Edward B. Lewis 1918–2004

Welcome Bender

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Edward B. Lewis died in Pasadena, California, on 21 July at the age of 86. Lewis was the Thomas Hunt Morgan Professor of Biology at the California Institute of Technology and had been at Caltech for most of his scientific life, beginning as a PhD student with Alfred Sturtevant in 1939. He received the 1995 Nobel Prize in Physiology and Medicine, along with Christiane Nüsslein-Volhard and Eric Wieschaus, "for their discoveries concerning the genetic control of early embryonic development". His fellow scientists bestowed on him numerous other prizes, notably the Thomas Hunt Morgan Medal of the Genetics Society of America and the National Medal of Science (US).

Lewis pioneered fine-structure mapping in fruit flies, and he developed the *cis-trans* test to show allelic interactions. This test was later adopted by Seymour Benzer to define 'cistrons' in phage T4. But even after bacterial geneticists developed the concept of the operon, the fruit fly studies remained enigmatic. Lewis coined the word 'pseudoalleles' to describe interacting mutations in what came to be called complex loci. During the 1950s and 1960s, Lewis focused increasingly on one particularly rich cluster of genes, which he eventually named the bithorax complex. Mutations in this region transformed segments of the insect's body into copies of adjacent segments. The most famous genotype resulted in a four-winged fly, in which the third segment of the thorax was completely transformed into the second thoracic segment. For geneticists, this was compelling proof that some genes act as switches, choosing among alternate pathways of development. Lewis discovered that a deletion in the bithorax complex transformed the third thoracic segment and all eight abdominal segments into copies of the second thoracic segment. He suggested that the middle thoracic segment was the evolutionary 'ground state', and that the genes of the bithorax complex built up developmental modifications to make more posterior segments distinct. These conclusions, and a wealth of other observations, were explained in his seminal 1978 review in *Nature* (**276**, 565–570).

When it became possible to clone genetic loci from flies, the bithorax complex was the first target, and work from several labs, including Lewis', mapped his mutations across a chromosomal region of hundreds of kilobases. The most severe mutations affected transcription units for proteins with prototypic homeobox DNA-binding motifs, and these genes were later found in mammals, conserved in function and in chromosomal order. The bithorax complex was also the first target of the *Drosophila melanogaster* genome sequencing community, and Lewis was the first to analyze that sequence for hints of his genetic units (*Proc. Natl. Acad. Sci. USA* **92**, 8403–8407; 1995). He continued his screens for new mutations to dissect the functions of the complex more finely until a few months before his death.

Lewis made less well-known but equally important contributions to the study of the somatic effects of ionizing radiation in humans. During the cold war era of atmospheric testing of atomic bombs, there were official assurances that the low doses experienced by the general population were below the threshold required to cause genetic changes. Lewis studied the incidence of leukemia in various populations exposed to radiation, including radiologists and survivors of the Hiroshima and Nagasaki bombs. In his influential 1957 paper in *Science* (**125**, 965–972), Lewis argued that the dose-response rate was linear, that there was no evidence for a threshold. The clear implication was that continued fallout would, at the very least, induce hundreds of leukemia cases. Lewis and his analysis were caught in a storm of controversy over the effects of radiation fallout, but his view and his estimates eventually prevailed. He continued his studies of radiation induction of other types of neoplasias through the rest of his career. Two more comprehensive summaries of Lewis' scientific career have been published recently (I. Duncan and G. Montgomery, *Genetics* **160**, 1–10, 1265–1272, 2002; H.D. Lipshitz, ed., *Genes, Development, and Cancer: The Life and Work of Edward B. Lewis*, Kluwer, Boston, 2004).

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Lewis was guided by what he saw in his flies and was rarely directed by the models of other biologists. He generally avoided molecular explanations for his observations, in part due to a feeling of humility towards most things biochemical, and in part from a suspicion that the available molecular mechanisms couldn't explain the complexity he saw in the flies. He noted recurring themes in the genetics of the bithorax complex, which he sometimes called his rules. These included colinearity (the genes are aligned on the chromosome in the order of the segments they affect), *cis* overexpression (mutations in one region will often cause overexpression of the function from the adjacent region) and transvection (complementation between pairs of alleles can be dependent on chromosome pairing). Molecular biologists today imagine that these phenomena reflect changes in chromosome structure, the current frontier in gene regulation. No doubt Lewis' mutations hint at other molecular phenomena yet to be discovered.

Those who knew Ed regarded him with something between affection and devotion. He was exceedingly generous; it was impossible to pay for any meal shared with him, he readily gave away compound mutant chromosomes that had taken years to construct. His modesty was genuine and was not the least eroded by the attention that came with his honors. He was cheerful by his genetic constitution; even his final affliction with cancer he took on as an interesting problem. Mostly we will remember Ed for his infectious enthusiasm for the study of life. He would raise desert tortoises, or octopi, or tarantulas with the same excitement he had for his mutant flies. The aquariums and terrariums shared space in his cluttered office with his fly station, his accumulated figures and photos, and his flute music. He never had more than two or three students or postdocs, he avoided academic politics, and he did most of his science by himself, in the middle of the night. Ed reminded us of the challenge of a good problem, the delight of a surprising result and the wonder that first drew us to science. ■

Welcome Bender is in the Department of Biological Chemistry and Molecular Pharmacology, Harvard Medical School, 240 Longwood Ave., Boston, Massachusetts 02115, USA.