

Commentary

Edward B Lewis (1918–2004)

E B Lewis died of cancer at the age of 86 on July 21 2004. A Caltech faculty member since 1946, Lewis spent his life working on the genetics of the fruit fly. In 1995, he shared the Nobel Prize in Physiology or Medicine for his contributions to our understanding of the bithorax complex (BX-C), a cluster of genes that regulate the identity of body segments in the posterior half of the thorax and abdomen of *Drosophila melanogaster*.

Lewis graduated with a B.Sc. degree in Biostatistics from Minnesota University after having studied the rough-eye mutant *Star-recessive*, S' (thought to be allelic to *Star*, S) in *Drosophila*. He moved to Caltech in 1939 to continue with graduate-level research. He became a student of A H Sturtevant and carried on working on S and S' . To begin with he was influenced by two ideas: (i) that new genes originate by duplication and divergence of preexisting genes (based on Bridges's interpretation of duplicated bands on the salivary gland chromosomes); and (ii) that the function of a gene can be



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influenced by its environment in *cis* (from Sturtevant's work on the position effect in *Bar*). Lewis, a pioneer of genetic fine mapping, showed that a crossover can take place between *S* and *S'* (he renamed the latter as *asteroid*, *ast*) and coined the term "position pseudoalleles" to describe the *cis-trans* position effect of *S* and *ast*. He started to work on the bithorax region not to study development, but as a source of new pseudoallelic series. During his studies, Lewis discovered pairing-dependent complementation and coined the term "transvection". He took advantage of transvection to devise an assay for chromosome rearrangements – which affect pairing –, and made use of the assay to measure the dose of fast neutrons – which cause rearrangements – at different distances from nuclear explosion sites. He continued to be active in the area of radiation hazards to human beings and contributed to the debate that led to the ban of atmospheric nuclear weapons testing.

While studying the BX-C over several years, Lewis's focus shifted from gene evolution to development. From his early work on the BX-C, Lewis suggested a model in which each of the pseudoalleles of this locus represents a gene, with the genes participating in sequential ligand-receptor binding reactions along the chromosome. Binding was postulated to occur between the repressor (supposed to be present in an anterior-posterior gradient within the organism) and *cis*-regulatory elements (whose affinities for the repressor were supposed to be in a proximal-distal gradient along the chromosome). Because of the unusual nature of his model, Lewis faced much opposition. Alternative explanations were offered by others, for example, that he was looking at mutations within a single protein coding unit. He resisted and successfully ruled out such suggestions. Lewis's work led to what can be seen now as manifestations of the elaborate, long-range, *cis*-regulatory mechanisms controlling animal development. The important concept that emerged was that in the normal context, the BX-C genes, expressed in a localized manner under the control of *cis*-regulatory elements, are necessary and sufficient for specifying the corresponding body segments.

With no publications over long periods of time, he continued his work and made important advances which were known only to Drosophilists through seminars or annual reports. After ten years had gone by without a single paper on the BX-C, Lewis was approached by the editor of *Nature* and asked to put together his views on the subject. The result was a scientific epic, "A gene complex controlling segmentation in *Drosophila*" (Lewis 1978). The genes of the BX-C are arranged in the same order on the chromosome as the body segments they influence, a Lewis finding. The 'colinearity' of the order of homeotic genes in a gene complex and their function along the anterior-posterior body axis turns out to be conserved in all bilaterian animals. This observation leads to the hypothesis that morphological changes during evolution are not due to the appearance of new homeotic genes but due to changes in their regulation or in their target genes. Almost 99% of the BX-C is non-coding and is full of regulatory elements like enhancers or silencers or novel elements that function through higher order chromatin structure (boundary elements and *Polycomb* response or memory elements). Lewis mapped domains, that he initially thought were of conventional genes, of such *cis*-regulatory elements by making use of a large number of mutations and showed that these domains too followed the principle of colinearity.

In his famous publication Lewis suggested that an antero-posterior gradient in a repressor (conceivably the *Polycomb* gene product) along the embryo, together with a proximo-distal gradient in the affinities for the repressor of each gene's *cis*-regulatory element along the chromosome, determined the localized expression of the BX-C genes. It was the work of Christiane Nüsslein-Volhard and Eric Wieschaus, who shared the Nobel prize with Lewis, that showed that the initial pattern of the BX-C gene expression is set by the transient action of segmentation genes. The *Polycomb* group of genes, it turns out, help the cell remember and maintain these expression patterns later on. The mechanism of how this memory system works, or how boundaries confer functional autonomy to *cis*-regulatory domains, is currently under intense investigation. Small sequence motifs, spread over long distances in certain combination, may be involved. It was to elucidate this puzzle that Lewis, in the last decade of his life, became interested in the organization and sequence analysis of the BX-C (which is spread over 320 kb).

Lewis's work on the BX-C has been hailed as "the most illuminating genetic system yet discovered in complex organisms" (Duncan and Montgomery 2002a,b) and he will long be remembered for it. His contribution to the fly community in terms of tools and techniques was enormous. He produced most of the balancer chromosomes that were the key to the success of *Drosophila* as the system of

choice for genetic studies of development. It was Lewis too who was responsible for the protocol of feeding ethylmethanesulphate to flies for mutagenesis. The story of the BX-C that he began with classical genetics went through the period of molecular genetics and is now flourishing in the new postgenomic era. Many who work in these areas and had occasion to interact with him will cherish his intensity and involvement.

E B Lewis is survived by his wife Pamela (the discoverer of *Polycomb*) and two sons.

References

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