Edward B. Lewis

1918–2004

BIOGRAPHICAL *Memoirs*

A Biographical Memoir by
Howard D. Lipshitz

NATIONAL ACADEMY OF SCIENCES

EDWARD B. **LEWIS**

May 20, 1918–July 21, 2004

Elected to the NAS, 1968

Edward B. Lewis was a pioneering geneticist whose work on the common fruitfly began as a high school science project and resulted in his sharing the 1995 Nobel Prize in Physiology or Medicine. Ed was a modest, generous man and a scientist with never-ending curiosity. His science was innovative, groundbreaking and, ultimately, revolutionary. His Nobel Prize capped a sixty-year career in *Drosophila* (fruitfly) genetics research at Caltech, leading the way to the unexpected discovery that master regulatory genes that evolved hundreds of millions of years ago in the common ancestor of flies and mammals, program the body plan of all animals today.

Edward B. Lewis

By Howard D. Lipshitz

Early life

Edward B. Lewis was born in Wilkes-Barre, Pennsylvania on May 20, 1918. He was the second son of Edward Butts Lewis, a watchmaker and jeweler, and Laura Mary Lewis (née Histed). His brother, James Histed Lewis, was five and a half years older; a sister, Mary Louise Lewis, died of a fever at age two the night before James was born.

The Great Depression led to closure of the jewelry store in which Edward Sr. worked and the family struggled to make ends meet. A great uncle, Thomas Wyllie, president of the Pittston Stove Company, assisted both Jimmy and Ed financially, enabling them to go to college. After completing high school in 1929, Jimmy worked for a year at his great uncle's company, managing to save $1,600 for his college tuition. When he won a scholarship, Jimmy was able to send some of his savings home to support his parents. However, those years of financial struggle took a terrible toll; Edward Sr. died of a stroke at the age of 60 in 1945.

Laura Lewis, Ed's mother, encouraged him to study animals. This he did with great avidity and with a particular focus on toads and snakes, in part because of his allergy to

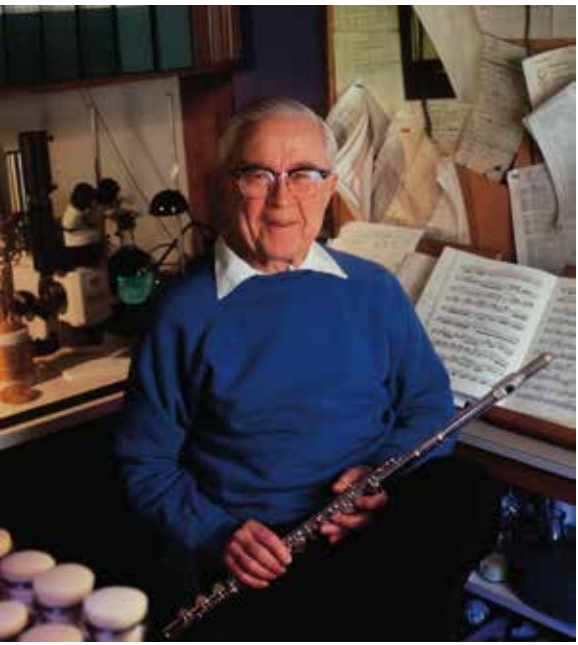

Figure 1. Ed Lewis with flute. This picture was taken in Ed's office-cum-lab after he was awarded the 1995 Nobel Prize for Physiology or Medicine. The prize medal (a copy—the original was stored in a safe-deposit box) can be seen on Ed's right, next to his 'fly-pushing' microscope. Behind the Nobel medal is the Lasker Award, which Ed received in 1991. The fact that the picture was highly posed is evidenced not just by the presence of the awards, which he never displayed, but also by the fact that sheet music covers Ed's *Drosophila* notebooks. In fact, Ed had a music stand in the rear of the lab next to the tattered couch on which he would nap.

the fur of conventional pets. Once Laura found a rattlesnake stored in a closet because Ed hadn't yet built its terrarium. As a teenager Ed used to pay a daily visit to Wilkes-Barre's Osterhout Public Library, whose excellence he praised throughout his life. In the library he read, not only books, but also the scientific journals to which the library subscribed. Thus it was that in late 1934 he spotted an ad for fruit flies in the journal Science. Ed was a member of the E. L. Meyers High School biology club; for $1 the club obtained the flies, launching Ed on his future career.

Ed began playing the flute at age ten, when his great uncle Tom had given him a wooden Haynes flute. A few years later his father gave him a silver flute, undoubtedly at considerable sacrifice. Ed went on to play in the high school orchestra as well as the Wilkes-Barre Symphony, and remained an accomplished and enthusiastic flautist for the rest of his life (Figure 1). Following high school, Ed spent a year at Bucknell College on a music scholarship.

In 1937, he transferred to the University of Minnesota to continue his undergraduate education in biostatistics and genetics, although he continued his flute playing as a member of the university orchestra. He was attracted to the University of Minnesota because it had low out-of-state tuition fees and because participation in the Reserve Officers' Training Corps there was not compulsory.

During his college years, Ed was assisted financially by his brother Jimmy, who by then had graduated from George Washington University with a master's degree in international law and joined the U.S. State Department. Jimmy was an inspiration to Ed, who admired his brother's ability to read rapidly and broadly. Ed himself was a slow reader and writer. He attributed his low scientific publication rate in part to these handicaps.

A characteristic shared by Ed and Jimmy was short stature. At a banquet following publication of his collected papers (Lipshitz 2004, 2007) Ed recalled a student asking what was the hardest thing he had to overcome in his career:

> *I should have written the student and said that the hardest thing was to write up my experiments for publication...But instead of telling the student I suffer from writer's cramp, I wrote him that the hardest thing to overcome was my short stature...I was aware that short stature was an even greater problem for my brother...He once said that a Japanese diplomat had told him that he was the only American the diplomat liked because he did not have to look up to him![1]*

Jimmy and Ed Lewis shared a love of opera and of bouillabaisse; both were greatly influenced by the Great Depression, particularly by their parents' struggle. Both were self-motivated and successful but kept their success in perspective. Both were quiet, modest men with tremendous personal integrity and intellect; and both died of metastatic prostate cancer at the age of 86.

At the University of Minnesota, Clarence P. Oliver, Professor of Genetics, gave Ed a desk in his laboratory along with the freedom to continue the *Drosophila* work that he had begun in high school (Lewis 1939). By passing examinations in several courses without actually attending the lectures, Ed was able to complete his B.A. degree in biostatistics in two years.

Caltech

In 1939, Ed began his graduate research at Caltech under Alfred H. Sturtevant, a renowned *Drosophila* geneticist. His Ph.D. thesis focused on how the position of genes relative to each other in the chromosomes affects their function (Lewis 1941, 1945). Importantly, Ed invented a test for gene function known as the 'cis-trans' test, which is still taught to undergraduate students in introductory biology courses, and which formed the foundation for his later discovery of the rules by which the *bithorax* family of mutants control the establishment of the body plan.

Completing his Ph.D. in 1942, Ed enrolled as a cadet in the U.S. Army Air Corps training program in meteorology at Caltech. He was awarded an M.S. degree in meteorology in 1943. He served at army bases in Hawaii and then as a weather officer for the U.S. Tenth Army in Okinawa. He was stationed on a command ship in the harbor and would begin his shift daily at 4 a.m., preparing the weather forecast for relay to the reconnaissance planes that flew over the battle zones.

In 1946 Ed was appointed an instructor in the Biology Division at Caltech, having been recruited to that position in 1943 by the university president, Robert A. Millikan, before he left for military service. Ed spent his entire independent career at Caltech, was appointed the Thomas Hunt Morgan Professor of Biology in 1966 and attained emeritus status in 1988. He remained active in research until his death.

Ed met and married Pamela Harrah, a Stanford graduate, in 1946. Their meeting was arranged by George W. Beadle, who had returned to Caltech from Stanford in 1946 to chair the Biology Division. That same year Ed had taken responsibility for supervising the extensive Caltech *Drosophila* Stock Center and was looking for a stock keeper. While still at Stanford, Beadle called Pam into his office and said, "Hey Pam, how tall are you?" to which Pam replied, "5' 3"." Beadle then said, "Your new Boss is 5' 4" tall, he's 28 and maybe you will like him so much, you will fall in love and decide to stay there at Caltech."[2]

A few months after meeting, Ed and Pam were married and remained so until Ed's death 58 years later. Ed and Pam had three sons: Hugh, Glenn, and Keith. Pam is an accomplished artist whose paintings, almost always feature insects.

Ed's daily sleep-wake rhythm was unusual, more closely resembling a 12-hour than a 24-hour cycle. He attributed this in part to the rhythm he had been forced to follow as weather officer during the war. For the decade that my research group was located across the hall from Ed's on the third floor of Caltech's Kerckhoff Memorial Laboratories, he would arrive early in the morning and begin work, then pause to practice his flute. Promptly at 8 o'clock, he would disappear to the gym to jog or swim for an hour before returning to continue the day's work. Often he would take a pre-lunch nap on the tattered couch at the rear of his office. Then at noon sharp his door would slam shut and he would head out for lunch at one of the faculty tables at Caltech's Athenaeum, always stopping by my office to invite me to accompany him.

Ed's wry humor came to the fore while walking to one such lunch in the late 1980s. Elliot Meyerowitz, Ed and I—all vertically challenged (Figure 2)—were passing through the olive walk leading to the Athenaeum's entrance when Ed suddenly stopped and exclaimed: "All great geneticists are short!" As Elliot and I vigorously affirmed this statement, Ed laughed and added: "Except Sturtevant." Sturtevant, Ed's Ph.D. supervisor, was one of his heroes, whose encyclopedic memory, precise and incisive mind, and ability to design simple but elegant experiments Ed would often discuss.

Figure 2. Howard Lipshitz, Ed Lewis and Elliot Meyerowitz (left to right) at a surprise party in the hallway of the third floor of Kerchoff Laboratories in May 1991 to celebrate Howard's naturalization as a U.S. citizen. In the background is Susan Celniker, Ed's long-term research associate, who carried out many molecular studies of Ed's bithorax complex mutants before moving to Berkeley to lead key aspects of the Drosophila genome project. I well remember Ed deciding in the late 1980's that it was time for Sue to teach him how to do a Southern blot. There was a flurry of activity with Ed rushing about learning how to digest DNA with restriction enzymes, pour, load and run an agarose gel. etc. I forget whether there was a successful outcome.

In the afternoons, Ed would do more lab work and some hated paperwork, then head home to an early dinner with Pam, followed by another nap. He usually returned to work at night, enjoying the peace and quiet of that period to carry out the bulk of his *Drosophila* crosses and genetic analyses.

Ed's approach to science was strongly influenced by the writings of the mathematician and philosopher Bertrand Russell, who emphasized the importance of abstraction as well as the fact that science is inductive not deductive. Many of Ed's papers are difficult to read because of the abstract models he formulated to explain his results. Abstraction framed his science. He chose to quote from one of Russell's books, which he had first encountered as a high school student, to begin his Nobel lecture: "The power of using abstraction is the essence of intellect and with every increase in abstraction, the intellectual triumphs of science are enhanced."

Fruitfly genes

Ed's initial *Drosophila* studies focused on gene function and evolution. His invention of the cis-trans test enabled him to determine whether genetic recombination might occur between members of what were then known as 'multiple allelic series' (closely linked alleles with similar phenotypes). The cis-trans test is simple in concept. In diploid organisms like flies it involves generating offspring that carry the two mutant alleles in cis on one chromosome and the two wild-type alleles in cis on the homologous chromosome. This can be represented symbolically for mutant alleles *a* and *b* as [*a b*/+ +] where the pluses represent the wild-type alleles and the virgule separates the genotypes of the homologous chromosomes. The phenotype of these flies is then compared to that of offspring that carry the mutant alleles in trans [*a* +/+ *b*], thus enabling one to ask whether the position of those alleles relative to each other affects the outcome. As can be seen, in an abstract sense the overall genetic constitution of the cis and trans combinations is the same: both carry two mutant alleles, *a* and *b*, and two wild-type alleles, + and +. They differ, however, in their position relative to each other.

In practice, it can be very difficult to obtain the double-mutant in cis [*a b*] since this requires genetic recombination between closely linked mutations, and the frequency of recombination decreases with distance. When Ed began his studies, it was thought that recombination could not occur between members of a multiple allelic series. Lewis, however, showed that it was indeed possible to obtain recombination between the alleles of several such series: first, *Star* and *asteroid* (his Ph.D. work) and, later, *Stubble* and *stubbloid, white* and *apricot*, as well as the *bithorax* mutant series (Lewis 1945, 1951, 1952).

Since the phenotypes of the cis and trans combinations differ greatly for all of these series, he was able to conclude that the position of the wild-type and mutant alleles relative to each other is very important for gene function. Furthermore, since *Star* and *asteroid* as well as the *bithorax* series of mutations map to polytene chromosome doublets, which Calvin Bridges (Bridges 1935) had hypothesized might represent tandemly duplicated genes that are in the process of evolving to perform new functions, Ed was led to propose that the separable 'pseudoalleles' might indeed represent tandemly-duplicated genes that are related both in structure and function.

Working almost alone over a thirty-year period from the mid-1940s to the mid-1970s, Ed invented genetic strategies of unprecedented ingenuity and sophistication. These

enabled him to discover that the *bithorax* family of mutants is, in fact, a cluster of genes —which he came to call the *bithorax* gene complex—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.

In 1951 Ed postulated that the *bithorax* gene cluster controls the development of particular body segments and that their function is to convert segments from a 'ground state' (the second thoracic segment) to more posterior segmental identity (Lewis 1951). Abrogation of the function of these genes thus leads to 'homeotic' transformation of, for example, the third thoracic segment into second thoracic segment, thus creating the second pair of wings (Figure 3).

Figure 3. Ed's famous *bithorax* mutant fly with a wing-bearing second-thoracic segment replacing the third segment, hence carrying four wings instead of the two characteristic of Diptera. Versions of this image appeared on the cover of the issue of *Science* magazine in 1983 that reported the molecular cloning of the *bithorax* complex, as well as in multiple textbooks. One of Ed's last projects was to produce a version that could flap the auxiliary pair of wings and actually fly! This was not just an idle pastime but a real scientific challenge: the homeotic gene code for the flight muscles differs from that for the wings they must flap. For Ed, the challenge, then, was to correctly mutate the genes in both the muscles and the wings in order to accomplish his goal. While he never succeeded, for Ed it was the journey rather than the destination that was most fascinating.

By the late 1950's, Ed's focus had shifted from the function and evolution of genes to how they control development. He thought this should be amenable to the same kind of mechanistic genetic analysis as had biosynthetic pathways in bacteria and their viruses (Lewis 1963). During the 1960s, Ed also identified genes that act as 'regulators of the regulators' – most notably *Polycomb*, the first allele of which Pam had discovered in 1947 while working as a technician for Ed. These genes switch the master control gene clusters on or off at different positions along the body axis. He also started to address the spatial and temporal control of development through analyses of genetically chimeric ('mosaic') flies.

He was able to ask whether the *bithorax* complex genes confer the fate of cells autonomously or whether the genes encode diffusible substances. Strikingly, the genes behaved autonomously, consistent with their encoding non-diffusible substances that give identity instructions to each cell in which they are expressed. With the recently discovered '*lac* operon' in mind, Ed suggested that the *bithorax* genes "evidently…[produce] a whole set of substances that repress certain systems of cellular differentiation and thereby allow other systems to come into play."[3] Subsequently, he postulated that the *bithorax* substances would function through both activation and repression. Twenty years later, molecular analyses proved this to be correct: the *bithorax* complex encodes proteins that regulate the transcription of mRNAs from their target genes.

Ed's most famous paper appeared in 1978 following a more than ten-year publication drought (Lewis 1978). Because this paper summarizes thirty years of research in six pages and presents almost all of the data in terms of an abstract model, it is very difficult to read. However, for those willing to make the effort, it is a revelatory paper; indeed, upon its publication it almost immediately established a new paradigm for the genetic control of development. The 1978 paper is replete with novel observations and strategies, not least of which is Ed's analysis of homeotic phenotypes in embryos rather than adults. These analyses proved that the *bithorax* complex genes function throughout development to establish cell fates.

To a geneticist, the most remarkable part of the 1978 paper is Ed's invention of what can be called 'add-back' genetics[4]. Standard genetics involves mutating or deleting genetic functions and inferring the wild-type role of genes from their mutant phenotypes, a strategy that Ed had applied very successfully to the *bithorax* complex since the inception of his analyses. In contrast, the add-back strategy began by deleting the entire *bithorax* complex and then adding back, bit-by-bit, wild-type pieces of the complex. In this way, Ed was able to define the location and the wild-type function of genes for which he had not yet obtained mutations. His results led him to propose that there are twelve different genes in the complex that turn on progressively one-at-a-time from more anterior (fewer genes 'on') towards more posterior (more genes 'on') segments. The fate of any particular segment would be specified additively by the sum of the 'substances' produced by the *bithorax* complex genes turned on in it.

The genetic approach Ed pioneered, when combined with the molecular methods pioneered by David S. Hogness at Stanford University, led to the deep insights that we

now have into the mechanisms by which animals develop. In the early- to mid-1970s, Hogness invented recombinant DNA methods for the analysis of whole genomes (Wensink et al. 1974, Glover et al. 1975, Grunstein and Hogness 1975). In 1978, he initiated a collaboration with Ed that led to the first positional cloning of a gene–part of the *bithorax* complex—and the first functional genomic analyses, which correlated the DNA map, the mRNA transcripts, the genetic mutations and their phenotypes (Bender et al. 1983a, b). This was followed by the unexpected discovery that genes in the homeotic complexes of *Drosophila* share a closely-related DNA sequence (the 'homeobox'), which encodes a protein domain that binds to DNA and regulates the production of mRNA transcripts from 'target' genes (McGinnis et al. 1984a, Scott and Weiner 1984).

The molecular analyses revealed that Ed, in his earlier 'additive control along the body axis by tandemly duplicated genes' hypothesis, had been both right and wrong. Right in that the genes in the complex had indeed evolved by tandem duplication: there are three tandemly duplicated protein-coding genes in the complex, which are characterized by the homeobox. Right too, in that the spatial expression of these genes is highly regulated along the body axis and, indeed, the genes do become active one after the other, from anterior to posterior, as Lewis had postulated. But he was wrong in concluding that there are twelve genes in the *bithorax* complex; there are only three.

Most of the twelve 'genes' that Lewis had identified are in fact cis-regulatory regions that control the time, place and level of expression of the homeobox-containing mRNAs, although they also produce long, non-coding RNAs that fascinated Ed (Drewell et al. 2002, Lewis 1986, Lipshitz et al. 1987). It turned out that the identity of each segment is not a simple additive effect of activating more of the genes. Lewis could not have predicted these molecular details solely on the basis of his genetic results; the synergism of molecular and genetic methods was required.

One of the most remarkable discoveries made in the mid- to late-1980s was that genes closely related to those studied by Ed are present in similar clusters in the chromosomes of all animals (McGinnis et al. 1984b), and that they control the development of these animals in much the same way as in the fly. Furthermore, his 'colinearity' rule—that the order of the homeotic complex genes in the chromosomes corresponds to the order along the body axis of the segments whose development they control—applies all the way from flies to mammals (Duboule 1998). A primordial gene complex must have predated the divergence of the ancestors of flies and mammals over five hundred million years ago.

Figure 4. Ed at the White House at a celebration for the U.S. recipients of the 1995 Nobel Prizes. The event was hosted by Vice President Al Gore and Hillary Clinton. The photo shows (from left to right) Betty and Jimmy Lewis (Jimmy was Ed's older brother), Pam and Ed, and Hillary Clinton. There were supposed to be many guests but the government was shut down over the budget, so only the U.S. Laureates and their families attended and, instead of the planned buffet, only tea and biscuits were served. Jimmy recalled at the time that it was just over 50 years since he first visited the White House as an aide to Secretary of State Cordell Hull to see President Roosevelt.

It was this extension and generalization of four decades of Ed's genetic analyses that led to the award, in 1995, of a share of the Nobel Prize for "discoveries concerning the genetic control of early embryonic development" (Figure 4). In typically modest fashion, Lewis' response to the news of the award was: "It's very nice, but actually what is more exciting is the science…It's much more exciting to get the discoveries than to win prizes."[5] The Nobel Prize didn't change Ed's life, his attitude, or his work-schedule very much. For the first six months after the award, Caltech provided him with a part-time secretary and a fax machine to assist with the extensive correspondence. Thereafter, the secretary returned to her normal assignment (Ed got to keep the fax machine).

Ionizing radiation

Less well known than his studies on the genetic control of development is Ed's work on the somatic effects of ionizing 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 U.S.A. and U.K. argued that there is a threshold dose of radiation below which cancer would not be induced.

In 1954, Admiral Lewis L. Strauss, the Chairman of the Atomic Energy Commission in the U.S.A., had issued a public assurance that the atomic weapons tests would result in an increase in background radiation in some locations within the continental United States that was "far below the levels which could be harmful in any way to human beings." Sturtevant, in his presidential address to the Pacific Division of the American Association for the Advancement of Science later that year responded: "There is, in fact,

Figure 5. George Beadle, Alfred Sturtevant and Ed Lewis (left to right) circa 1952. In 1954, Admiral Lewis Strauss, Chair of the Atomic Energy Commission (AEC), claimed that radioactive fallout from atomic weapons tests was "far below the levels which could be harmful in any way to human beings." Sturtevant responded by emphasizing that "there is no clearly safe dosage." Beadle, at the time Chair of the Caltech Biology division and an advisor to the AEC, ensured that Lewis was given access to data on leukemia cases among the Japanese survivors of the Hiroshima and Nagasaki atomic bomb blasts. Lewis then used these data in his calculations of the risks of exposure to low levels of ionizing radiation. (Photo courtesy of the Caltech Archives.)

no clearly safe dosage – all high-energy radiation, even of low intensity and brief duration, must be considered as potentially dangerous to the exposed individual."
(Sturevaht 1954.) Lewis took up the challenge to investigate the effects of low doses of ionizing radiation in cancer induction.[6]

In a landmark study published in the journal *Science* in 1957, Ed carried out risk estimates for leukemia in survivors of the Hiroshima and Nagasaki atomic bomb attacks, in radiologists, and in other populations exposed to low doses of radiation. His best estimate of the absolute risk of leukemia was one to two cases per million persons per rem (per 0.01 Sv in modern parlance) per year. Ed's analyses led him to the very important—but at the time highly controversial—conclusion that the threshold hypothesis was not supported. He also realized that the health effects of radioactive fallout from nuclear weapons tests had been underestimated by federal regulatory agencies. It had been thought that a dose of 2,000 rad (20 Gy) would be needed to induce cancer and that only bone cancer would occur. This error derived from the fact that it had not been understood that radiostrontium would concentrate in bones, thus irradiating the blood system producing cells in the bone marrow to cause leukemia. Ed pointed this out in the 1957 paper, where he calculated that there would be a 5 to 10% increase in leukemia incidence in the U.S. from a constantly maintained level of Strontium-90 that was one tenth of the 'maximum permissible concentration' recommended by the National Commission on Radiation Protection (Lewis 1957).

Shortly after publication of his 1957 paper, Ed was attacked publicly on NBC's 'Meet the Press' television show by Admiral Strauss, who challenged his scientific credentials. Neil Wald of the Atomic Bomb Casualty Commission in Japan and Austin Brues of the Argonne National Laboratories published scientific articles that criticized the accuracy of his data. The most detailed critique came from Alan W. Kimball, a statistician at the Oak Ridge National Laboratory, who challenged Ed's methods of data analysis. Sewall Wright and James F. Crow, both distinguished geneticists, engaged in an active dialog with Kimball. The former explained that "Lewis' tests are correct" and the latter pointed out that several of Kimball's theoretical criticisms were "irrelevant"for the type of analysis that Ed had conducted.[7]

History is on Ed's side: research over the 55 years since he published his landmark study has supported and confirmed his original conclusions. Current risk estimates from low doses of ionizing radiation are very close to his original estimates, (BEIR V 1990, BEIR VII 2006). Indeed, the 2006 Report in Brief of the U.S. National Academies summarizing the latest study of the Biological Effects of Ionizing Radiation explicity states that

> *A comprehensive review of available biological and biophysical data supports a 'linear-no-threshold' (LNT) model – that the risk of cancer proceeds in a linear fashion at lower doses without a threshold and that the smallest dose has the potential to cause a small increase in risk to humans.*[8]

Over the two decades that followed publication of the *Science* paper, Ed returned repeatedly to questions related to the somatic effects of low doses of ionizing radiation. In one of those studies 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 1959). His prediction was highlighted tragically after the meltdown of the Chernobyl nuclear reactor in the Ukraine 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.

Perhaps one final story captures Ed the man better than any other. In March 1997, I received a phone call from Ed, who was livid about the contents of an article in the *San Francisco Examiner* titled "Science student accused of cruelty to fruit flies."[9] The news-

paper article reported that a high school sophomore, Ari Hoffman, had won the Marin County science fair but had subsequently been disqualified because 35 of the 200 fruit flies he had used in his experiments had died. Apparently national science fair regulations ban experiments that injure or kill animals of any kind! Ari's project had been to examine the effects of different doses of radiation on mutation rate and fertility. Herman J. Muller had first shown, in 1927, that ionizing radiation causes mutations roughly in proportion to the dose given to the flies. For this work Muller received the 1946 Nobel Prize in Physiology or Medicine, so Ari was in good company. Fortunately, the article mentioned that Ari had been able to do the experiments because his father, Dr. William Hoffman, had a lab at UCSF and access to a radiation source. Soon Ed was on the phone to Dr. Hoffman, expressing his personal regret that Ari had lost the prize. He was ecstatic to find out that others must also have challenged the decision, resulting in reinstatement of the award.

But Ed didn't stop there. He obtained Dr. Hoffman's home address and dashed off a letter to Ari, enclosing a check "as a token award for your accomplishments from someone who has spent his career studying *Drosophila*. I also started in high school, long before anyone had thought of science fairs…" and inviting him to visit. Within days Ari had written back arranging the visit and telling Ed "the contents of that envelope are my most cherished souvenirs from the fruit fly ordeal…Having a Nobel Laureate support me and show interest in my work is something few can boast about…"[10]

Awards and honors

Ed Lewis received many awards and honors. Among these were: election as a member of the National Academy of Sciences, U.S.A. (1968), of the American Philosophical Society (1990) and as a foreign member of the Royal Society of London (1989). He received the Gairdner Foundation International Award (Canada, 1987), the Wolf Prize in Medicine (Israel, 1989), the Lewis S. Rosenstiel Award in Basic Medical Research (USA, 1990), the National Medal of Science (USA, 1990), the Albert Lasker Basic Medical Research Award (USA, 1991), the Louisa Gross Horwitz Prize (USA, 1992), and the Nobel Prize in Physiology or Medicine (Sweden, 1995).

With the permission of the American Philosophical Society, this memoir is a substantially revised version of one published in 2006 in their *Proceedings*, Volume 150, pp. 379-395. I am greatly indebted to Jon Roderick Lewis, Ed Lewis' nephew, for providing personal details of his father, James H. Lewis, and his grandparents, Edward Butts Lewis and Laura Mary Lewis. Jon also contributed several interesting anecdotes about Ed's early life of which I was not previously aware.

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NOTES

1. From a speech delivered at the Ritz-Carlton, Huntington Hotel, Pasadena, California on February 4, 2004.
2. Quoted in P. Berg and M. Singer. 2003. *George W. Beadle. An Uncommon Farmer: The Emergence of Genetics in the 20th Century.* New York: Cold Spring Harbor Laboratory Press. P. 196.
3. Lewis, E. B. 1964. Genetic control and regulation of developmental pathways. In *Role of Chromosomes in Development,* ed. M. Locke. New York: Academic Press, pp. 231-252.
4. Lipshitz, H. D. 2007. Genes, Development and Cancer: The Life and Work of Edward B. Lewis. Second Edition. Dordrecht: Springer. pp. 188-189.
5. Quoted in the *Los Angeles Times,* October 10, 1995. Page A18.
6. For detailed discussion see H. Lipshitz. 2007. ibid, pp. 415-431; H. Lipshitz. 2004. *From fruit flies to fall out: Ed Lewis and his science. J. Genetics* 83:201-218; J. Caron. 2004. Biologists and "the bomb." *Engineering & Science* 67:17-27.
7. Quoted in: H. Lipshitz. 2007. ibid, pp 425-426; Crow, J. F. and W. Bender. 2004 *Genetics* 168:1778-1783.
8. Report in Brief, BEIR VII. 2006. National Research Council.
9. *San Francisco Examiner,* March, 20 1997.
10. I am grateful to Ari Hoffman for permission to quote from his letter to Ed. Ari now practices internal medicine at UCSF.

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