Obituary

Edward B. Lewis (1918–2004)

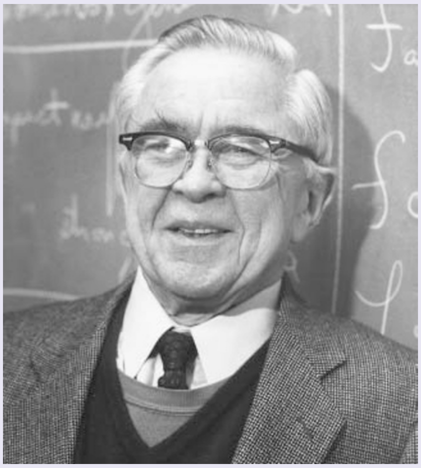
Ed Lewis, who died on 21 July at the age of 86, is remembered by all who knew him as a brilliant, eccentric and kindly scientist. He was a pioneer in exploring how genes design and build animals.

The 1995 Nobel Prize in Physiology or Medicine was a celebration of 85 years of study of the fruitfly *Drosophila*. The prize went to three biologists — Lewis, Christiane Nüsslein-Volhard and Eric Wieschaus — and we know now that the genes they discovered in *Drosophila* organize growth and development in all animals. Through decades of hard work, using endless patience and wonderful powers of observation, Lewis discovered and defined the first of these 'designer' genes. He called them the Bithorax complex; they give each body segment a distinct blueprint of instructions. If one segment's blueprint is damaged, that segment produces components that really belong to a different segment. Thus, as Lewis impressively demonstrated, a mutant fly could be made with an extra pair of wings. It was later found that the genes of the Bithorax complex all have a DNA sequence called a homeobox, or Hox; this allowed the identification of equivalent genes in mammals and elsewhere.

Hox genes occur in clusters, and Lewis surprised everyone by finding that the arrangement of Hox genes in a cluster mirrors the order of the body parts, from head to tail, that those genes specify; this principle is common to all animals. But why? No one really knows — Lewis's ideas still drive research. Lewis was also the first scientist to think in detail about where new genes come from. In 1951 he suggested that they arise by duplication of existing genes, one of which could then diverge from its parent. Molecular biologists confirmed this for Hox genes in the 1980s.

Lewis's methods seem extremely simple: mate flies carrying different mutations, study the progeny, and then do more crosses. However, he was a master of both genetic logic and the details of fly anatomy, and, using both, he derived sophisticated insights into what genes are, how they are arranged and how they influence each other. He loved making models of gene regulation, creating ornate abstract constructs. These constructs with their special terminology were demanding, and by the time people had absorbed one, Lewis had moved on and built another.

To explain his ideas, he used animation. Being small, he could get under a table and move a magnet around, while, on top,



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Geneticist who pioneered studies of 'designer' genes in animal development

coloured pieces of metal sprung to life like whirligig beetles, imitating genes and their targets. We remember him at a conference in Crete, suffering from stage fright and equipped with a cardboard tube, bits of coloured plastic, three tennis balls and an obliging chairman, attempting unsuccessfully to explain an abstruse aspect of gene regulation. It was all good fun, but Lewis was serious about his work, for he was battling with life's mysteries. The questions he defined still impinge on embryology, molecular biology, gene regulation, chromosome structure and evolution.

Lewis loved animals, harbouring snakes as a child. He and his wife Pam coddled their octopuses and desert tortoises. Lewis began work on *Drosophila* in high school, when a teacher encouraged him to study genetics. As an undergraduate at the University of Minnesota he worked with the geneticist C. P. Oliver, a student of Hermann Muller, who was himself a student of Thomas Hunt Morgan — the godfather of developmental genetics. As a graduate student at the California Institute of Technology (where,with a brief break during the Second World War, he would remain), Lewis's mentor was Alfred Sturtevant, also a former student of Morgan's. Thus Lewis was simultaneously the scientific grandson and great-grandson of Morgan.

Morgan began his career as an embryologist, but switched to *Drosophila* and genetics, leading the investigations that showed chromosomes to be the basis of inheritance. Lewis completed the circle, using genetics to study development. Nevertheless, he did not start with this intention. Instead he aimed to explore the nature of the gene itself — "how it functions, how it mutates, how it evolves".

His work also impinged on the study of cancer. In 1927, Muller reported that X-rays cause mutations in *Drosophila*. In 1955, Lewis discussed this work over lunch with some physicists, who had suggested that radiation damage to humans occurs only above a certain threshold dose. Lewis knew that Muller had found no such threshold in flies. Although it was not known then, Lewis also suspected that mutations can cause cancer. So he looked at data obtained from survivors of the Hiroshima and Nagasaki bombings, as well as from others exposed to radiation. He discovered a consistent dose–response relationship for leukaemia and other cancers, with no sign of a lower threshold. His papers questioned contemporary complacency about the safety of atomic-bomb testing and had considerable political and scientific impact. For his rigorously correct conclusions, he was attacked by the head of the United States Atomic Energy Commission.

For those who suspect that the present emphasis on publication is overdone, Lewis provides a superb role model. He published rarely and did not seem to care where. Some of his papers came out in such obscure journals that they were exchanged, like samizdat, as faded Xerox copies. His famously difficult 1978 paper in *Nature*, a compilation of decades of work on the Bithorax complex, finally brought him the wider attention he deserved.

A sweet, courteous and humble man, Ed worked in his lab to the end, probing possible connections between Hox genes and the cancer from which he was suffering. His credo, with which he ended his Nobel lecture, was: "Progress will still need to be driven by the logic of genetics and by further increases in abstraction," following from his favourite quote from Bertrand Russell: "The power of using abstraction is the essence of intellect, and with every increase in abstraction the intellectual triumphs of science are enhanced." **Matthew P. Scott and Peter A. Lawrence**

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