EDWARD B. LEWIS

20 MAY 1918 · 21 JULY 2004

I NEVER saw Ed Lewis in an immodest mood. He came closest on a Monday in October 1991 at a biology faculty lunch table at the Caltech Athenaeum.

By then it was clear that Ed's forty-five-year-long studies of the *bithorax* gene complex in the fruit fly, *Drosophila*, were of fundamental importance for understanding the genetic basis of all animal development (about which, more below). Thus, his colleagues on the Caltech faculty all felt that it was just a matter of time before he was going to receive the Nobel Prize. And it must be admitted that each year we—and he—would become slightly tense as the annual announcement date drew near, wondering whether it was finally his turn.

That day, discussion at the lunch table had turned to the early-morning announcement that Erwin Neher and Bert Sakmann had received the Nobel Prize in Physiology or Medicine for their studies of single ion channels in cells. Ed—not one to follow developments in cellular physiology—was at the opposite end of the table from Henry Lester, a faculty member in whose lab Neher had spent a sabbatical period in 1989. Henry was expounding at some length on the power of the "patch clamp" technique, and the reasons it deserved the award. Suddenly, from the opposite end of the table came an interjection from Ed: "Pinch clamp? Pinch clamp! Why would they award the Prize for invention of the pinch clamp?" When the laughter subsided, Henry clarified[1] and Ed was gradually mollified.

Ed Lewis's personality was characterized by modesty, humility, generosity, kindness, and never-ending curiosity. His science was innovative, groundbreaking, and, ultimately, revolutionary. His share of the 1995 Nobel Prize in Physiology or Medicine capped a sixty-year career in *Drosophila* genetics that had led the way to the discovery that evolutionarily conserved "master regulatory genes" program the body plan of all animals. Lewis had not begun with an interest in developmental biology; rather, his studies of the nature and evolution of genes had led—in the circuitous fashion that is the hallmark of science—to a gradual shift of focus as he came to realize that the gene cluster he was studying represented an entrée into the rules that govern the assembly of the animal. With the advent of molecular cloning methods and the discovery in the mid-1980s that the gene cluster is conserved in organization and function in all metazoans—thus predating the pre-Cambrian explosion of animal forms more than five hundred million years ago—the gener-

[1] Patch clamp: sophisticated physiological technique that allows recording of electrical currents as small as a picoampere through a single ion channel in a cell membrane. Pinch clamp: metal device to control flow through flexible tubing; used in chemistry laboratories.

ality of his studies became apparent and, as mentioned above, prizes began to be awarded on an almost annual basis.

Despite numerous honors, Lewis never lost his humility; neither did he alter his daily routine of many hours at his "fly pushing" microscope. As metastatic prostate cancer weakened him, he set up a microscope at home, where he continued his genetic crosses. He stayed in daily contact with family and close friends by email from home, managed to complete and submit a brief historical article to the journal *Genetics* in mid-June,[2] and finally succumbed to the disease on 21 July 2004.

Edward B. Lewis was born in Wilkes-Barre, Pennsylvania, on 20 May 1918, the second son of Edward Butts Lewis, a watchmaker and jeweler, and Laura Mary Lewis (née Histed). His brother, James ("Jimmy") 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. Edward's full name was supposed to be Edward Butts Lewis Jr. but his parents forgot to fill his middle name out in full on the birth certificate, so his middle name ended up simply as "B."[3]

Young Edward's parents supported his educational and musical aspirations. This was done despite the hardships of the Great Depression, which led to the closing of the jewelry store in which Edward Sr. worked and a difficult struggle 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 Wyllie's company, thus managing to save $1,600 for his college tuition. By winning a scholarship, Jimmy was able to send some of his savings home to support his parents. However, those years took a terrible toll, probably contributing to Edward Sr.'s untimely death of a stroke at the age of sixty in 1945.

Laura Lewis, Ed's mother, encouraged him to study animals, which he did with a particular focus on toads and snakes. Her patience was, however, tested at least once, when she found one of his rattlesnakes in the closet—he hadn't built the terrarium for it yet. 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

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[2] E. B. Lewis, Did Demerec discover intragenic recombination in 1928? *Genetics* 168 (2004): 1785–86.

[3] I am greatly indebted to Jon Roderick Lewis, Ed Lewis's nephew, for providing personal details of his father, James H. Lewis, and his grandparents, Edward Butts Lewis and Laura Mary Lewis. He also contributed several interesting anecdotes about Ed's early life of which I was not previously aware, and kindly provided comments on a draft of this article.

the journal *Science*. Ed was a member of the E. L. Meyers High School biology club, which at that time was chaired by his friend, Ed Novitski, who also went on to become a distinguished *Drosophila* geneticist. For $1 the club obtained the flies, launching both Eds on their future careers.

In his autobiography, Ed emphasized that "by allowing Novitski and me freedom to use the biology lab and its supplies to carry out our experiments on *Drosophila*, our biology teacher, who also was the athletic coach, could not have been more helpful in furthering our careers. There was none of the present attitude that one cannot become a scientist without having had the benefit of teachers skilled in the art of keeping their students constantly motivated."[4] In other words, Ed was self-motivated from the outset.

Following high school, Ed spent a year at Bucknell College on a music scholarship. He had begun 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. For the last forty years of his life, he and his wife, Pam, often spent weekends in La Jolla, during which the high point for Ed was playing chamber music on Sunday morning at the home of the well-known virologist Marguerite Vogt, of the Salk Institute. Vogt, an accomplished pianist, had spent the years from 1950 to 1963 at Caltech, during which time she became a close friend of the Lewises. In conversation Ed often praised her earlier work on homeotic mutants of *Drosophila*—conducted under difficult circumstances in Nazi Germany during World War II—as being "many years ahead of its time."[5]

In 1937, Ed 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 (at that time, $25 per year) and because participation in the Reserve Officers' Training Corps (ROTC) was not compulsory.

During his college years, Ed was assisted financially by his brother, Jimmy, who had by then graduated from George Washington University with a master's degree in international law and had joined the U.S. State Department. Jimmy went on to a distinguished career in the U.S. diplo-

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[4] E. B. Lewis, Autobiographical Sketch. In *Genes, Development and Cancer: The Life and Work of Edward B. Lewis*, ed. H. D. Lipshitz (Boston: Kluwer Academic Publishers, 2004), 497–502.

[5] M. Haas and E. B. Lewis, Cover legend, *Cancer Research* 58.22 (15 November 1998).

matic corps, serving as special economic assistant to the ambassador in London (during World War II) and as economic counselor in Copenhagen (after the war). He served as a delegate to the Paris Peace Conference in 1946, as minister-counselor for economic affairs in Geneva, and as deputy director-general of the General Agreement on Tariffs and Trade (GATT), ending his career in Helsinki as deputy ambassador to Finland. Ed frequently talked about what an inspiration Jimmy was to him and how he envied Jimmy's ability to read rapidly and broadly. Ed himself was a slow reader—and writer—attributing his low scientific publication rate in part to these handicaps.

A characteristic shared by Ed and Jimmy Lewis—as well as by the author of this memoir—is short stature. In a brief after-dinner speech at a banquet in his honor, following the celebration of the publication of his collected papers, Ed couldn't resist mentioning

> a letter I received only a few years ago from a student asking what was the hardest thing I had to overcome in my 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, which probably seemed rather a flippant reply although I was serious. I was aware that short stature was an even greater problem for my brother, who had a long career in our foreign service and who was a few inches shorter than I. 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![6]

Jimmy and Ed Lewis also 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 prostate cancer at the age of eighty-six.

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. 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. He maintained close ties to the university throughout his life and was a generous donor to it; the university awarded him an honorary degree in 1993, the fifty-fourth anniversary of his graduation.

In 1939, Lewis began his graduate research at Caltech under Alfred H.

[6] At the Ritz-Carlton, Huntington Hotel, Pasadena, California, on 4 February 2004.

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. Significantly, Lewis invented a test for gene function known as the *cis-trans* test, which is still taught to undergraduate students in introductory biology courses. It formed the foundation for his later discovery of the rules by which the *bithorax* family of mutants controls 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 and was awarded an M.S. degree in meteorology in 1943. Subsequently he served at bases in Hawaii and then as a weather officer for the U.S. Tenth Army in Okinawa, a post he assumed shortly after D-Day in the spring of 1945. During this time he was stationed on a command ship in the harbor. He 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 on Okinawa. Ed spent many years trying to explain to me—unsuccessfully, I regret to report—why it always rains on the afternoon of the day following a major storm in Southern California, as well as why it rains more heavily in the foothills of the San Gabriel mountains—where our home was located—than down the hill at Caltech itself!

Ed's daily sleep-wake rhythm was unusual, more closely resembling a twelve-hour than a twenty-four-hour cycle. He attributed this in part to the rhythm he had been forced to follow as a weather officer during the war. For the decade—1986 to 1995—when my lab was located across the hall from his on the third floor of Caltech's Kerckhoff Memorial Laboratories, he would arrive early in the morning to begin work and would follow this with his flute practice, which would echo melodiously through the building. Promptly at eight 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. After lunch, more lab work and some paperwork (which he hated!), then 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. In earlier years, he might have napped again in his office before starting the next day's work; but, by the time we became close colleagues, Pam had battled an infection that had led to partial unilateral paralysis, so Ed usually returned home late at night to nap there before returning to the lab shortly after dawn.

In 1946 Ed was appointed an instructor in the biology division at

Caltech, having been recruited to that position in 1943 before leaving for military service, by the university president, Robert A. Millikan. He spent his entire independent career at Caltech, was appointed Thomas Hunt Morgan Professor of Biology in 1966, and attained emeritus status in 1988, though he remained active in research until his death. The trends in U.S. politics in the twenty-first century distressed Ed, who would half-seriously say that it was time to move to Canada. Although I, of course, extolled the virtues of Toronto, I knew that his ties to Caltech were so strong that he would never leave. And he didn't.

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 twenty-eight and maybe you will like him so much, you will fall in love and decide to stay there at Caltech."[7] A few months after meeting, Ed and Pam were married; they remained so until Ed's death more than fifty-seven years later. It was Pam who, working as a technician in the laboratory in 1947, discovered the *Polycomb* gene, which Ed 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 Ed's final, albeit unfinished, projects was to self-publish a book of her paintings. Ed and Pam had three sons: Hugh (a lawyer in Bellingham, Washington), Glenn (who died as a teenager in a mountaineering accident on Christmas Eve, 1965), and Keith (a molecular biologist, who lives near Berkeley, California).

Ed's approach to science was strongly influenced by the writings of the British philosopher Bertrand Russell, who emphasized that abstraction is important and 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; however, abstraction framed his science, which can best be understood in those terms. 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."[8]

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[7] Quoted in P. Berg and M. Singer, *George W. Beadle. An Uncommon Farmer: The Emergence of Genetics in the 20th Century* (Woodbury, N.Y.: Cold Spring Harbor Laboratory Press, 2003), 196.

[8] B. Russell, *The Scientific Outlook* (London: George Allen & Unwin, 1931), 87.

Genetics is an abstract discipline; therefore Ed was at home in genetics, and his first love was always genetics. Almost all of his papers on *Drosophila* present the data in terms of abstract models. Throughout his career he distrusted and avoided overarching theories, instead deriving genetic rules and abstract models directly from the data. It should be noted that Ed not only abstracted models, but always made them current, based on what was happening in other disciplines such as biochemistry and molecular biology.

It is very important when reading Ed Lewis's papers to distinguish between what he called "rules" and what he called "models." Each rule is a description of a particular genetic phenomenon that he had discovered. The models, in contrast, are his abstractions of those phenomena. What is striking—even fifty years after many of Lewis's rules were framed—is that there remains very little understanding of their underlying molecular basis.

Lewis's *Drosophila* research spanned almost seven decades, beginning in the mid-1930s. His laboratory notebooks, begun as a graduate student in 1939 and ending shortly before his death almost sixty-five years later, reveal that he carried out an average of a thousand genetic crosses a year throughout that period—a rate that is unlikely ever to be equaled.

Lewis'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 mutations 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 alleles *a* and *b* as [*a b*/+ +] where the pluses represent the wild-type alleles. The phenotype of these flies is then compared with that of offspring that carry the alleles in *trans* [*a* +/+ *b*], thus enabling one to ask whether the position of the 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.

Now, in practice, it can be very difficult to obtain the double-mutant in *cis* [*a b*] since this requires genetic recombination between closely linked alleles, and the recombination frequency is proportional to the distance between them. Furthermore, when Lewis 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. 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 B. Bridges had hypothesized might represent tandemly duplicated genes that are in the process of evolving to perform new functions—Lewis was led to propose that the separable "pseudoalleles" might indeed represent tandemly-duplicated genes that are related both in structure and in function.

Working almost alone, over a thirty-year period from the mid-1940s to the mid-1970s, Lewis 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* homeotic gene complex or BX-C, for short) 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. This they accomplish by transforming the identity of one body segment into another: so-called "homeotic" transformations.

Already by 1951, Lewis had postulated that the *bithorax* family mutants control the development of particular body segments and that the second thoracic segment is in some sense the developmental "ground state." The function of the *bithorax* genes is, thus, to convert segments from this ground state to more posterior segmental identity (i.e., from second thoracic to third thoracic as well as abdominal identity). Abrogation of the function of the genes in the *bithorax* complex leads to homeotic transformation of, for example, the third thoracic segment into the second thoracic segment, thus creating the second pair of wings.

By the late 1950s, Lewis's focus had shifted from genes, their function and evolution, to how they control development, which he thought should be amenable to the same kind of mechanistic genetic analysis that had been used for biosynthetic pathways in bacteria and their viruses. While the series of rules that Lewis was to discover, rules about how genes control development, could in no way have been derived from the results of those earlier studies on biosynthetic pathways, he was correct in principle. Indeed, it was the genetic approach pioneered by Lewis that, when combined with the molecular methods pioneered by others, led to the deep insights that we now have into the mechanisms by which animals develop.

During the 1960s, Ed Lewis also identified genes—most notably *Polycomb*, the first allele of which Pam had discovered in 1947—that act as "regulators of the regulators," switching 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 by *bithorax* complex genes through his analyses of genetically chimeric ("mosaic") flies. Using these mosaics he was able to ask whether the *bithorax* complex genes confer the fate of cells autonomously or whether the genes encode diffusible substances, which would be expected to function cell non-autonomously. Strikingly, the genes behaved completely cell autonomously in the epidermis, 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, Lewis 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."[9] 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 (see below).

Lewis's most famous paper appeared in 1978[10] following a more than ten-year publication drought. Because Lewis summarizes thirty years of research in about six pages and presents almost all of his data in terms of an abstract model, the paper 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 Lewis's analysis of homeotic phenotypes in embryos rather than adults. These analyses proved that the *bithorax* complex genes function throughout development to establish segmental cell fates. Furthermore, they set the stage for ready acceptance by the *Drosophila* community of the large-scale genetic screens for embryonic pattern mutants that were begun in 1978 by Christiane Nüsslein-Volhard and Eric Wieschaus, who shared the 1995 Nobel Prize with Lewis.

To a geneticist, the most remarkable part of the 1978 paper is

[9] E. B. Lewis, Genetic control and regulation of developmental pathways. In *The Role of Chromosomes in Development*, ed. M. Locke (New York: Academic Press, 1964), 231–52.

[10] E. B. Lewis, A gene complex controlling segmentation in *Drosophila*. *Nature* 27 (1978): 565–70.

Lewis's invention of what can be called "add-back genetics."[11] Standard genetics involves mutating or deleting genetic functions and inferring the wild-type role of genes from their mutant phenotypes, a strategy that Lewis had applied very successfully to the *bithorax* complex since the inception of his analyses. In contrast, add-back genetics began by deleting the entire *bithorax* complex and then adding back, bit by bit, wild-type pieces of the complex. In this way, Lewis 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, which turn on progressively one at a time from more anterior (fewer genes "on") towards more posterior (more genes "on") segments. Thus 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.

In the early- to mid-1970s, David S. Hogness and his colleagues at Stanford University invented recombinant DNA methods for the analysis of whole genomes. In 1978, Hogness and his postdoctoral fellows, Welcome Bender and Pierre Spierer, initiated a collaboration with Lewis 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.[12] This was followed in the mid-1980s by the unexpected discovery by Matthew P. Scott and his colleagues in the U.S. and Walter Gehring's laboratory in Switzerland 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.

The molecular analyses revealed that Lewis, 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, along the body axis as Lewis had postulated. But he was wrong in concluding that there are twelve genes in the *bithorax* complex; there are

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[11] H. D. Lipshitz, ed., *Genes, Development and Cancer: The Life and Work of Edward B. Lewis* (Boston: Kluwer Academic Publishers, 2004), 165–66.

[12] W. Bender, M. Akam, F. Karch, P. A. Beachy, M. Peifer, P. Spierer, E. B. Lewis, and D. S. Hogness, Molecular genetics of the bithorax complex in *Drosophila melanogaster*, *Science* 221 (1983): 23–29.

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. Also, it turned out that the identity of each segment is not a simple additive effect of activating more of the genes (three genes could not additively regulate the identity of that many segments). 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 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 as in the fly. Furthermore, Lewis's "colinearity" rule—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. Thus, a primordial gene complex must have predated the divergence of the ancestors of flies and mammals more than five hundred million years ago. It was this extension and generalization of four decades of Lewis'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." David Hogness summarized it as "one of the best awards that the Nobel committee has made."[13] In typically modest fashion, Ed Lewis's 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."[14]

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, but Lewis got to keep the fax machine. The celebratory dinner at Caltech in honor of Lewis's award was, for him, more an opportunity to play his flute in a chamber music recital, than to bask in the glow of laudatory speeches. Subsequently, he did attend more public relations functions for Caltech than he had in the past; but this was driven by his dedication to—and love of—that institution rather than by the limelight, to which he never was attracted. He used his prize money to establish a trust with Caltech that would go towards undergraduate scholarships when he died, saying that "Caltech has

[13] Quoted in the *Los Angeles Times*, 10 October 1995, A18.
[14] Ibid.

provided the kind of excellent environment that has allowed me to carry out the research that has led to the award of the Prize. . . . In these days of high tuition costs, scholarships are needed more and more." Undoubtedly, he had in mind the struggle that he and Jimmy had gone through to attend college during the Depression.

More than anything else, however, Ed derived pleasure from returning to his beloved flies, through which he conducted his daily dialogue with the laws of nature. His greatest challenge was not just to make a four-winged *Drosophila*, but to make one 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, then, the challenge was to mutate the genes correctly for both the muscles and the wings in order to accomplish his goal. While he never succeeded, for Ed even more than for most scientists it was the journey rather than the destination that was most fascinating.

Ed's journey returned, in the mid-1980s, to gene evolution, but now using the newly invented molecular tools and, still later, the completed sequence of the 120 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's work on the somatic effects of ionizing radiation, which began 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. 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., 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." In a landmark study published in the journal *Science* in 1957,[15] Lewis 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 year; low but certainly not negligible. Lewis's analyses also led him to the very important—but at the time highly controversial—conclusion that the threshold hypothesis was not supported.

[15] E. B. Lewis, Leukemia and ionizing radiation, *Science* 125 (1957): 965–72.

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 two thousand rad would be needed to induce cancer and that only bone cancer would occur. This error arose because 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. Lewis pointed this out in the 1957 paper, where he calculated that there would be a 5 to 10 percent 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" (MPC) recommended by the National Commission on Radiation Protection.

Shortly after publication of his 1957 paper, Lewis 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 Lewis's data. The most detailed critique came from Alan W. Kimball, a statistician at the Oak Ridge National Laboratory, who challenged Lewis's methods of data analysis. Sewall Wright and James F. Crow, both distinguished geneticists, engaged in an active dialogue with Kimball. The former explained that "Lewis' tests are correct"[16] and the latter pointed out that several of Kimball's theoretical criticisms were "irrelevant"[17] for the type of analysis that Lewis had conducted.

History is on Lewis's side: research over the nearly fifty years since he published his landmark study has supported and confirmed his original conclusions. Current estimates by the National Research Council on the Biological Effects of Ionizing Radiation (BEIR) range from 1.0 to 3.4 cases per million persons per rad (or rem) per year,[18] close to Lewis's original estimate of 1.0 to 2.0 such cases.

Following publication of the *Science* paper, Lewis was called to testify before a U.S. Congressional Joint Committee on Atomic Energy in June 1957. Subsequently he served on the National Advisory Committee on Radiation of the U.S. Public Health Service as well as on committees of the National Academy of Science concerned with estimating risks of ionizing radiation.

Over the two decades that followed publication of the *Science* paper, Lewis returned repeatedly to questions related to the somatic effects of

[16] Quoted in Lipshitz (2004), ibid., 399.

[17] Quoted in J. F. Crow and W. Bender, Edward B. Lewis, 1918–2004, *Genetics* 168 (2004): 1773–83 (p. 1779).

[18] *BEIR V* (Washington, D.C.: National Academy of Sciences, 1990).

low doses of ionizing radiation.[19] 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.[20] Lewis's prediction was highlighted tragically after the meltdown of the Chernobyl nuclear reactor in 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.

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 emphasized that he saw himself 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.

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

Ed Lewis exhibited a rare combination of intellectual rigor 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 Thomas Hunt Morgan and his co-workers starting in 1910.

Perhaps one final story captures Ed Lewis 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* entitled "Science student accused of cruelty to fruit flies."[21] The newspaper article reported that a high school sophomore, Ari Hoffman, had won

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[19] For detailed discussion see Lipshitz (2004), ibid., 389–404; J. Caron, Biologists and "the bomb," *Engineering & Science* 67 (2004): 17–27.

[20] E. B. Lewis, Thyroid radiation doses from fallout, *Proc. Natl. Acad. Sci. USA* 45 (1959): 894–97.

[21] *San Francisco Examiner*, 20 March 1997.

the Marin County science fair but had subsequently been disqualified because thirty-five of the two hundred 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—and fruit flies certainly are animals! 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 young 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 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 cheque "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. . . . if you and your family [are in Los Angeles] and have time we would be pleased to have you visit the lab here." Within days Ari had written back arranging to visit and telling Ed that "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."[22]

Ed will not be remembered only as a great scientist and a fine human being. His friends and colleagues will remember him for his love of life and all things living. He had boundless energy: when not pushing flies he was playing the flute, jogging or swimming, attending opera performances in Los Angeles, San Diego, or San Francisco, playing chamber music, constructing Halloween costumes based on paintings by his favorite artist, René Magritte, jogging on the beach in La Jolla, or scouring its tide-pools for interesting denizens. Unlike all other Caltech faculty, he didn't really have an office; his was a mixture of office, lab, music room, and marine aquarium—always cluttered, always fascinating. Diagrams of his models of "transvection" dating from the 1950s would be propped in the corner; microscope slides with his latest polytene chromosome squashes would be scattered near the microscope;

[22] I am grateful to Ari Hoffman for permission to quote from his letter to Ed. Ari graduated from Stanford with a degree in biological sciences and commenced studies towards an M.D. degree at UCSF in the fall of 2005.

giant sheets of paper bearing the complete DNA sequence of the *bithorax* complex, with different parts shaded in different colors, would be taped to the blackboard that spanned one wall. In one marine aquarium, a pair of clownfish would hover near a sea anemone, excavating the gravel in preparation for consummation of their relationship; in another, each chamber of a multi-chambered box contained a piece of polychaete worm that he had brought back from La Jolla, had cut up, and was in the process of regenerating. At home, a glass tank in the pantry would contain his and Pam's latest batch of baby desert tortoises. Adjacent would be a tank festooned with Pam's annual crop of baby praying mantids; one of his numerous awards—selected because it was weighty enough—would be used to hold the lid on the tank. A tank in the corner of the living room would contain a giant plecostomus or several colorful koi. Even as his illness weakened him, he would proudly escort visitors around his backyard, pointing out his latest crop of ripening tomatoes and the various trees that were coming into fruit.

Ed Lewis was a consummate scientist: always curious, never satiated with knowledge. He is sorely missed as a role model, colleague, and friend to several generations of geneticists worldwide.

Elected 1990

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