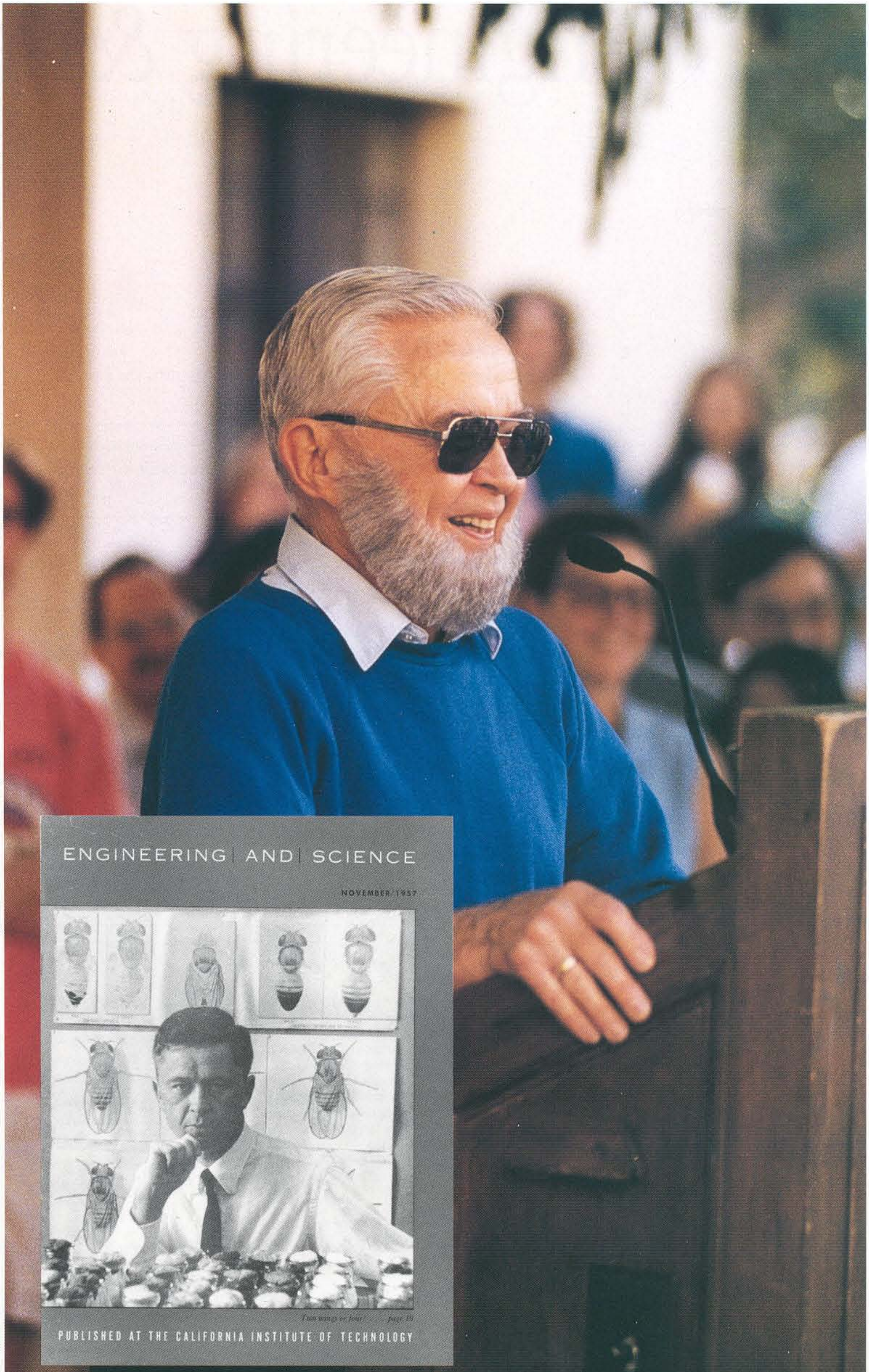
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Two wings or four?
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Edward B. Lewis
Nobel Laureate 1995

In a remarkably consistent career, Lewis has worked with Drosophila *for 60 years, continuing a tradition that had been brought to Caltech by Thomas Hunt Morgan.*

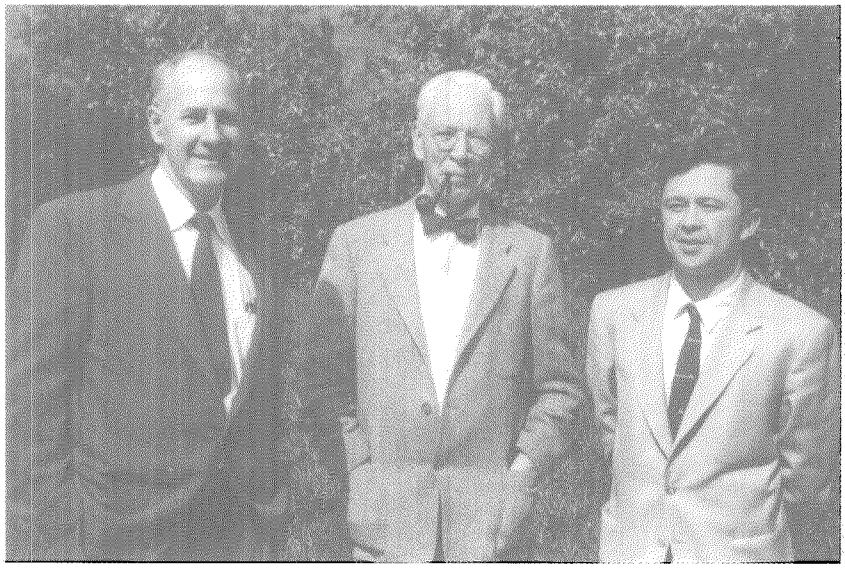
It's not Santa Claus, but Ed Lewis, just returned (incognito) from Switzerland where a happy Caltech crowd was waiting to help him celebrate his Nobel Prize. The inset shows Lewis on the cover of the November 1957 *E&S*.

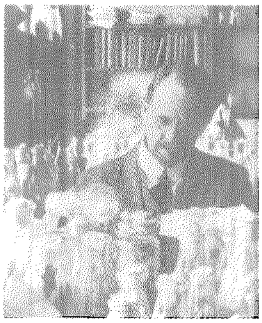
Edward B. Lewis appeared on the cover of *E&S* once before—in November 1957, looking much younger, of course, but still surrounded by the jars of the fruit flies known to biologists as *Drosophila melanogaster*. In the cover article, a mere three pages long, entitled "Two Wings or Four?", Lewis described the discovery of a group of *Drosophila* genes called the bithorax complex and the construction of a strain of mutant flies with four wings instead of the usual two. The 1957 article concluded: "We now have a working model for picturing the genetic control of development. Whether it is the correct model or not remains to be seen. In pursuing that model, however, we should make progress in our understanding of the living organism."

Lewis's model was indeed correct. And the progress he made over the next decades "in our understanding of the living organism" won him the 1995 Nobel Prize in physiology or medicine. Lewis shared the prize with Christiane Nüsslein-Volhard of the Max Planck Institute in Tübingen and Eric Wieschaus of Princeton University who, according to the official release from the Nobel Committee, "were able to identify and classify a small number of genes that are of key importance in determining the body plan and the formation of body segments." Lewis was cited, in part, for discovering "how genes were arranged in the same order on the chromosomes as the body segments they controlled." "Together," said the committee, "these three scientists have achieved a breakthrough that will help explain congenital malformations in man."

Although other discoveries in the past dozen years have shown the relevance of Lewis's research to medicine, he has worked only with flies. In a remarkably consistent career, Lewis has worked with *Drosophila* for 60 years, continuing a tradition that had been brought to Caltech by Thomas Hunt Morgan. Morgan was the first to use *Drosophila* for genetic studies; he began working with this organism at Columbia University in 1908. Soon this tiny fly, with its 10-day life cycle, became the most famous experimental animal in the world, and by breeding generation after generation of flies, Morgan and his students established that genes, located on the chromosomes, are the units of heredity. In 1928, at the persuasive invitation of Caltech's Robert Millikan, Morgan moved to Pasadena with his stocks of flies and his whole research group—a group that included Calvin Bridges and Alfred Sturtevant, who in 1911 had made the discovery that genes are arranged on a chromosome in linear order like beads on a string. Morgan, who won the Nobel Prize in 1933, recognized the contributions of Bridges and Sturtevant by generously dividing the prize to support the education of their children.

Lewis remembers Morgan from the early forties as someone by then no longer very active in the laboratory, but whose legacy had already imprinted itself on Caltech's biology division. "Morgan didn't like any speculation that smacked of mysticism," Lewis remembers. "Instead, he and his students carried out simple, clean experiments designed to test specific hypotheses." Lewis has clearly followed in the same "reductionist" tradition.





Thomas Hunt Morgan (below) founded *Drosophila* research, as well as Caltech's biology division, of which he was its chairman until 1946. (Fruit-fly bottles looked pretty much the same 80 years ago.) Right: George Beadle, (on the left) who succeeded Morgan as chairman, with Alfred Sturtevant, and Ed Lewis circa 1960.

The laws of genetics had never depended upon knowing what the genes were chemically and would hold true even if they were made of green cheese.

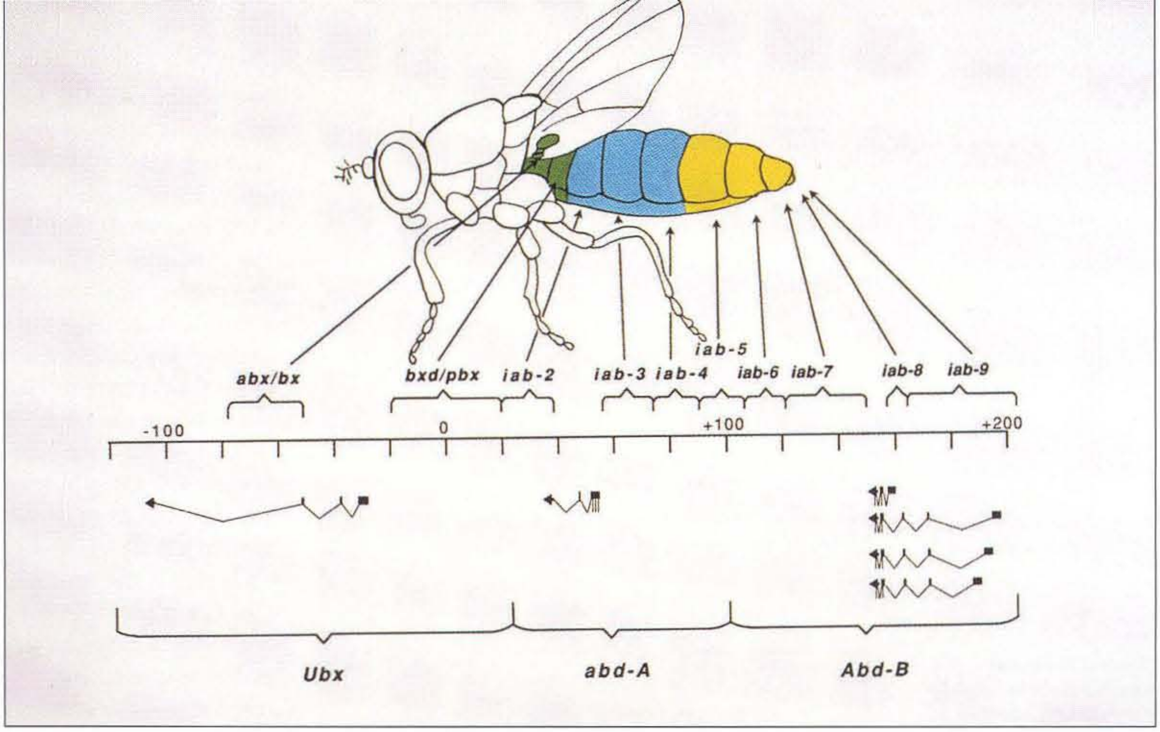
When Morgan was collecting *his* Nobel Prize, Lewis, the son of a watchmaker in Wilkes-Barre, Pennsylvania, was a freshman in high school. There happened to be a good public library in Wilkes-Barre, where Lewis discovered in its one scientific journal, *Science*, an ad offering stocks of *Drosophila* from Purdue University. In 1934 Lewis and his friend Edward Novitski (now professor of genetics, emeritus, at the University of Oregon), ordered some and cultured them in their high-school biology laboratory. Novitski carried on a correspondence with Professor Rifenberg at Purdue, where he eventually went to college, and also with Calvin Bridges at Caltech, who sent the young men free batches of flies.

After a year at Bucknell University on a music scholarship (he still plays the flute), Lewis transferred to the University of Minnesota, where he encountered Professor Clarence P. Oliver, who, in the Morgan tradition, "gave me a desk in his lab and complete freedom to carry out *Drosophila* work. I was working in the lab whenever I could, although it wasn't for course credit. You wouldn't expect this to happen at a big university, but it did." It was here that Lewis began work on a rough-eyed mutation, first called 'star-recessive,' but later renamed 'asteroid.' Novitski had found the mutation at Purdue and sent it to him. These mutations did not quite behave like a series of mutations of the same gene, as would be expected. Lewis graduated from Minnesota in two years (1939) with a degree in biostatistics (because zoology would have taken another year). Then he was awarded a teaching fellowship at Caltech. Lewis chose as his adviser Alfred Sturtevant, who, like Morgan, encouraged his students to go their own way. Lewis continued with his work on the rough-eyed flies: "It looked as though the gene might be either subdivisible, or, the way we really interpreted it, the gene was really a cluster of genes that acted like a single one."

After earning his PhD in 1942, Lewis studied meteorology at Caltech, as an Army Air Force cadet, and oceanography in a crash course at UCLA. After a stint of forecasting weather at Hickam Field on Oahu, he was assigned to the Tenth Army and shipped out to Okinawa in April of 1945, where he lived aboard one of the command ships that had the necessary weather data, "such as it was." In 1946 he returned to Caltech, where Millikan had promised him there would be a job waiting. Little had changed at Caltech. "It was much the same as when I was a graduate student," said Lewis, "because the same faculty members were still here. I came back as an instructor. There was always freedom to do research and a lot of interaction with faculty, not only in biology."

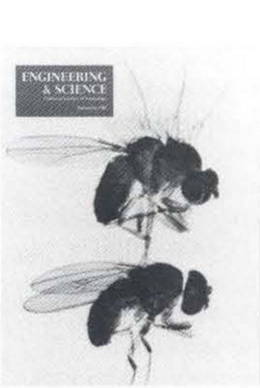
Lewis considered it a lucky time, a golden age. "I feel sorry in a way for young people who come in now. There's so much to learn and so much competition. The era of 'big science' was just getting off the ground then. Everything seemed exciting, all the problems. They also seemed beyond solution. That sounds contradictory—to be excited about something that's beyond solving. We didn't know what the genes were, so we tried to deduce how they worked from purely genetic experiments. Genetics is an

The genes of the bithorax complex regulate development of the fruit-fly's posterior half; these genes (*abx/bx* through *iab-9*) are lined up on the molecular map in the same order that they are turned on in the fly. They fall into three functional domains, color-coded here on the fly's body, each containing a highly conserved segment of DNA called a homeobox. They're named *Ubx* or *Ultrabithorax* (green); *abd-A* or *abdominal-A* (blue), and *Abd-B* or *Abdominal-B* (yellow).



abstract subject, which allows one to deduce many properties of the genes without any knowledge of what the genes are made of. Actually, the dogma of the time was that they were proteins, but this didn't help, and in fact was completely wrong."

Drosophila genetics had many advantages then, and now, according to Lewis. "There was an immense background of information available as well as hundreds of mutants. All of the obvious things had been done by then, so you could go into greater depth of analysis than you could in any other organism. You could begin to try to see how a gene is constructed, even though DNA hadn't yet been determined to be the hereditary material. The laws of genetics had never depended upon knowing what the genes were chemically and would hold true even if they were made of green cheese."



The four-winged fruit fly, born in the 1950s, made the *E&S* cover in 1981 and the Nobel Prize cake in 1995.

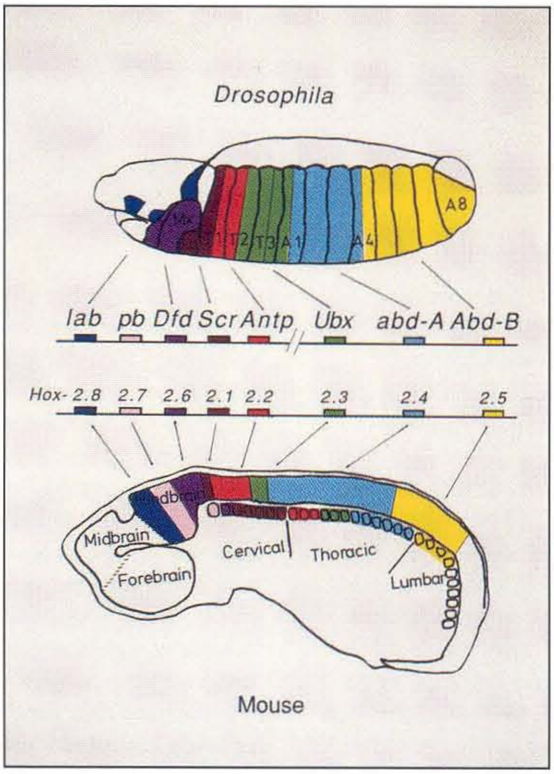
Returning to his original pre-war hypothesis for the origin of new genes, Lewis now found a gene cluster that at first appeared to be a single gene but turned out to be a group of very closely linked genes. These genes determined the development of the posterior half of the *Drosophila* fly—part of the thorax and the entire abdomen—and were indeed the very cluster he had been looking for. He named it the bithorax complex.

This is where the four-winged fly came in. Using x-rays to induce mutations in the bithorax complex, Lewis constructed a strain of fruit flies with four wings, the second set of which actually resulted from a duplication of the thoracic segment. Although the four-winged fly became the most visible symbol of the bithorax complex (it graced another *E&S* cover in 1981 and, created in frosting, the cake at Lewis's campus Nobel celebration), it was really just a "stunt," according to Lewis. "It wasn't connected to the theory," says Lewis. "It was just a byproduct of the theory that we were testing."

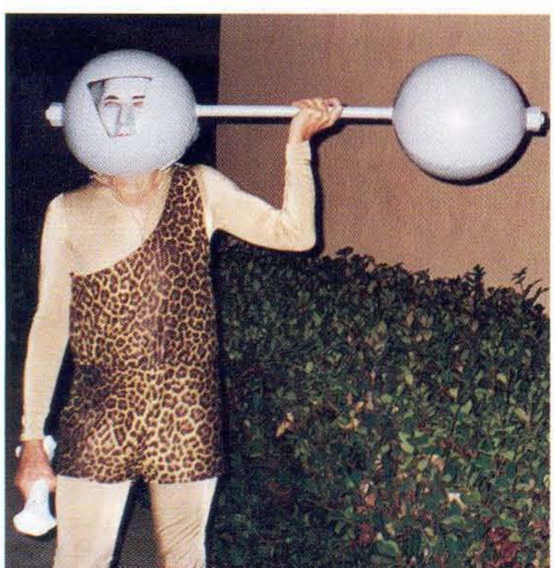
The genes of the bithorax complex are called homeotic genes, a word coined more than a hundred years ago to mean a type of variation in which "something has been changed into the likeness of something else." Calvin Bridges found the first homeotic gene in 1915, and hypothesized that gene duplications occur naturally and in tandem. Lewis carried the idea further to theorize that the original gene maintains its old function, while the copied gene takes on a new role. Lewis speculated that all these genes were descended from an ancient homeotic gene as the result of a series of duplications and diversifications by mutations. This theory provides an elegant and simple mechanism to explain how simple forms of life evolve into more complex ones. It also yielded a dividend: with the bithorax complex, Lewis had found a critical group of functionally related developmental genes—genes that control how an organism develops from egg to adult. He has stuck with this system ever since, trying to learn everything that these genes can reveal about this process.

Over the next few decades Lewis experimented on the bithorax complex, painstakingly knocking out genes with x-rays, cross-breeding mutated flies for hundreds upon hundreds of generations to discover which body parts were controlled by

Homeotic gene expression is highly correlated among species, as can be seen here in the fruit-fly embryo (top) and mouse embryo (bottom). The fly and mouse genes are arranged in clusters: the mouse has four, only one of which is shown, while two clusters control the development of the fly—the Antennapedia complex (red through purple) determines the fly's anterior end and the bithorax complex (green through yellow), the posterior end. The homeobox sequences of the two species are very similar.



Winning the Nobel Prize can't keep Lewis from the *really* important things, like the graduate students' Halloween party at Prufrock House. This is indeed Lewis in the leopard skin peering out of the barbell; he's dressed as a René Magritte painting called *Perpetual Motion.*



which genes. Lewis's exhaustive analysis of mutations in the bithorax complex spelled out how normal embryonic development can go awry. And he found some extraordinary things. "We discovered that during early development, the genes control how the body segments develop in a hierarchical manner. The closer a body segment is to the posterior of the organism, the more genes of the complex are turned on, always in an order that apparently coincides with the order of the genes in the chromosome. This law seems to hold as well for the homeotic complexes in vertebrates, including human beings." In *Drosophila*, the fact that more and more genes are turned on toward the fly's posterior end means that the abdomen is the most highly developed part of the fly. Lewis calls this the "abdomenization" of the organism, a phenomenon, he likes to tell in public lectures, that is probably familiar to older members of the audience. (Lewis, 77, stays trim with daily swims in the Caltech pool.)

In the 1980s other researchers isolated a similar cluster, which they named Antennapedia, that performs the same function for the anterior part of the fly. (Its name comes from a mutation that causes legs instead of antennae to sprout from the fly's head.) Together, these two gene complexes, which represent less than one percent of the fly's total complement of genes, play a regulatory role far out of proportion to their numbers. They are the architects of the body plan, which tell all the parts how and where to form. Then, Walter Gehring and his colleagues at the University of Basel (Switzerland) and Matt Scott and A. J. Weiner, while in Thom Kaufman's lab at Indiana University, independently isolated a short sequence of DNA—only 180 base pairs long—from both the bithorax and Antennapedia complexes. Named the homeobox by Gehring, this DNA fragment was used to identify similar complexes in other organisms, including human beings.

The ubiquitous homeobox is so highly conserved among so many animals, commencing with the most primitive worms, that it is now a powerful marker for tracing evolutionary lineages throughout the animal kingdom. Its discovery also substantiates the theory that the homeotic gene clusters arose by a process of tandem duplication, lending intriguing credence to Lewis's original theory that all the homeotic genes were descended from one ancient gene. Such an ancestral gene would have left its trace as a single conserved fragment of DNA—like the homeobox.

Although he never abandoned *Drosophila* during all the intervening decades, Lewis did

Sans beard, Lewis enjoys his homecoming party with colleagues (from left) Norman Horowitz and Herschel Mitchell, both emeritus professors of biology, and with Annamarie Mitchell. At far right, Lewis arrives at the festivities with his wife, Pamela.

make a deviation to put his knowledge to service in some of the controversial public health issues of the fifties. From using x-rays to create specific genetic mutations, it was only a small jump to the suggestion that x-rays could also cause mutations in body cells that could lead to cancer. This hypothesis had first been advanced in 1928, again using *Drosophila*, by H. J. Muller, another student of Morgan's. (He later won the Nobel Prize for demonstrating that x-rays can induce mutations.)

In 1957, in a paper in *Science*, Lewis showed that there is a linear relation between the amount of exposure to radiation and the incidence of human leukemia down to doses as low as 50 rads. He was called to testify before the Joint Congressional Committee on Atomic Energy to present his findings. Although the idea that cancer is caused by mutations is accepted now, it was very controversial at the time, says Lewis. Physicians weren't trained in genetics, and geneticists were reluctant to consider the effects of mutations on body cells. As a result of his landmark paper, he was appointed to the National Committee on Radiation, an advisory committee to the U.S. Public Health Service; later he served on committees of the National Academy of Sciences on biological effects of ionizing radiation, and on the National Council of Radiation Protection. In the late fifties Lewis also helped stop an experiment to inject radioactive tritiated water into the Los Angeles basin's groundwater to track its route.

Meanwhile, Lewis had been promoted to full professor in 1956. In 1966 he was named the Thomas Hunt Morgan Professor of Biology, when Sturtevant, who first held the chair, retired. "It had something to do with maintaining the *Drosophila* tradition," says Lewis, "and I was the only full-time faculty member doing *Drosophila*." In an article, "Remembering Sturtevant" published this month in *Genetics*, Lewis describes Sturtevant's fascination with pedigrees, perhaps not unusual for a geneticist, which had inspired Sturtevant to compile an intellectual pedigree of his own. "Sturtevant, of course, was a direct descendant of T. H. Morgan and of E. B. Wilson, another eminent biologist who was a contemporary and friend of Morgan's at Columbia. Morgan and Wilson were, in turn, direct descendants of Martin and Brooks, two men who were at Johns Hopkins University where Morgan had obtained his doctorate; Martin was descended from T. H. Huxley and Brooks from Louis Agassiz; and so it went."

Lewis himself is shown in these pedigrees as a direct descendant of Sturtevant and Muller. At Lewis's homecoming celebration (he was en route to a conference on homeotic genes in Switzerland when the Nobel Prize was announced), almost every speaker evoked the continuing *Drosophila* tradition at Caltech and the contributions of Morgan, Bridges, and Sturtevant in founding modern genetics. Lewis himself paid tribute to their "enormous insight and intuition." But it was Lewis's own insight and intuition to which this Nobel Prize pays tribute, as well as to his single-minded and almost single-handed dedication to a line of basic research in classical genetics that continues to yield remarkable insights in an age of 'big science.' □ *—JD*