he was sent to the army laboratories in Pune, a major military cantonment (called Poona in colonial times and that today houses India's National Institute of Virology and National AIDS Research Institute). Michael gained his first experience of laboratory pathology research in Pune studying typhus and bush typhus with some remarkably talented medical scientists. They included Douglas Black (later President of the Royal College of Physicians) and Bill Hayes (who discovered bacterial conjugation and recombination). It was this experience that gave Michael his interest in infectious disease and led him into virology, for the typhus Rickettsia had not yet been distinguished from viruses. His research on typhus provided the material for his MD research thesis. On demobilization in 1947, Michael was appointed to a junior post in the Pathology Department in Cambridge and a fellowship at Clare College. Together with Peter Wildy, he began to study herpes simplex virus and exploited the then novel cell culture techniques that allowed human and animal viruses to propagate in vitro. Whereas the Pathology Department was rather old fashioned, Michael sought out the new electron microscope at the Cavendish Physics Laboratories to visualize virus particles, and he thus became friends with Max Perutz, John Kendrew, and the young Jim Watson.

It was his success in Cambridge that led him to be appointed without his actually applying for the position to the first UK Chair in Virology at the University of Glasgow. The University planned to establish an Institute of Virology, including a Medical Research Council Unit of Virology with Michael as Director. Before moving there, however, Michael spent 6 months at the end of 1958 at Caltech with Renato Dulbecco, who was becoming interested in tumor viruses and in whose laboratory Howard Temin and Harry Rubin had just succeeded in developing an in vitro cell transformation assay for Rous sarcoma virus. Polyoma virus of mice had recently been discovered, and with the related simian virus SV40, it became a model for neoplastic transformation. In Glasgow, one particularly important contribution by Michael, together with Ian Macpherson, was the development in 1962 of BHK21 hamster kidney cell line, an immortal, easily clonable cell line that nevertheless maintained growth control in culture as a monolayer but could be morphologically transformed by DNA tumor viruses. Later, murine 3T3 cells served a similar purpose, but BHK21 was the first cell line with these properties to be characterized, decades before the discovery of telomerase and the mechanisms of immortalization. Working with BHK21 and derivatives, Michael described density-dependent inhibition of growth by normal cells and neighbor suppression of tumor growth, namely the ability of normal cells to suppress the growth of a number of transformed cells when grown in close contact.



Michael Stoker

Michael regarded his 9 years in Glasgow as the most fruitful of his career. He brought Peter Wildy with him from Cambridge, and he recruited key young investigators such as Lionel Crawford, Ian Macpherson, Kenny Fraser, John Subak-Sharpe, and later Mike Fried to the Institute. In the Glasgow Veterinary School, Bill Jarrett and collaborators acquired the Institute's cell biology techniques and discovered feline leukemia virus and bovine papilloma virus as models for studying naturally occurring animal cancers. Thus, Glasgow became a vibrant center for viral oncology. Michael established the famous intensive virology course along the lines of Cold Spring Harbor Laboratory courses, and there is hardly a virologist in the UK during the 1960s and 1970s who did not pass through the Glasgow Virology Institute.

In 1968, Michael was invited to be Director of Research at the Imperial Cancer Research Fund (ICRF) Laboratories in London (now part of Cancer Research UK). He arrived with some key colleagues from Glasgow and appointed new cell and molecular biologists based on a model similar to the one he established at the Virology Institute—namely to provide excellent facilities and give the investigators free reign without a hierarchy but to promote lots of interchange and common internal seminars. There was plenty of healthy competition, but the ICRF prospered intellectually; among many important advances at ICRF, David Lane and Lionel Crawford discovered that SV40 T antigen interacted with an unknown cellular protein called p53 on account of its molecular weight.

Although Michael was adept at running sizeable research institutes and setting their direction of travel, he never developed a large laboratory himself. He was content to train one or two research students and postdoctoral fellows at a time. Thanks to his gift for devolving responsibilities and trusting others to expedite day-to-day management duties, he was able to find time to conduct his own experimental work. At ICRF, he allowed two redoubtable colleagues to meet the needs of the ambitious and sometimes unruly scientists among his staff. They were Bill House, brought from Glasgow to oversee all the management aspects of keeping laboratories safe, active, and up to date, and John Tooze (later Executive Secretary of the European Molecular Biology Organization, EMBO), who helped to make research policies coherent, drafted superb reports and who acted as a talent scout.

Although Michael had a modest demeanor, he was held in much esteem by junior and senior colleagues alike. Future Nobel laureates such as Paul Berg and Harold Varmus came on sabbaticals. Michael recruited three remarkable senior figures to join him at ICRF. Renato Dulbecco spent a 5 year sojourn in London (1972–1977) before returning to the Salk Institute in La Jolla, and it was during this time that he was awarded the Nobel Prize for Physiology or Medicine. John Cairns, Jim Watson's predecessor as Director of Cold Spring Harbor Laboratory, came to direct the ICRF Mill Hill laboratories, where he made penetrating observations on the epidemiology of human cancer from the perspective of a molecular geneticist. Guido Pontecorvo, universally called Ponte, had been the founding Professor of Genetics at the University of Glasgow and was a world authority on the genetics of the fungus *Aspergillus*. On moving to the ICRF at the age of 60, he ran a tiny lab but acted as an uncle to all; he switched to mammalian cell genetics and, through his discovery of cell fusion mediated by polyethylene glycol, Ponte greatly expanded somatic cell genetics and its medical applications, including the generation of hybrid myelomas producing monoclonal antibodies.

Michael heeded the fruitfulness of Ponte's late flowering and, when he himself retired as Director of ICRF at 60 and returned to Cambridge to run a small lab, his observations on the attachment and migration of epithelial cells in monolayer culture led him to discover "scatter factor." He noted that some strains of fibroblasts induced epithelial cells to separate from their neighbors instead of remaining in a tight pavement. This led to the isolation of a protein, independently found in Japan to be hepatocyte growth factor, which plays a fundamental role in embryo development, organ regeneration, and cancer spreading.

This kind of patient, observational research, combined with a powerful analytical mind, characterized Michael's brilliance. Nowadays, big labs and multidisciplinary collaborations have become the favored way of conducting research and indeed have reaped rich rewards. Yet Michael and Ponte exemplified the power of small science leading to big insights—an approach that today's biomedical research funders would do well to ponder.

Michael was knighted in 1980. He was elected a Fellow of the Royal Society in 1968, and he served as Foreign Secretary and Vice President 1978 to 1983, a busy voluntary post that Sydney Brenner dubbed a travel agency. After returning to Cambridge, from 1980 to 1987, he became President of Clare Hall, a newly established graduate college of the University. He served on the Council of EMBO and on several other international advisory bodies. Although Michael thoroughly immersed himself in medical research, he had broad interests and hobbies. He enjoyed sailing and became an accomplished painter, to his own surprise winning the Baron ver Heyden de Lancey Prize of the Medical Art Society.

The mainstay of Michael's even temperament and contentment was his wife, Veronica, whom he first met as a student in Cambridge and with whom he enjoyed a happy marriage for 62 years. They frequently welcomed colleagues and friends to their home. Sadly, Veronica predeceased Michael by 9 years. They are survived by their five children, seven grandchildren, and three great grandchildren.

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