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Professor Edward Lewis

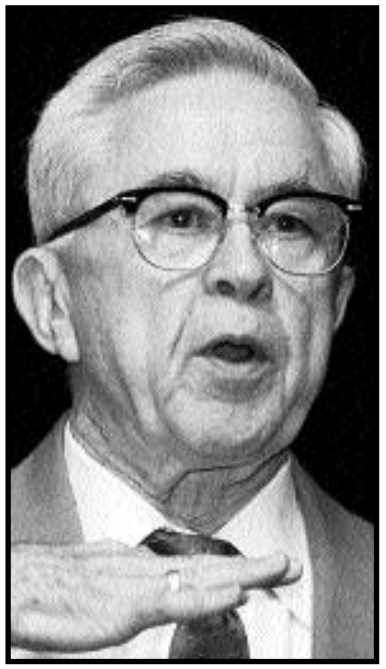
Nobel prizewinning classical geneticist who discovered 'master regulator' genes

ONE OF the greatest geneticists of the 20th century, Edward Lewis pioneered the use of genetics to understand animal development. He was the first to discover genes that function as "master regulators" of the animal body plan. It was for these discoveries that Lewis was awarded the 1995 Nobel Prize in Physiology or Medicine.

Lewis's career in research spanned almost seven decades, beginning in the mid-1930s and continuing until shortly before his death at the age of 86. His studies used the humble vinegar ("fruit") fly, *Drosophila melanogaster*, which Thomas Hunt Morgan had introduced for the study of genetics in 1910. Initially, Lewis's focus was on how the position of genes relative to each other in the chromosomes affects their function. As a PhD student at the California Institute of Technology (Caltech) in Pasadena Lewis invented a test for gene function known as the "cis-trans" test, which is still taught to undergraduate students in introductory biology courses.

Joining the Caltech faculty after the Second World War, he continued his studies of gene function and evolution, but his interest gradually shifted towards understanding how genes program development. Working almost alone, over a 30-year period from the mid-1940s to the mid-1970s, Lewis invented genetic strategies of unprecedented ingenuity and sophistication. These enabled him to discover a cluster of genes that function as master regulators of the body plan. The effects of mutations in these genes are striking: they convert flies from two-winged into four-winged or from six-legged into eight-legged versions. Lewis also identified genes that act as "regulators of the regulators", switching the master-control gene cluster on or off at different positions along the body axis.

With the advent of recombinant DNA methods, in the mid-1980s, laboratories in the US and Europe unexpectedly discovered that genes closely related to those studied by Lewis are present in similar clusters in the chromosomes of all animals and that they control the development of these animals in much the same way that Lewis had identified in the fly.



Lewis: publicly attacked *AP*

From the mid-1980s until shortly before he died, Lewis continued his studies of the master regulatory gene cluster. He also returned to his initial interest in gene evolution, using the newly invented molecular tools and, still later, the completed sequence of the 150 million "letters" in the fly's DNA blueprint. His first love and ongoing tool of choice, however, remained classical genetics, the field to which he had made so many contributions.

Less well known than his studies on the genetic control of development is Lewis' work on the somatic effects of ionising radiation, which initiated at the height of the cold war in the mid-1950s. Lewis was drawn into the debate about the effects of low levels of radiation in causing cancer in humans.

At that time many scientists and government officials in the US and UK argued that there is a threshold dose of radiation, below which cancer would not be induced. In a landmark study published in the journal *Science* in 1957, Lewis carried out risk estimates for leukaemia in survivors of the Hiroshima and Nagasaki atomic bomb attacks, in radiologists, and in other populations exposed to low doses of radiation. This led him to the very important – but at the time highly controversial – conclusion that the threshold hypothesis was not supported.

Lewis also realised that the health effects of radioactive fallout from nuclear weapons tests had been underestimated by federal regulatory agencies, which had not understood that radiostrontium would concentrate in bones, thus irradiating the blood system-producing cells in the bone marrow to cause leukaemia. Later, he reported that drinking cow's milk contaminated with radioactive iodine from fallout or from other sources was likely to affect the thyroid of infants and children far more than the adult organ. Lewis's prediction was highlighted tragically after the meltdown of the Chernobyl nuclear reactor in 1986, which led to a significant increase in thyroid cancer among children who had consumed cow's milk contaminated with the radioiodine that had been released into the atmosphere over northern Europe.

Shortly after publication of his 1957 paper, Lewis was attacked publicly by the chair of the US Atomic Energy Commission, Admiral Lewis Strauss, and by others, who challenged his scientific credentials and his methods of data analysis. History is on Lewis's side: research over the nearly 50 years since he published his landmark study has supported and confirmed his original conclusions. Lewis was called to testify before a US Congressional Joint Committee on Atomic Energy in June 1957, and subsequently served on the National Advisory Committee on Radiation of the US Public Health Service and on committees of the National Academy of Science concerned with estimating risks of ionising radiation.

Lewis, who preferred the peace and quiet of his laboratory to the public arena, was haunted by the public attention and the politically motivated attacks that accompanied his radiation studies. He always emphasised that he saw his role, not as an advocate for or against nuclear weapons and weapons tests, but as a scientist whose responsibility was to provide accurate information to policy-makers, thus positioning them to make educated decisions.

Edward B. Lewis (the "B" did not stand for anything) was born in Wilkes-Barre, Pennsylvania, in 1918. His mother and his father, a watchmaker and jeweller, supported his educational and musical aspirations despite the hardships of the Great Depression. Lewis began his studies on Drosophila as a high school student in Wilkes-Barre, when he spotted an ad for fruit flies in a scientific magazine. His approach to science was strongly influenced by the writings of the philosopher Bertrand Russell, who emphasised the importance of abstraction. Many of Lewis's papers are difficult to read because of the abstract models he formulated to explain his results; however abstraction framed his science, which can best be understood in those terms.

After spending a year at Bucknell College in Pennsylvania on a music scholarship – he remained an accomplished and enthusiastic flautist for the rest of his life – Lewis transferred to the University of Minnesota to continue his undergraduate education in biostatistics and genetics. After receiving his BSc degree in 1939, Lewis began his postgraduate research at Caltech under the renowned geneticist Alfred H. Sturtevant. Completing his PhD in 1942, he enrolled as a cadet in the US Army Air Corps training programme in meteorology at Caltech and was awarded the MSc degree in meteorology in 1943. Subsequently he served at bases in Hawaii and then as a weather officer for the US Tenth Army in Okinawa.

Returning to Caltech after the war, in 1946 Lewis was appointed an instructor in the Biology Division. He spent his entire independent career there, was appointed the Thomas Hunt Morgan Professor of Biology in 1966, and attained emeritus status in 1988, but remained active in research until his death. He worked day and night in his small, cluttered laboratory, a couch in one corner enabling him to sleep at will.

In 1946 he met and married Pamela Harrah, a Stanford graduate. It was Pam who, working as a technician in Lewis's laboratory in 1947, discovered the Polycomb gene, which Lewis went on to report in his famous 1978 paper in Nature as the first "regulator of the regulators". Pam is an accomplished artist; one of Lewis's final projects was to publish a book of her paintings.

Lewis was a consummate biologist. In his laboratory and home, aquaria were always present, in which he bred octopuses, clown fish and other marine animals. The pleasure he and Pam attained as they periodically raised the offspring of their pair of desert tortoises was palpable.

He received many awards and honours, among which were election as a member of the National Academy of Sciences (1968) and the American Philosophical Society (1990) and as a foreign member of the Royal Society (1989). He was awarded, jointly, the Nobel Prize in Physiology or Medicine in 1995.

Ed Lewis exhibited a rare combination of intellectual rigour and iconoclasm that was coupled with remarkable personal and scientific integrity and humility. He was kind, gracious and generous in both his personal and his scientific life. In his science he continued the tradition of sharing data and materials that was begun by Morgan and his co-workers starting in 1910. He is survived by his wife Pam and their sons Hugh and Keith. A third son, Glenn, lost his life in a mountaineering accident in 1965.

HOWARD LIPSHITZ

Edward B. Lewis, geneticist: born Wilkes-Barre, Pennsylvania 20 May 1918; Instructor, California Institute of Technology 1946-48, Assistant Professor of Biology 1948-49, Associate Professor 1949-56, Professor 1956-66, Thomas Hunt Morgan Professor of Biology 1966-88 (Emeritus); Nobel Prize in Physiology and Medicine (jointly with Christiane Nüsslein-Volhard and Eric F. Wieschaus) 1995; married 1946 Pamela Harrah (two sons, and one son deceased); died Pasadena, California 21 July 2004.