Edward B. Lewis, 1918–2004

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A BRIEF BIOGRAPHY (J. F. Crow)

EDWARD B. Lewis (Figure 1) started experimenting with Drosophila as a high school student and never stopped. His enthusiasm never waned. Except for 4 years as a meteorologist during World War II, he continued to work with Drosophila until a very short time before his death.

Early life: Ed was born in Wilkes-Barre, Pennsylvania, on May 20, 1918. His father was a jeweler and watchmaker, who learned the trade, but never finished high school. The jewelry store in which he worked was forced to close during the depression of the 1930s and the family had a hard struggle to make ends meet. Nevertheless, the parents never wavered in supporting their two sons. Ed’s brother was 5 years older and was in college when times were the worst. Yet, he managed to get a masters degree in international law and went on to a distinguished career in the foreign service. By the time Ed was in college, his brother was able to provide some financial help, which, along with a job supported by the National Youth Administration, enabled Ed to stay in school.

Ed’s great uncle gave him a flute when he was 10 years old. It was wooden, but his father replaced it with a silver one a few years later. This must surely have represented a considerable sacrifice for the family in those bleak depression years. Ed loved the flute and continued to play at a near-professional level throughout his life. While still in high school, he was a member of the Wilkes-Barre Symphony. He started college at Bucknell on a music scholarship and later played in the University of Minnesota Orchestra. In later years, he found it amusing, and perhaps slightly embarrassing, that A. H. Sturtevant confused the university orchestra with the great Minneapolis Symphony. At Caltech he frequently arranged for lessons with professionals and was an avid performer of chamber music. Along the way he developed a passion for opera and in later life rarely missed a chance to attend a performance. A second interest that started in childhood was animals, especially toads and snakes, which he kept in homemade terraria. This interest also continued throughout his life. Visitors to his home always saw an aquarium, usually with an octopus and several exotic fish and often a terrarium.

Remarkably, two distinguished Drosophila geneticists, Edward B. Lewis and Edward Novitski, attended the same high school in Wilkes-Barre at the same time. Their start with Drosophila began when Lewis noticed an advertisement in the journal Science for Drosophila cultures at one dollar each. He and his friend Novitski used their Biology Club’s meager treasury to order cultures. When the flies came, the two budding scientists immediately began experiments in the high school biology laboratory, thanks to an interested and indulgent biology teacher. After high school Novitski went to Purdue to study with the man who had supplied the original Drosophila cultures, S. A. Rifenburgh. Aided by his music scholarship, Ed Lewis stayed at Bucknell for a year and then moved to the University of Minnesota, chosen because of low out-of-state tuition and no compulsory ROTC. Both Eds were skilled in the art of shortening their college years by passing exams in lieu of courses. Taking advantage of this, Lewis finished at Minnesota in considerably less than the regulation time and Novitski did likewise. Both ended up as fellow graduate students at the California Institute of Technology.

Caltech: Ed Lewis arrived at Caltech in the fall of 1939 and began study with Sturtevant. Ed was in Cold Spring Harbor in 1939 (Lewis 2004) and in 1941 attended the Symposium, learning salivary chromosome analysis from B. P. Kaufman. Continuing the hurry-up habit of his college years, he completed his Ph.D. work at Caltech in 3 years, graduating in 1942. By this time the United States was at war and Ed spent one more year at Caltech, learning meteorology and receiving a
master’s degree in this subject. He also had a brief excursion into oceanography. In 1943, as he left for military service, he was told by President R. A. Millikan that when the war was over he could return to Caltech as an instructor. He served 4 years as a captain in the U.S. Army Air Corps, most of the time as a weather forecaster in Hawaii and Okinawa. In 1946 he returned from overseas and took up the promised position as instructor at Caltech. His duties included assisting in the laboratory in the introductory genetics course. Later he took over the entire course. He rose rapidly through the ranks, becoming professor in 1956. In 1966 he became Thomas Hunt Morgan Professor of Biology, a position that he held until his retirement in 1988.

**Marriage and family life:** In 1946 Ed met Pamela Harrah. George Beadle had recently been brought to Caltech as chairman of the Biology Division and Pam came along as part of his group. She was an active, alert, intelligent, and charming young woman, who shared Ed’s interests in animal life, including arthropods; she wielded a mean insect net. She was also an accomplished artist and enjoyed doing personalized paintings for her friends. These artworks included various objects and symbols that characterized their subject and had a strong surrealist bent. As one of his last acts, Ed arranged for her pictures—many done for well-known geneticists—to be collected and published. Pam also wrote poetry and perceptive character sketches. She had studied genetics at Stanford and soon became a research assistant to Sturtevant and assisted with the Drosophila stocks, of which Ed was curator. Among other things, she discovered the mutant Polycomb, later to play an important role in understanding gene regulation.

In 1946 Pam and Ed were married. Phoebe Sturtevant, wife of A. H. Sturtevant, worked in the Drosophila room at Columbia University. She is said to have told Pam that the way to find a good husband is to work in a Drosophila lab. Pam and Ed were a devoted couple and remained so throughout their life together. They had three sons. One of them, Glenn, died in a mountain-climbing accident on Christmas Eve 1965. The other two, Hugh and Keith, have gone on to careers of their own. Hugh is a lawyer in Bellingham, Washington, and Keith is a molecular geneticist in Berkeley.

Pam and Ed became even closer after Pam contracted an infection that led to a partial unilateral paralysis, both physical and visual. This made it inconvenient for her to get around, but it did not deter her nor dampen her enthusiasm in the least. She still attended opera performances, went on trips, and frequently entertained students and other friends in their home. Visiting scientists were always welcome.

**Personal and scientific life:** Ed’s work schedule was unique. Exercise was an important part of his day and he remained physically fit until his bout with cancer. His movements were quick, mirroring his mind. In the morning was breakfast and exercise. Typically he had lunch at the Athenaeum, with its stimulating assemblage of faculty members from all departments. He then had a nap, returning to the lab in the evening and staying much of the night. There were variations in this pattern, but there was one constant: always he did his major work at night. He usually managed to squeeze in time for flute playing, frequently in his laboratory.

This schedule was sometimes interrupted, especially on weekends, with a trip, often to see an opera. Occasionally during the week he would find someone in the laboratory who was interested in a late night movie, so they would pick up Pam and all see it together. He also enjoyed a local tradition of costume parties. Several times his costumes were judged the most inventive.

Ed worked quietly in the lab and was never one to
attract attention. Drosophila research had its ups and downs; during the phage heyday, Ed received little attention. But he never veered from his path. Nevertheless, over the years, he began to attract attention as his pioneering work came to be appreciated. He was also dragged into a public controversy over the carcinogenic effects of low-level radiation. Yet his manner never changed, nor did his work habits. Even the Nobel Prize was taken in stride. He accepted it gladly, but he did not let it go to his head or change his living pattern.

**Honors:** Ed was a member of the National Academy of Sciences, American Philosophical Society, American Academy of Arts and Sciences, and the Royal Society of London. He was, successively, secretary, vice-president, and president of the Genetics Society of America. He received essentially all the honors that a geneticist can aspire to. These included the Morgan Medal of the Genetics Society of America, the Wolf Prize, the National Medal of Science, the Lasker Award, and finally in 1995 the Nobel Prize, which he shared with Christine Nüsslein-Volhard and Eric Wieschaus. Although his style was to work a problem thoroughly before publishing and to write sparingly, he nevertheless authored over 50 articles, all solid and several of them classics. Some of the most important are reprinted in Lipshitz (2004a).

**EARLY WORK WITH DROSOPHILA (J. F. Crow)**

**Minnesota:** At Minnesota Ed’s mentor was C. P. Oliver, who had been a student of H. J. Muller. Oliver had obtained what was at the time a very surprising result. Heterozygotes between two different **lozenge** (lz) eye alleles produced a few wild-type progeny and these were always accompanied by a crossover between flanking markers (Oliver 1940). This was one of the first instances in which a single gene appeared to have two components or to actually be two genes.

Several years earlier, Sturtevant (1925) had noted that heterozygotes for the eye mutant **Bar** sometimes gave rise to wild type or to extreme mutants, and these changes involved crossing over in the region. This was interpreted as unequal crossing over, or as was ultimately realized, equal crossing over following out-of-register synopsis. Curiously, it was Sewall Wright (1929) who first suggested that **Bar** might itself be a duplication, as it turned out to be. With Oliver’s work the stage was set and in the next decade several well-known genes were shown to be duplicates, even the classical multiple-allele series, **white** eye.

On June 17, 2004, just a month before his death on July 21, Ed submitted an item for Perspectives in Genetics. This was an article pointing out that Demerec, working with *Drosophila virilis*, had found as early as 1928 what is probably the first documented case of intragenic recombination. Ed’s article follows this article (Lewis 2004). It shows Ed’s concern for history as well as Demerec’s unselfish assistance to a young scientist.

At Minnesota, Ed studied a mutant sent to him by Novitski, **Star-recessive** (S). It behaved as an allele of the eye-mutant, **Star** (S), and was thought to be part of a multiple-allele series. Yet among 3235 progeny of an S/S heterozygous female was one wild type. Although this was promising, he was discouraged when 6059 progeny from subsequent experiments failed to deliver a recombinant (Lewis 1939). He continued to regard S and S’ as parts of a multiple-allelic series.

**Pseudoalleles:** Ed then moved to Caltech to work with Sturtevant, who in the Morgan tradition encouraged Ed to work on whatever he wanted to do. Despite the uncertainties and discouragement of the Star system—it must not have seemed very promising at the time—he persisted and it eventually paid off.

After a series of experiments, Ed concluded that **star-recessive** was really a second locus and renamed it **asteroid** (ast). At that time no one was thinking that recombination could occur within a gene, only between genes. Ed coined the expression “pseudoalleles” to describe the situation in which what was formerly thought to be a single gene was separable into parts by crossing over. In these experiments he was able to enhance the frequency of crossing over some fourfold by making the strains heterozygous for inversions on other chromosomes, the “Schultz-Steinberg” effect. The S and ast loci were very closely linked, the corrected distance between them (i.e., the expected value without added inversions) being estimated as 0.02 cM. There was a definite position effect, **trans**-heterozygotes being appreciably more abnormal than **cis**-heterozygotes. The **cis-trans** effect had been carried over from chemistry into genetics by Haldane (1941, p. 16). Lewis was the first to exploit the **cis-trans** position effect and to call it such. This new kind of position effect was soon found to be quite general as other loci were studied in various laboratories.

Ed was interested in another aspect of this pair of loci. Earlier, Bridges and Muller had each pointed out that duplications provide a way for a species to acquire new genes. After duplication, one of the pair can mutate to a new function while the other retains the old one. In this way a species can acquire a new function and increase the number of genes. It can have its cake and eat it. Thus complexity increases by duplicating and modifying existing genes rather than creating new ones. Bridges had pointed out that in salivary gland chromosomes there were frequent double bands, and he interpreted these “doublets” as possible duplications. Ed was pleased to note that the S and ast loci are included in Bridges’ 21E1-2 doublet. If the two genes are descended from one ancestral gene, they would be expected to have similar functions, and therefore interact, so the position effect seemed entirely reasonable (Lewis 1945).

**Proof of reciprocal exchange:** At this time, all of Ed’s studies and those of many other labs had the defect that two complementary crossover products could not be identified as coming from a single meiosis. Although
there was little doubt by this time that pseudoalleles were separable, there was a lingering possibility in Ed’s rigorous mind that the process might not be reciprocal, but that it might rather be some form of conversion. Ed cleverly solved this problem for X-linked loci by using attached-X chromosomes. He used this trick to prove that the apricot allele of white eye is a separate locus, which he designated apr, and that the separation process is standard, reciprocal crossing over. Starting with a pair of attached X’s that had apr on one X and w on the other, Ed was able to get attached X’s, which had apr w on one X and + + on the other. This happened in six cases, which showed unambiguously that the process was indeed reciprocal (Lewis 1952). I still remember my excitement, admiration, and pure pleasure on reading this article.

Actually doing the experiment was not as easy as it sounds. Getting the original attached-X chromosomes with apr on one chromosome and w on the other required using triploids, in which a crossover could occur between the free X and one of the attached-X’s. Getting such events and identifying them called for judiciously placed markers and some elaborate breeding experiments. The potential + + recombinants could be recognized by being wild type, but then how did he know that the other X carried the recessive alleles apr and w? Ed was able to show this by obtaining a crossover that homozygosed these alleles and in other cases by detaching the X’s. The whole experiment was a real tour de force! Ed later applied this same idea to the more difficult analysis of the bithorax system in chromosome 3 by using third chromosomes with right arms attached.

**Transvection:** Ed’s next discovery he called transvection (Lewis 1954b). He found this while observing two mutants, bx (bithorax) and Ubx (ultrabithorax) in a cis-trans test. As expected, the cis heterozygote, + / bx bithorax showed only the dominant effect of bithorax, enlarged halteres. The transheterozygote bx/+ bithorax showed a more extreme mutant phenotype. The surprise came when the two chromosomes were prevented from synapsing closely, because of a strategically located chromosome rearrangement. In this situation the mutant phenotype was even more extreme. Ed interpreted this as the result of gene products moving from one chromosome to another, which would be less effective when the pairing was inhibited.

Ed was able to use this phenomenon to provide a particularly efficient method for detecting chromosome rearrangements. Any chromosome break within ~500 salivary bands will interfere with pairing enough to show the characteristic transvection phenotype. This means that chromosome rearrangements can be detected in the immediate generation after the break occurs, a great saving of time compared to standard methods that require at least one more generation. Ed applied this to quantifying the effects of different kinds of ionizing radiation in producing chromosome breakage. In particular, neutrons were considerably more effective than X rays or gamma rays (Lewis 1954a).

Finally, Ed made several technical advances. One was a procedure for treating flies with EMS, a highly potent mutagen. The method soon became standard and was widely used. The second innovation was a machine for allowing large numbers of flies. The flies were suspended in a liquid and counted as they passed through a narrow tube. The equipment was bulky and crude by modern equipment standards, and it had only limited use. It did come in handy, however, in a few labs for mutation experiments that involved counting large numbers of flies.

**LATER DROSOPHILA WORK (W. Bender)**

**The bithorax complex:** In the late 1940s and early 1950s, Lewis focused increasingly on bx and a group of phenotypically similar mutations, including bithoraxoid (bxo) and Bithoraxlike (Bxl), later renamed Ultrabithorax (Ubx). This group of mutations was particularly attractive because it appeared to mark a large cluster of related genes, perhaps derived by tandem duplications, and because the distinctive phenotypes of each mutation facilitated the analysis of multiple mutant genotypes. He showed that these “pseudoalleles” mapped very close to each other (separations of 0.02 cM or less) and that they gave complicated and intriguing patterns of complementation (Lewis 1951). Ed eventually came to call the cluster of related functions the “bithorax complex” (BX-C). Over the next five decades, Ed’s studies revealed a remarkably ordered group of regulatory genes that fashion the body plan of the fly, segment by segment. His insights came to dominate the way biologists viewed gene regulation, development, and evolution. The progression of discoveries will not be reviewed here; two comprehensive and scholarly descriptions of those developments have recently appeared (Duncan and Montgomery 2002a, Lipshitz 2004), and Ed provided his own overview (“The bithorax complex: The First Fifty Years”) on the occasion of his Nobel prize (Lewis 1996). Here we will attempt to highlight recurring themes in Lewis’ approach and how they led to unique insights.

**Making mutants:** From the start, Ed began to induce new mutations. He typically used X rays, and he frequently recovered mutations associated with cytological rearrangements. (Ed was exceptionally skilled at the cytology of salivary polytene chromosomes, and he frequently mapped out rearrangements that included five or more breakpoints.) Ed had no aversion to alkylating agents—he wrote the protocol that virtually all Drosophila workers use for EMS mutagenesis (Lewis and Bacher 1968). However, EMS did not give the number or the variety of BX-C alleles that came with ionizing radiation. In retrospect, the BX-C has relatively little protein-coding sequence, and most single-base changes...
give no obvious phenotype. This was a lucky accident for the later molecular analysis, since rearrangement mutations were much easier than point mutations to locate on the DNA map.

Lewis’ search for new alleles was persistent and increasingly sophisticated. Of course, he looked for loss-of-function phenotypes in screens over deficiencies, and whenever dominant gain-of-function alleles were recovered, he did extensive screens for reversion of these phenotypes. Ed also invented a novel strategy to identify BX-C mutations without prior bias as to phenotype. He utilized his transsection effect to screen for rearrangements that disrupt pairing in the complex (Lewis 1986). Initially, these screens delivered breakpoints anywhere between the third chromosome centromere and the locus of the BX-C, in the middle of the right arm (~10% of the genome). These would then have to be screened by cytology to find the fraction that broke within the chromosome bands containing the BX-C. Later, Ed played the same game with a homozygous-viable inversion that placed the BX-C much closer to the centromere, making the screen much more efficient. In the past few years, Ed, together with Andrew Dowsett, constructed minichromosomes containing the BX-C and was using telomere loss to create terminal deficiencies impinging on the complex. These screens generated many stocks, and Ed also oversaw the national stock center for many years. The science would not have been possible without the unsung efforts of many associates who made the fly food and flipped the stocks.

The new alleles added to the list of distinctive functions in the BX-C; the rearrangements were essential for the definition of the “iab” domains that specified the development of the abdominal segments. Some mutant classes, like iab-4, produced normal-looking flies, although they had internal transformations; they would never have been recovered in more conventional screens. The rearrangements sometimes provided partial duplications or deficiencies in the region. These allowed Ed to construct two series of deletions, progressing inward from either end of the complex. The rearrangement breakpoints were mapped by complementation with the deficiencies, since they could not be mapped by recombination. More importantly, Ed used the deletion series to build up a functional map of the complex, adding successively larger segments of the complex to genotypes otherwise deficient for the entire region. This approach provided a compelling demonstration of the existence of functional units for each segment and for their striking arrangement along the chromosome in the order of the segments that they affected (Lewis 1978).

Tandem genes: Ed’s early studies of bithorax were colored by his expectation that the locus included tandem genes that interacted with each other at the level of the chromosome. As he discovered additional mutations with new segmental transformations, he postulated additional “genes,” each of which produced a distinctive “substance.” Eventually, he modeled the function of the complex with one gene and one substance per segment (Lewis 1978, 1981). (He recognized that there were two or more substances for some segments; the anterior portion of the third thoracic segment was transformed by the bithorax substance, and the posterior part by the postbithorax substance.) Mutations in most of these genes caused dramatic segmental transformations; some mutants were so transformed that they died as larvae (Ultrabithorax) or as embryos (iab-2 and iab-8). Ed did not dwell on the lethality distinction; he was more concerned with enumerating all the “genes” and confirming that their map order was colinear with the body plan.

In 1985, two groups published reports of screening for lethals of the BX-C region (Sánchez-Herrero et al. 1985; Tiong et al. 1985). They both reported only three lethal complementation groups in the complex, Ultrabithorax, abdominal-A (equivalent to Lewis’ iab-2), and Abdominal-B (equivalent to Lewis’ iab-8). Subsequently, one of the groups combined all three mutations on one chromosome and claimed that the triple mutant was phenotypically equivalent to a deletion for the entire complex (Casanova et al. 1987). This work was contemporaneous with the discovery of the three homeobox transcription factors in the BX-C (Regulski et al. 1985), and so the community quickly adopted the notion that were only three “genes” in the complex and that the additional functions mapped by Lewis must be regulatory. Even though his own complementation data largely fit with the three-gene model (Karch et al. 1985; Celniker et al. 1990), Ed was reluctant to embrace this revision. There was room to argue about the phenotypic analysis, especially of the triple mutant, but Ed also continued to believe that his nine functional units must have arisen by tandem duplication of an ancestral gene and that there ought to be remnants of the ancestor in each repeat.

The issue was revisited 10 years later, with the determination of the DNA sequence of the BX-C. The sequencing group at the Drosophila genome center, initially led by Mike Palazzolo, chose, out of admiration for Lewis and his work, the BX-C as the first large chromosome segment to be sequenced (Martin et al. 1995). Ed and his colleagues had the first crack at the sequence (Lewis et al. 1995), and they used sophisticated search algorithms to detect repeating units that might map to the genetically defined functions. Although recurring sequence motifs were discovered, none could be said to reveal an underlying repeat structure.

Still, the chromosomal order of Ed’s functional units is beyond challenge, and it is still difficult to imagine how they could have formed except by duplication. Recent research papers from Ed’s lab examine noncoding RNAs made throughout the BX-C, which might have independent functions (Bae et al. 2002; Drewell et al. 2002). Perhaps these gene products will reveal the traces of deep structure.
The four-winged fly made the point more dramatically than ever before or since. Ed worked hard to perfect that transformation, most notably by constructing a triple-mutant chromosome (anterobithorax, bithorax, postbithorax) that gave a more complete duplication of the anterior edge of the thorax. Even this transformation was not perfect; the duplicated thorax had only rudimentary flight muscles, and Ed investigated many genotypes to try to enhance the muscle transformation. It is not widely known that Ed put a comparable effort into making a 10-legged fly, although without success. (Any mutation that sufficiently transformed the second abdominal segment to the thoracic state died before making an adult.) Ed’s preoccupation with making perfectly transformed flies reflected perhaps an attempt to achieve mastery of the genetic system or an esthetic sense for perfection. It also revealed Ed’s appreciation of the power of an image. Before the description of the homeotic mutations, one might have imagined that the network of developmental decisions would be hopelessly complex, that no understanding would come before a complete description. Homeotic mutations made obvious that there is a decision tree and at least some logical generalizations to the program of animal development. This optimism motivated many other geneticists (including Christiane Nüsselein Volhard and Eric Wieschaus) to search for other master regulators, and it underlies the interpretation of the phenotypes they found.

Evolution: Lewis drew the connection between his mutant flies and the body plans of evolutionary ancestors, even in the early years when the mutant transformations were quite incomplete (Lewis 1955). The analogy became more credible when Ed was able to produce mutant flies with four wings (Lewis 1963), resembling a dragonfly. It was more obvious still when he showed that a deletion of the complex gave embryos with a succession of 10 thoracic-like segments (Lewis 1978), resembling a centipede. Ed saw the BX-C as central to arthropod development and enjoyed making cartoon movies of evolution, showing how the various BX-C functions refined the insect body plan. No one had the audacity to extrapolate the lesson to vertebrates; the discovery of the homeobox and the surprising conservation of HOX gene clusters in mammals suddenly elevated the relevance of Ed’s studies. The mammalian HOX genes were immediately seen to be arranged in a chromosomal order with their expression pattern along the body axis, obeying Lewis’ rule of colinearity. It was a foregone conclusion that the mammalian genes specified segment identities long before mouse knockouts proved the point (Wellik and Capecchi 2003). After the discovery of the HOX gene conservation, functional homologies were sought and found for many other Drosophila gene families, including those involved in specification of the eye, the heart, and the dorsal-ventral axis (Scott 1994; De Robertis and Sasai 1996). The current relevance of “model organisms” rests on these conservations; the homologies between the homeotic clusters in flies and humans are the archetype example.

Homeotic mutations: Lewis’s greatest impact on biology is embodied in his four-winged fly (Figure 2). It demonstrated that mutations can cause logically simple changes in the body plan. Although “homeotic” mutations were discovered before Ed’s birth (Lewis 1994), the four-winged fly made the point more dramatically than ever before or since. Ed worked hard to perfect that transformation, most notably by constructing a triple-mutant chromosome (anterobithorax, bithorax, postbithorax) that gave a more complete duplication of the anterior edge of the thorax. Even this transformation was not perfect; the duplicated thorax had only rudimentary flight muscles, and Ed investigated many genotypes to try to enhance the muscle transformation. It is not widely known that Ed put a comparable effort into making a 10-legged fly, although without success. (Any mutation that sufficiently transformed the second abdominal segment to the thoracic state died before making an adult.) Ed’s preoccupation with making perfectly transformed flies reflected perhaps an attempt to achieve mastery of the genetic system or an esthetic sense for perfection. It also revealed Ed’s appreciation of the power of an image. Before the description of the homeotic mutations, one might have imagined that the network of developmental decisions would be hopelessly complex, that no understanding would come before a complete description. Homeotic mutations made obvious that there is a decision tree and at least some logical generalizations to the program of animal development. This optimism motivated many other geneticists (including Christiane Nüsslein Volhard and Eric Wieschaus) to search for other master regulators, and it underlies the interpretation of the phenotypes they found.

Radiation and Cancer (J. F. Crow)

A lesser known facet of Ed’s life, at least among geneticists, was his influence on radiation carcinogenesis. More than any other person, he was responsible for a shift in public policy on radiation protection from exclusive consideration of genetic effects to greater emphasis on somatic effects, carcinogenesis in particular. It all started when Ed had his customary lunch with a faculty group. Included were physical scientists, who believed that there was a threshold for somatic radiation effects. Ed had been influenced by several statements of Muller arguing that cancer was, at least in part, due to somatic mutations (Muller 1927 and later). Then, Ed thought, it should have the same linear kinetics as germinal mutation.

Ed’s colleagues in the physical sciences were expressing the standard view of the time. The Committee on Biological Effects of Atomic Radiation assumed that there was no threshold for genetic effects, but that there was one for somatic effects, including carcinogenesis (National Academy of Sciences 1956; Crow 1995). Ed decided to look at the data. To him, they suggested linearity at low doses.

Ed was the first to publicly challenge the conventional wisdom. There was considerable interest in this question at Caltech at the time, especially by Beadle, who encour-
aged Lewis to look into the problem and helped him to obtain data from the Hiroshima and Nagasaki studies. In 1957 Ed published an article in Science in which he suggested, using data from a variety of sources including the Japanese studies, that the effect at low doses might well be linear with no threshold (Lewis 1957). He estimated the average risk for leukemia as 1.0–2.0/million persons/rad/year, a value that has stood up remarkably well. Ed was studiously conservative in not arguing for absence of a threshold, but simply pointing to the evidence.

He was invited to testify before the Joint Congressional Committee on Atomic Energy (JCAE 1957), which he did on June 3, 1957. Again he was cautious. In his words: “The point here, however, is that in the absence of any other information it seems to me—that my personal opinion—that the only prudent course is to assume that a straight-line relationship holds here as well as elsewhere in the higher dose region” (JCAE 1957, p. 959). The next day I testified before the same committee about genetic effects, backed up by a stellar team that included Sturtevant and Muller; both also spoke. Ed and I were invited back by the same committee 2 years later. He did not attend, but sent a statement.

For genetic effects, the linear, nonthreshold assumption aroused little controversy, partly because of the eminence of Sturtevant and Muller, although the estimated numbers were in considerable doubt. The reaction to somatic effects was quite different and Ed quickly found himself embroiled in controversy. His work was challenged by Neil Wald from the Atomic Bomb Casualty Commission in Japan, by Austin Brues of the Argonne Laboratories (Brues 1958), and by no less than Admiral Lewis L. Strauss, chairman of the Atomic Energy Commission (AEC; Lipshitz 2004a, p. 396). Ed’s critics also included Caltech faculty and administrators. The most detailed criticism came from A. W. Kimball, a statistician at the Oak Ridge Laboratory.

Kimball had recently done a statistical study of the Oak Ridge mega-mouse experiments (Kimball 1956). These involved mutations at seven loci, among which the individual rates were different. Kimball asked what the confidence limits would be if these seven loci were used as a basis for inferring the average rate for all loci. For this, he assumed that the underlying rates followed a gamma distribution and this led to confidence limits much larger than would be expected if they were distributed binomially. This analysis met with general approval and was regarded as a major improvement for drawing wider inferences from the data.

Kimball applied similar reasoning to Ed’s data. One minor criticism, which made no difference in the interpretation, was that Ed had stated a 95% confidence limit, which should have been 90%. (Ed had consulted a reference book that had it wrong.) Much more important was Ed’s statistical model. For example, he used a $\chi^2$ test to compare two groups of people with different average radiation exposures. Kimball argued that with variable exposure, variation in susceptibility, and other complications, there would be considerable nonbinomial variance, so the assumption underlying the $\chi^2$ test was inappropriate. He sent Ed a proposed letter to the journal Science, which Ed sent to me and to Sewall Wright, who had recently become my colleague in Wisconsin.

That summer, 1957, I was in Mishima, Japan, and wrote in longhand supporting Ed’s $\chi^2$ calculations: “I have read Kimball’s proposed letter. You are testing whether two samples, 10/23,060 and 26/156,400, can be regarded as drawn from the same population. Whether the individuals in the population have a constant probability of developing leukemia is, I believe, irrelevant.” My view was that we were concerned with the difference between these two populations, not with the larger universe with which Kimball was dealing. I thought we could rely on physical and biological insights to extend the results to other populations.

Sewall Wright supported Ed and me. A flurry of correspondence connecting Pasadena, California, Oak Ridge, Tennessee, Madison, Wisconsin, and Mishima, Japan followed. Although Kimball raised some important points, especially if one wants to generalize, I believed and still do that Ed’s calculations were appropriate for the problem at hand. Kimball’s letter to Science was eventually withdrawn and his critique was later published in the Journal of the National Cancer Institute (Kimball 1958). He and I continued to correspond about the most appropriate procedure, but as he said: “I think it is safe to say that we do not disagree about the exact meaning of the probabilities computed from the various tests of significance, but we do have differences of opinion as to how the results should be stated.” I would say “interpreted” rather than “stated.” Eventually the discussion died down as additional data came from other sources. Nevertheless, whether a threshold exists or not is still debated. The consensus, I think, is that the linear, nonthreshold hypothesis, if not correct, is at least a prudent assumption for setting radiation standards. And Ed is the one mainly responsible for this now-conventional view.

Ed wrote several subsequent papers and letters analyzing other sets of data. One of them (Lewis 1971) suggested that radiation was responsible for increases in leukemia following treatment for hyperthyroidism. This became increasingly important in later years as I-131 exposure to the thyroid was an important consequence of radioactive fallout from nuclear tests. Notably, in all his writings, Ed was not an opponent of the AEC position, but was eager for the truth. This is best illustrated by one of his last analyses. Tamplin and Cochran (1974) had argued that α-emitting particles from plutonium created a “hot-particle” problem. The idea was that a highly localized dose could produce a many times greater effect than if it were evenly distributed. Ed ana-
alyzed the data on lung cancers in a group of dogs exposed to plutonium inhalation and found that the rate was no different from what would be predicted from the total dosage if the particles were randomly distributed; there was no evidence for a hot particle effect (Lewis 1976).

For further reading on Ed’s work on radiation, there are three excellent sources: Lipshitz (2004a, pp. 389ff., 2004b) and Caron (2004). Furthermore, the Lipshitz book has a great deal of information about Ed’s life and work and includes reprints of several of his most important articles, including his Nobel Prize address.

REMEMBRANCES

I treasure my copy of Genes, Development and Cancer, with Howard’s autograph and a note:

For Ray and June, with thanks for our lifetime of friendship, Ed.

At the time it was written both Ed and I realized that Ed’s lifetime was nearing its end. And we did not share its beginning; he returned to the Caltech faculty in 1946, just as I joined on leave from Wisconsin. But within these limits ours was indeed a lifetime of friendship. I welcome this opportunity to add a brief note of remembrance, for all of his colleagues and friends over the years.

To begin, of course, were our common interests in Genetics. Even though Ed mainly studied Drosophila and I worked with warm blood, we were together over the decades when genetics made such remarkable advances. All of us, members of the biology faculty, were proud of our colleague’s accomplishments, admiring his research style and valuing his presence. We shared a devotion to biology in broad senses at a time when much was happening, a dedication to our teaching, our students, and the Institute. In the outside world, Ed and Pam and June and Ray enjoyed opera among many things, particularly the development of the Los Angeles Opera and attending and supporting opera in San Francisco and San Diego. Our families were close; we grieved with them on Glenn’s death, and they with us when our son Griff died.

Our common concern with national science policy and events at that level also brought us into frequent interaction, always agreeable. Over all the years our lives intertwined in many ways in “a lifetime of friendship.” Along with the other remembrances, therefore, I have chosen here to remember Ed Lewis as a never-to-be-forgotten friend, an admirable human being.

RAY OWEN

I remember visiting Ed Lewis’ office at night. Ed worked in a small space in the front of the room. He had a binocular microscope against the wall in front of him and a computer to his left. The rest of the office was filled with stacks of journals, optical equipment, and unidentifiable boxes. He had a marine aquarium stocked with exotic fish in the back. There was one chair reserved for visitors in the front, which Ed usually had to clear before it could be used. In the evening, if he wasn’t working at the microscope, he was practicing on his flute. He was an excellent flutist and could, I am sure, have become a professional if he had so desired. He worked late at night, and I often wondered what Pam thought of this arrangement.

This brief picture is the one that comes to me when someone asks me to recall Ed.

NORMAN HOROWITZ

Life fascinated Ed. And he was full of it. When not pushing flies (which he did at a rate of a thousand crosses a year for 65 years), he was playing the flute; jogging or swimming at the Caltech gym; attending opera performances in Los Angeles, San Diego or San Francisco; playing chamber music with friends; jogging on the beach in La Jolla, or scouring its tide pools for interesting denizens. Unlike all other Caltech faculty, Ed didn’t really have an office: in its place was a mixture of office, lab, music room, and marine aquarium—always cluttered, always fascinating. He worked there day and night, a tattered couch enabling him to nap at will. A chance visitor would see giant diagrams of his models of transvection dating from the 1950s propped in the corner; sheet music strewn on the couch or bulging out of a half-open file-cabinet drawer; a human skeleton color coded for HOX gene expression patterns dangling from the ceiling; glass slides with his latest polytene chromosome squashes scattered near the microscope; and giant sheets of computer print-out bearing the complete sequence of the bithorax complex—with different parts shaded in different colors—taped to one wall. In one marine aquarium, a pair of clown fish would hover near a sea anemone, excavating the gravel in preparation for consumption of their relationship; in another, each chamber of a multi-chambered box would contain a piece of the polychaete worm that Ed had brought back from La Jolla, cut up to observe its beginning; he returned to the Caltech faculty in 1946, its development; he answered “scientific curiosity,” in the persona of the dispassionate scientist. The accuracy of his analysis was his first commitment and this persona was effective. However, had curiosity alone been his driving force, he might have waited for the political attention to wane. Instead, in the winter and spring of 1957, Ed worked near-sleepless nights on top of his teaching and primary research duties
because he was concerned for the people being exposed to fallout.

As I struggled to understand his work and articulate it accurately, Ed was patient. Often I would e-mail him late at night and he would write back almost immediately. The more I interacted with him, the more I realized how deeply he understood people and cared about them, both as individuals and collectively.

Ed presented himself as a careful scientist wary of politics. Yet, in addition, he was an informed, concerned citizen. The day after I mentioned proposals for the resumption of underground testing, he forwarded me an e-mail analysis of the relevant Department of Energy budget from a watchdog group. Ed worried about the liberal use of dental X rays and mammograms. He feared that mammograms are recommended to women too early—before the possible benefit of early detection outweighs the risk of radiation-induced cancer from the exam.

When my thesis was done, Ed invited me to dinner. We met Pam, his wife, at their house. With admiration, he showed me her paintings. Then he introduced their baby tortoises, his whole face aglow.

Ed was remarkable not only for his mind, but also for his goodness. He was sustained, I believe, by his wholehearted engagement with the things he loved. I will remember him as the man who, without fail, expected or not, always invited me into his office and offered me a chair to sit and talk, often for hours at a time.

Jennifer Caron

I first met Ed in the early summer of 1978 when I interviewed for a postdoctoral position with him. I was intimidated by the thought of meeting him, as he was an icon in the Drosophila genetics field. Of course, it turned out that Ed was easygoing and very welcoming. What impressed me most was his great enthusiasm. On the way to the Athenaeum at Caltech for lunch, I remember him walking backward in front of me while he excitedly explained his results with Polycomb. At dinner I was introduced to Ed and Pam’s famous hospitality. I began working in Ed’s lab in December of 1978. I decided to look for genes that were functionally related to Polycomb and began screening for dominant enhancers of Polycomb. It seemed to me that the project was going quite well, and with the lab, we published eight papers together and made critical contributions to the field of Drosophila genetics.

I continued my interest in Ed’s work by following the first molecular mapping of the mutants in the Ultrabithorax region of the bithorax complex. I watched Welcome Bender race between the sub-basement of Alles, where he executed the molecular biology, to the third floor of Kerkhoff (Ed’s home for 65 years) where the genetics took place. Fascinated by the complicated gene regulation of the complex, I asked Ed if I could work as a postdoc in his lab. In the Morgan tradition, he said I could join the lab if I brought my own fellowship. So, in 1983, with a National Institutes of Health fellowship in hand and a proposal to generate dominant mutants in an Sab Mep homozygous fly, I began what was the start of a 13-year, life-altering journey with Ed, which included not only a scientific education, but also a personal one.

The same year that I began in the lab, Ed won the first of his many awards, the Thomas Hunt Morgan Medal of the Genetics Society of America. During my 13 years in the lab, we published eight papers together and made toasts to his numerous achievements. Our journey started with Transabdominal, a spectacular dominant mutant that presented the first case in which the sexual dimorphism of the fly was altered by an inversion that brought a cis-regulatory element from a known gene, stripe, in close proximity to the coding region of another, Abdominal-B; it was evolution in action. Ed allowed me the freedom to pursue the molecular biology of Abdominal-B despite his own predilection for classical genetics. He was a brilliant, nonlinear thinker, always making connections between seemingly disparate topics. He was intuitive, creative, inductive, and abstract. His mind was a stunning work of art.

When we weren’t discussing the complex, we discussed music, politics, fossils, and marine life, often during lunch, always as his guest. Ed presided over his own version of an Algonquin table at the Caltech Athenaeum, hosting scientists from far and wide, engaging in animated discussions and reflections on the revolutions transforming traditional biology and genetics. He was at the epicenter of the transformation, always the visionary pushing the envelope.
Ed and his wife Pam took me to my first opera—Andre Chenier—introduced me to James Galway at the Hollywood Bowl, and showed me where to find fossil sand dollars at Fort Funston. Ed and Pam loved to travel and went to at least one international meeting every year. With characteristic generosity, he never failed to return bearing gifts from Italy, Denmark, or Sweden.

Our last collaborative effort, published in 2003, centered on a sequence comparison of the region from Antp to Ubx in D. viridis, D. melanogaster, and Anopheles. This work brought together our shared interests in genetics, development, and evolution. Ed was a gentleman, a scholar, a musician, and a scientist—a true renaissance man, a latter-day Leonardo Da Vinci who enriched my life and all those around him.

I can’t remember when I first met Ed Lewis. It must have been at a Genetics Society meeting in the 1940s. But not long afterward we became the closest of friends. I spent three extended periods at Caltech and was there for several shorter visits. A high point of each visit was the inevitable chamber music session. This would include Ed on flute, my wife Ann on clarinet, me on viola, and assorted others that Ed had rounded up. Usually this was at his house, but sometimes we went to Sunday soirées at the home of Marguerite Vogt in La Jolla. The musicianship was not of Carnegie Hall quality but the enthusiasm was world class.

Ed and I never did a research problem together, but we often talked. This was no intense when he was working on his idea that there is no threshold for radiation-induced leukemogenesis. There were frequent discussions of statistical problems. We both made estimates of the consequences of a specified level of radiation, he for somatic and I for genetic. In each case Linus Pauling took our numbers and calculated the worldwide effects from radioactive fallout, present and future, making each of us a bit uncomfortable with the extrapolation.

Later we saw each other regularly as members of the National Advisory Committee on Radiation (Figure 3). The committee made one important and controversial recommendation, namely that regulation of radiation levels for the public should be in the hands of the Public Health Service rather than the Atomic Energy Commission. For me, and I think the others, it was a close call: AEC had the expertise, but it seemed poor public policy for the agency responsible for developing nuclear energy to be the one to police it.

LITERATURE CITED


