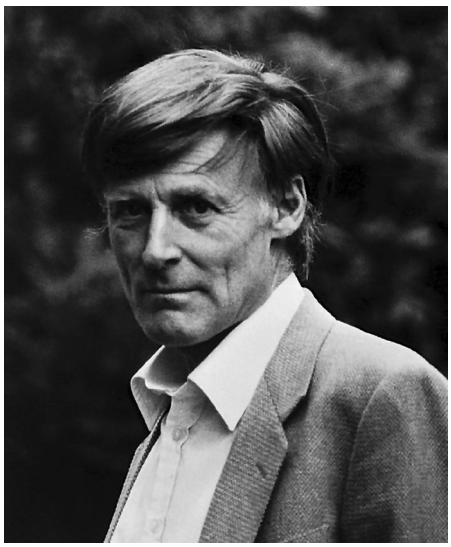
H. John F. Cairns (1922–2018)

It is hard to imagine a time when it was not known that DNA carries the genetic information of all living organisms, and it is even harder to conceive that even after this fact was established in the 1940s, no one had a picture of the structure of DNA or any idea how DNA was duplicated or replicated before cell division. This was the era in which John Cairns completed his medical training at Oxford University. In 1950, after practicing medicine for just 4 years and publishing a couple of clinical research papers in *The Lancet* and *Nature*, Cairns made a radical move—personally, geographically and professionally. He moved with his pregnant wife Elspeth and their infant son to Melbourne, Australia, and from there launched a distinguished career in virology research, first with Macfarlane Burnet at the Walter and Eliza Hall Institute and subsequently as an independent researcher. During the first few years of his full-time research career, Cairns was undoubtedly following the published work of Chargaff, Franklin, Watson and Crick—work that would culminate in establishing the structure of DNA and provide a plausible model for DNA replication. These discoveries ultimately launched the golden age of molecular biology in which Cairns would play a large part. During the 1950s, Cairns spent 2 years at the Walter and Eliza Hall Institute, 2 years in Uganda (at the Virus Research Institute in Entebbe) and the remainder of the decade at the Australian National University in Canberra. During these years, he developed and sharpened his remarkable experimental and intellectual research skills studying the mechanisms by which vaccinia and influenza viruses multiply inside and emerge from animal cells. A dozen or so papers were published, establishing that influenza virus is assembled only at the cell surface and that mature viruses are released in a trickle rather than a burst. Cairns also used autoradiography to show that vaccinia virus DNA is replicated in 'factories' located in the cytoplasm and, remarkably, he produced the first genetic linkage map for an animal virus by crossing a collection of mutant poxvirus.

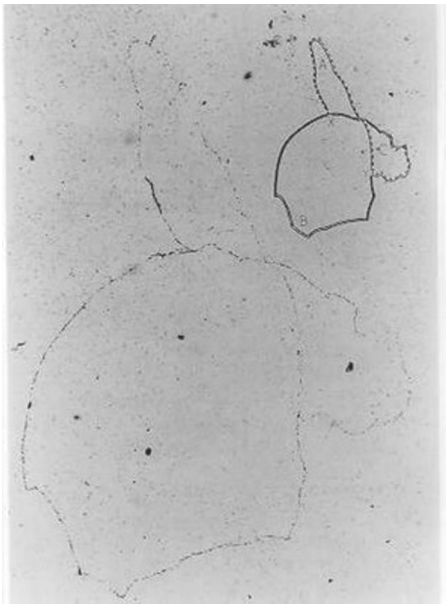
In 1957 Cairns spent a short sabbatical at The California Institute of Technology, where he literally lived with the question of how *Escherichia coli* replicates its DNA; he shared an apartment in Pasadena with Matt Meselson and spent evenings listening to him and Frank Stahl discussing the merits of cesium versus other heavy metals for their classic density gradient experiments demonstrating semi-conservative DNA replication. His second foray into the US research environment was to spend a year in Al Hershey's lab at the Cold Spring Harbor Laboratory (CSHL) on Long Island, New York. It was there that he figured out how to visualize individual radioactive DNA molecules (T2 phage genomes) using autoradiography. All the seeds had now been sown for Cairns to realize that he might be able to capture an image of an actively replicating *E. coli* chromosome. To the immense surprise of the biology community in general and the emerging molecular biology community in particular, the *E. coli* genome turned out to be circular. Cairns produced one of the most famous images in biology (pictured below), from which he coined the term 'replication fork' for the Y-shaped junctions viewed in this partially replicated genome, junctions that look just like a classic fork in the road. It is at these forks that the DNA strands are being prised apart and replicated, so that two complete genomes are available to be segregated into the daughter cells produced after cell division. Cairns went on to show that human cells manage to replicate their enormous genome in a period of just a few hours, by each chromosome's having dozens of replication forks simultaneously copying the DNA.

Around this time, Cairns was recruited away from the Australian National University in Canberra to become the director of the CSHL in New York from 1963 to 1968. Despite having to spend the majority of his time fund-raising to rescue the CSHL from bankruptcy, Cairns achieved another molecular biology milestone. At the time, only one DNA polymerase had been isolated from *E. coli*, by the Kornberg lab. It was generally assumed that this polymerase was responsible for duplication of the entire *E. coli* genome, and Cairns set out to determine whether or not this assumption was correct. Not only was his answer surprising to the molecular biology community but also his experimental approach was stunning. Cairns and his assistant, Paula De Lucia, carried out what is known as a brute-force mutant hunt. Thousands of individual cells were isolated from a mutagenized *E. coli* culture, and each cell was separately incubated to spawn a culture containing a billion bacterial cells that was then analyzed for DNA polymerase content. The first 3,477 cultures tested had normal DNA polymerase levels; the 3,478th



culture had virtually none (the mutated gene was named *polA* as a subtle nod to Paula De Lucia's contribution). The fact that cells deficient in this enzyme could grow normally de facto demonstrated that this polymerase was not required for duplication of the *E. coli* chromosome. It was this discovery that stimulated Kornberg and others to search for additional polymerases and ultimately led to the identification of a large multi-protein replication machine responsible for copying the entire *E. coli* genome.

When James Watson was recruited to take over as director of the CSHL in 1968, Cairns became an American Cancer Society Professor, the most prestigious award conferred by the society, and he turned his attention to reading and thinking about issues related to cancer. One product of these endeavors was a Perspective in *Nature* proposing that rapidly proliferating epithelial cells might be organized to minimize the accumulation of mutations, and that stem cells might always inherit daughter DNA molecules containing the original parental DNA strands. This became known as the 'immortal strand hypothesis', and subsequent studies have strongly supported this model of DNA strand segregation in certain kinds of epithelial stem cells. Another product was the highly influential and now classic book entitled *Cancer Science and Society*, which presented numerous meticulously researched, thought-provoking arguments about cancer; this book became essential reading for biologists and epidemiologists



alike working on cancer, as it seamlessly integrated basic biology with the global epidemiology of cancer. Finally, during this period of thinking about issues related to cancer, Cairns was appointed in 1973 as director of the Imperial Cancer Research Fund's Mill Hill laboratories in London. Over the next 7 years, Cairns fostered basic biological research using model organisms such as bacteria, flies, slime molds, amphibians and mice to understand fundamental biological pathways that were likely to be relevant to the transformation of normal cells into cancer cells. Cairns created and fostered an exceptionally stimulating, interactive, nurturing and cutting-edge research environment that launched the careers of many students and postdocs who had the privilege of training in the rarified atmosphere that surrounded Cairns wherever he went. In his own lab at Mill Hill, Cairns discovered new pathways for DNA repair in *E. coli* exposed to the kinds of alkylating agents that are commonly used for cancer chemotherapy; all of the DNA-alkylation-repair pathways identified in *E. coli* turned out to also exist in humans and to be important players in both cancer susceptibility and cancer treatment.

In 1980, Cairns was appointed as Professor of Cancer Biology at the Harvard School of Public Health, and during the final decade of his professional career he discovered that under certain kinds of non-lethal selective conditions, non-growing (stationary) bacteria accumulate mutations that enable them to grow. The discovery of this novel mutational mechanism, later termed 'adaptive mutagenesis', was interpreted by others to support Lamarckian evolution and to contradict the work of Luria and Delbruck showing that mutations spontaneously arise in bacterial populations in the absence of selection, an observation that supported Darwinian evolution and won these scientists the Nobel Prize. In fact, Cairns' highly cited, but controversial, 1988 *Nature* paper, modestly entitled "The Origin of Mutants," pointed out that mutations can arise both before and after selection is applied. This work expanded the views of mutagenesis outside of the benign laboratory conditions of exponential growth.

Throughout his career Cairns gravitated to, and was a magnet for, young scientists—undergraduate students, graduate students, postdocs and untenured professors. Looking for someone to have lunch with, he would scan the cafeteria, rejecting opportunities to sit with the famous, powerful and influential, seeking instead the company of the young and enthusiastic who would represent the next generation. His office door was always open, and he spent endless hours discussing ideas and editing manuscripts with scientists from many labs and a variety of disciplines. He always offered the gift of insight and invaluable advice, and he helped many of us to improve our writing, although I would venture to say that none of us could ever match his eloquent, erudite, crystal-clear, punchy prose. What may be less well known about John Cairns was his terrific sense of humor and his ability to be silly when the moment seemed right. A perfect example would be the dinner before which he peeled off the passionfruit sticker that read "Ripe when Wrinkled" and stuck it on his forehead.

Upon assuming Professor Emeritus status in 1991 and returning to his birthplace, Oxford, Cairns launched into writing a second book entitled *Matters of Life and Death: Perspectives on Public Health, Molecular Biology, Cancer, and the Prospects for the Human Race*. Virtually no other scientist had worked at the highest levels in the diverse fields of molecular biology, molecular genetics, cancer research and public health. In this book, Cairns drew on his unique experience to present a series of essays that displayed his uncommon vision and superb clarity of thought. Not surprisingly, Cairns received significant recognition during his extraordinary career, including election as Fellow of the American Academy of Arts and Science (1967), as Fellow of The Royal Society (1974) and as a MacArthur Foundation Fellow (1981).

John Cairns died peacefully on 12 November 2018, just shy of 96 years of age. He is survived by his wife of over 70 years, Elspeth Cairns, who was the enabling partner in this remarkable career, plus three children, four grandchildren, four great-grandchildren, and innumerable scientific progeny. ❐

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