

Sir Anthony EPSTEIN FRS (1921 – 2024), virologist

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Unveiling speech by Professor Alan Rickinson

Sir Michael Anthony Epstein, known to his colleagues as Tony, made one of the most important discoveries of the 20th century in the field of cancer research. He discovered a virus, now known as the Epstein-Barr virus (EBV), which he initially linked to a rare blood cell cancer called Burkitt Lymphoma but which subsequent work has shown to be a key factor in the development of at least seven different human tumours. Collectively, these EBV-associated tumours are responsible for some 200,000 new cancer cases globally per year. Epstein's finding was therefore of enormous importance, not only in its own right but also in opening up a worldwide search for other virus-associated human tumours. That work has culminated in the identification of, in total, seven types of virus that are now linked to particular human cancers. EBV was the first such virus to be identified and Tony Epstein is therefore rightly regarded as the founding father of human tumour virology.

He began working on possible connections between viruses and cancer in the 1950s after medical school in Cambridge and specialising in pathology at the Middlesex Hospital in London. At the time, such a research subject was deeply unfashionable and Epstein's decision to take this route was seen by most people as bizarre. However, a key event occurred in March 1961 when Denis Burkitt, a then unknown surgeon working in a missionary hospital in Uganda, delivered a lecture in Middlesex Hospital on "The commonest children's cancer in tropical Africa: a hitherto unrecognised syndrome". Epstein heard the lecture and was immediately inspired by the idea that this cancer might be caused by a virus, possibly an infection that was common only in certain parts of Africa.

This led to a collaboration through which fresh samples of the tumour were flown from Kampala to London and delivered to Epstein's laboratory for analysis. His team, that included a research assistant Yvonne Barr and subsequently a young clinical fellow Bert Achong, used the traditional virus hunting methods of the day; crucially, however, they also had an entirely new tool, the electron microscope, which was powerful enough to allow tiny virus particles to be visualised within infected cells. Using his experience in electron microscopy gained while spending a sabbatical year in the Rockefeller Institute

in New York, Epstein began searching the African tumour samples for evidence of virus particles.

The early results were disappointingly negative but in December 1963, after almost two years of work, the breakthrough came. A tumour arrived whose individual cells could be grown in culture in the laboratory, making a permanent cell line which could be studied in more detail; within the lab, that cell line was called “EB1” after Epstein and Barr. When Epstein examined EB1 cells in the electron microscope, he saw in the very first grid square a cell containing particles with the classic appearance of a herpesvirus. Even though only a small proportion of EB1 cells showed evidence of such infection, excitement mounted when collaboration with a research team led by Werner and Gertrude Henle in Philadelphia proved that the virus in question was distinct from the three other types of human herpesvirus known at the time. The Henles then suggested that this new agent should be called “EB virus” after the name of the cell line ... and so Epstein-Barr virus had its official christening ceremony, without any of the attendees realising just how momentous the moment would prove to be!

Over the ensuing 60 years, EBV has been a major research topic for many laboratories around the world. Once molecular detection methods had been devised, it became clear that, while virus particles could only be seen in a small fraction of cultured cells, the genome (DNA) of EBV was carried as a hidden (latent) infection in every cell in every African Burkitt Lymphoma examined. This was the key evidence showing that the virus is indeed involved, along with other co-factors, in the multi-step path to cancer causation. Very similar evidence is now in place linking EBV with six other human malignancies seen worldwide, including familiar names such as Hodgkin Lymphoma and even a subset of stomach cancers.

Remarkably, Tony Epstein will be remembered not only for his discovery of EBV but also for his visionary leadership over several decades of work towards the development of an effective EBV vaccine. His commitment to that goal began in the 1970s and continued during the 30 years in which Tony was an inspirational Professor of Pathology at the University of Bristol, and indeed remained with him for the rest of his life here in Oxford. It is entirely fitting that he should have lived long enough to see that goal on the cusp of being realised, with major pharmaceutical companies now having EBV vaccines entering clinical trials. His legacy is already assured and the fruits of that legacy, the prevention of EBV-associated disease through vaccination, will long be celebrated.