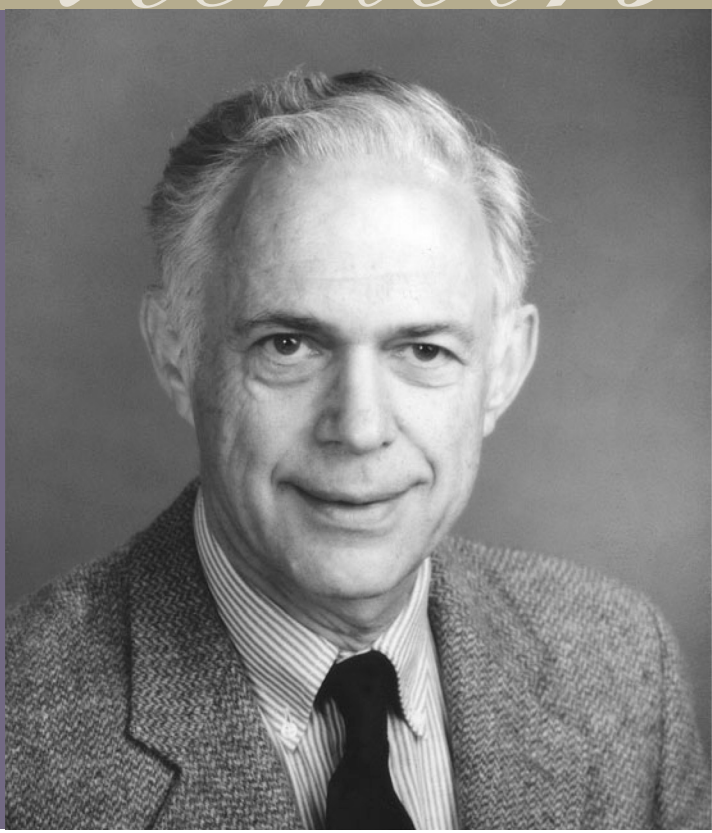
Allan M. Campbell

1929–2018

BIOGRAPHICAL *Memoirs*



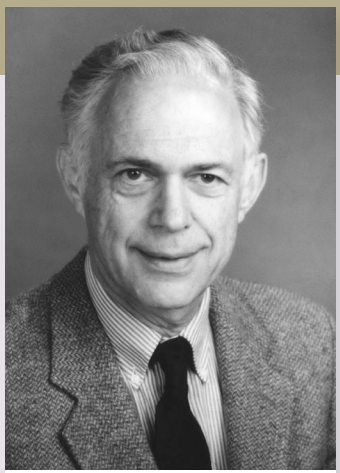
A Biographical Memoir by
Michael Feiss,
Patrick Cleary,
Donald Court
and Sankar Adhya

NATIONAL ACADEMY OF SCIENCES

ALLAN MCCULLOCH **CAMPBELL**

April 27, 1929–April 19, 2018
Elected to the NAS, 1971

Allan McCulloch Campbell was one of the world's foremost investigators of viral genetics. At the time of his passing, Allan was the Barbara Kimball Browning Professor in the School of Humanities and Sciences, Emeritus, at Stanford University. He left a legacy of ground-breaking fundamental genetics, critical tools for genetic analysis, and an abundance of challenging ideas.



Allan Campbell

By Michael Feiss, Patrick Cleary, Donald Court and Sankar Adhya

Allan Campbell was born on April 27, 1929, in Berkeley, California. Despite an obvious early talent in mathematics, Campbell chose to pursue laboratory research. He admitted early that experimental science kept him in touch with reality, whereas mathematics caused him to dwell within a dream world of abstractions. Campbell earned his bachelor's degree in chemistry at the University of California, Berkeley, and master's and doctoral degrees from the University of Illinois.

The Campbell Model

One of Allan Campbell's seminal works is the "Campbell model." While at the University of Rochester in New York, Campbell explored how some viruses manage to become part of the chromosome of their hosts for generations. These proviruses, or prophages, are then able to wait for the opportune time to awaken, make progeny, kill their hosts, and disseminate. "How else might it have been? Many of the current practitioners of science in general think that science proceeds by logical steps in a linear fashion from A to Z," said the late Harrison Echols, professor at the University of California, Berkeley. Allan had a superbly creative mind. When jarred by unexpected experimental

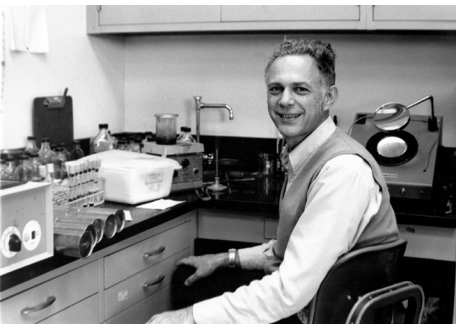
results, he approached sideways to solve how λ DNA integrates into chromosomes by suggesting that linear-phage DNA becomes circular before integration into the bacterial chromosome. Allan postulated two steps after the phage DNA is ejected from the infecting virus particle into the host cell.[1] First, the incoming phage DNA circularizes. Second, a reciprocal recombination event occurs between the circular phage and bacterial DNA molecules at specific sites on both DNA partners. This results in a cyclic permutation of the phage gene order relative to the gene order obtained in standard virus-versus-virus crosses. The model was a deceptively simple mechanism, obvious in hindsight, but it represents one of the most important concepts in molecular biology. At the time, Allan's idea contrasted with other models of prophage localization. A favored model was the synapse model, which proposed that the prophage laterally "attached," or "synapsed," with bacterial DNA.[2] The Campbell model helped pave the way for tools that today are mainstays of biological research, such as the engineering of DNA segments capable of inserting into and excising from chromosomes. The model also led to our understanding of latency and the provirus lifestyle among mammalian viruses. Allan's work was ultimately the basis for our understanding of several human viruses and their potential to persist for decades, only to reemerge and cause chronic and sometimes serious disease at some point in the future.

Conditional Lethal Mutants

Another landmark of Allan Campbell's pioneering works was the development of concepts about and subsequent isolation of mutants in essential genes of viruses (later applied to other microbes). Allan isolated and characterized conditional lethal mutants—mutants that could grow under one condition, such as at a specific "permissive" temperature, but not at a different, "non-permissive" temperature. Such mutants allow the researcher to study wild-type behavior of the gene product in question and the mutant behavior at the other condition.[3]

Permutations

After joining the faculty in the Department of Biology at Stanford University in 1968, Campbell continued his research focus on phage λ, working to clarify the molecular details of λ DNA insertion and excision from the bacterial DNA. The "Campbell model" was eventually confirmed by Campbell himself and several laboratories working independently. Using galactose-transducing phages and prophage deletions, the lab explored the construction of lambda strains with specific gene deletions and duplications, as discussed in the next section.[4,5] Allan and Alice del Campillo Campbell, his spouse and



Campbell at work in his laboratory at Stanford University in 1970. (Photo Wendy Campbell.)

longtime collaborator, also focused their work on understanding the biosynthesis and regulation of biotin, encoded by a regulon immediately adjacent to prophage λ.

Mutant Gene Functions

Following Allan's creation and distribution of the set of nonsense and thermolabile mutants, many labs began to study the mutant's defects. Allan's student Kathy Brooks found that *O* and *P* mutants lysogenized poorly at low multiplicity and efficiently at high multiplicity of infection. Additionally, the *O* and *P* mutants failed to produce an intracellular pool of replicated chromosomes, leading to the conclusion that the *O* and *P* proteins sponsored DNA replication.[6] In another early study of gene function, Allan and Alice showed that a thermolabile R mutant encoded a heat-sensitive endolysin.[7] Thus, Allan devised a method to assign phage gene functions using genetic tools long before biochemical processes were invented.

An Ideal Mentor

The four of us entered the Campbell laboratory within about two years of each other, during a time of strong science funding in the 1960s, likely in response to the Soviet Union's success with the Sputnik satellite. There was an explosion of bacteriophage λ biology for us to digest. Those in the lab had to deal with new and ever-changing jargon, and lots of bacterial and phage strain numbers and genotypes. Lab members included we four, Alice, and later Koki Sato, Dan Dykhuisen, Vince Simmons, and Gary Ketner overlapping with some of us. The members were divided into two groups: those working with λ and those with biotin. We frequently invaded each other's territory, both experimentally and intellectually. Discussions among us were spirited, educational, and passionate, thanks to Allan fostering an intellectually permissive atmosphere. Our group had weekly data meetings. In addition, there was the bimonthly "Lambda Club," which was also composed of other phage research groups, including that of another giant of lambdology, Dale Kaiser in the Department of Biochemistry at Stanford. In hindsight, we all agree that those days were among best times of our scientific lives. Hypothesis after hypothesis was discussed, most to be discarded through lively arguments.

Everyone in the laboratory at the time got a copy of Allan's Episomes monograph, which among other things detailed the proof that his model for prophage integration was correct.[8] Early on, Allan stated, without explaining, that the fundamental groundwork leading up to his model was genetic studies of chromosome mechanics in corn. That tantalizing observation preceded discovery of "mobile genetic elements and DNA insertions" in corn and bacteria at the molecular level.[9] Regrettably, we never asked him to elaborate. An important point here is that Allan operated at a stratospheric level intellectually. In casual research discussions, it was clear that Allan had a grand and broad perspective on virtually any topic that came up. His depth and breadth on microbial genetics matters was a bit daunting. If you stayed on to converse with him, the discussions often led to the interface of what was known and what wasn't. Being at that interface then led to discussions about how one might design experiments to answer questions that had come up.

Another aspect of the Campbell laboratory was a generous culture, leading to free-flowing discussions. For example, a key point in discussion by one of us (Mike) dealt with viral DNA packaging, and the thought came up that it might be interesting to make a phage with two copies of the site, soon to be called *cos*, that lambda uses to recognize and initiate DNA packaging. Could one make a phage with a *cos* duplication, and what would be the effect of having two such sites? Without hesitating, Don said "Oh, here's how you can do that." Don had been working on making phages with a single deleted gene; the same methodology generates duplications.[4] Making and studying the *cos* duplication phage occupied the next few years of Mike's life, leading to insights about lambda's DNA packaging process. We learned that one way to have a career in genetics was to have an interesting mutant that would tell you things about the biology of the creature under study. The trick was to ask good questions and make good choices about what mutants to make and study. Another lesson was that the best kind of mutants were those that did not behave as anticipated. The natural world is generally more interesting than the researcher imagines it to be. The unexpected outcome is challenging but also a window to learn new things or lead to new research directions.

Allan, in a hands-off sort of way, took sincere interest in the futures of his former students. For those of us who continued in phage biology, microbial genetics, or infectious disease, a focus of his interest was the science itself. That focus was a refreshing and enduring facet of our relationship with Allan.

Allan was such an important figure in our lives; as a mentor and friend, he guided us to become thoughtful productive scientists. We only hope that we have emulated him and become good mentors ourselves. He never told us directly what to do but through discussions and advice made sure that we developed our own ideas and paths in research. It was an invaluable experience for us to be in Allan's lab and was the best of times, at least for us four. Allan had a wonderful life, as did those he mentored.

Insightful Scientist

Allan combined acute thinking with curiosity. It was not uncommon for us to take our plates out of the incubator in the morning and find Allan there wondering what the plates said. This provided challenging moments of trying to think very fast to keep up with Allan or, failing that, defaulting to the claim that the plates had not been looked at yet. Allan's presence reflected his keen curiosity and engagement with the experiments.

Clarity of thought was Allan's major strength. His bent toward mathematics seemed to be the basis for his need to ask clear questions in order to seek deeper understanding. He usually constructed experiments where answers were definitive, yes or no without gray areas. We often witnessed seminar speakers pause in thought and sometimes embarrassment after one of Allan's penetrating questions. He was a master at finding true holes in an argument. "Allan attended essentially all of the departmental seminars, he listened closely, and then would offer the most insightful—and sometimes devastating—question, but he would deliver it with utmost courtesy and sensitivity," recalled Philip Hanawalt, his colleague at Stanford. "He would deliver his evaluations of thesis presentations by students so gently that they would never feel intimidated or threatened."

Campbell at Cold Spring Harbor Laboratory grounds with Asis Das and Charles Yanofsky attending the 60th Bacteriophage meeting in 1995.
(Photo Wendy Campbell.)

We assume that his creativity and logical approach to science was influenced by the fact that from early training and throughout his professional life, he kept company with elite biologists, such as Mike Doudoroff, Roger Stanier, James van Neil, Sol Spiegelman, Irwin Gunsalus, Salva Luria , Francois Jacob, Miroslav Demerec, Barbara McClintock, Al Hershey, Charles Yanofsky, Dale Kaiser, Paul Berg, Enrico Calef, Giuseppe Bertani, and Warner Arber. Perhaps his career ladder was more orches-

trated than was immediately apparent, although our impression was that Alice guided him through the hurdles of everyday life relevant to his scientific career, as Allan spent his waking hours primarily thinking about important biological questions. Allan's son, Joseph Campbell, also a biologist, remembers once suggesting to his father that he pursue "trendier" science topics that had more research grants available. His response was: "I worked very hard all my life so that I can work on whatever I thought was interesting, not what the world thought was interesting."

Allan was a gentle, charitable, and kind teacher who supported his students in so many ways. During our group meeting presentations, he would often ask a question that one could not answer on the spot, and then he would always insist that he/she go to the literature for an answer, never providing the solution himself.

Although, honest, apolitical, extremely smart, and analytical, we never heard him exaggerate or boast about his accomplishments, nor did he market himself.

Allan recognized that we scientists like our own ideas and can therefore be biased when interpreting data. He wrote, "But the more appealing an idea is, the more wary one should be of data that seem to support it." When Allan edited in our manuscripts containing the phrase "It's interesting that," he would write in the margin "… the reader will decide whether your data or conclusions are interesting, delete." That honesty, humility, and need to find the truth did not distract, however, from his ability to argue on behalf of his own experimental data and conclusions. He consulted and argued regularly with giants in the field.

Campbell was a "scholar's scholar," said William C. Steere, Jr., another Stanford colleague. "He was a terrific and helpful sounding board for research topics quite distant from his own research," remarked his colleague Robert Simoni.

Allan was a member of the National Academy of Sciences and a fellow of the American Academy of Microbiology, the American Association for the Advancement of Science, and the American Academy of Arts and Sciences. For his accomplishments, he also received the Abbott ASM Lifetime Achievement Award from the American Society of Microbiology in 2004. He joined the editorial board of *Annual Review of Genetics* and then assumed the editor position in 1984, stepping down in 2010 after a stunning twenty-six years. Although his love was in bacterial and bacteriophage genetics, "he always led fascinating discussions at the board meetings and helped assemble the contents of each volume, ranging from the simplest creatures to the more complex and at the same time

elucidating unusual features of genetics, imparting new knowledge from a broad and creative base, and encouraging the reader to appreciate the amazing intricate details of the life," warmly recalls Nancy Bonini, the current co-editor of the *Annual Review.* Allan wrote two reviews himself for the journal, including one that details his personal journey to discover phage integration.[10]

Outside the lab, Campbell enjoyed gardening, hiking, attending the opera with his wife, and traveling. He kept in shape by taking brisk, rambling walks around campus and, until a few years ago, bicycling to work every day. One of his annual traditions was to bike to Stanford football games with his children. "He wasn't a big sports person, but he just thought it was a nice traditional thing to do. Our parents, both being scientists, valued education, engaged me and my brother in critical thinking, taught us to ask a lot of questions and to be curious," said daughter Wendy. Campbell died on April 19, 2018, in Palo Alto. Campbell's wife of fifty-nine years, Alice, passed away soon after his death in 2019. They are survived by daughter Wendy Nelson and son Joseph Campbell and five grandchildren: Andrew, Eli, and Ray Nelson and Theodore and Grace Campbell.

Campbell with family in 1968. From left to right: Daughter Wendy, Wife Alice, Allan, son Joseph.
(Photo Wendy Campbell.)

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5. Feiss, M., S. Adhya, and D. L. Court. 1972. Isolation of plaque-forming, galactose-transducing strains of phage lambda. *Genetics* 71:189–206.

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7. Campbell, A. M., and A. Del Campillo-Campbell. 1963. Mutant of lambda bacteriophage producing a thermolabile endolysin. *J. Bacteriol.* 85:1202–1207.

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