

The 1995 Nobel Prize in Physiology or Medicine

Flies Take Off at Last!

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The Nobel Prize in Biology (correctly stated, in Physiology or Medicine) for 1995 was awarded jointly to Edward B Lewis (77 years old) of the California Institute of Technology, Christiane Nüsslein-Volhard (52) of the Max Planck Institute for Developmental Biology in Tübingen and Eric Wieschaus (48) of Princeton University. Among other reasons given in the citation, the award was “.. for discovering how genes control the early structural development of the body”.

These three workers studied the genetic basis of development — meaning the set of processes that convert an egg to an adult — in the fruit fly *Drosophila melanogaster*. They asked, in what manner do genes contribute to the changes that take place as the fly's egg first becomes a larva and eventually an adult?

Specifically, are there genes that guide the anterior-to-posterior patterning of the fly's body into head, three distinct thoracic segments and eight abdominal segments? The answer is: yes, there are such genes, and an unexpectedly small number at that. Their existence, as well as the roles they play, can be inferred from what happens in mutant flies lacking one or the other of these genes.

To start with, let us recall that the fly is an insect. Also, it is a member of a larger group, the arthropods, that are characterised by a basic body plan that consists of paired repeated segments called metameres. Metameric design is obvious when we look at the larval worm-like stage of the fly, but close observation shows that it also exists in the adult. In other words larval segments resemble each other markedly, but the segments in the adult are very different from one another. In effect, the question asked by all three prize winners was, why are all segments not the same?

E B Lewis started his work in the 1940's with a mutant, known as *bithorax*, that had been



Figure 1 A typical four-winged fly generated when certain bithorax mutant alleles are brought together in heterozygous combinations (Reprinted from Current Science. 69:799. 1995)

1995 Nobel Laureates in "Biology"



Edward B Lewis

Christiane Nüsslein-Volhard
and Eric Wieschaus

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isolated earlier by the distinguished geneticist, C B Bridges. Bridges had found that flies with two copies of the mutant *bithorax* gene (*bx / bx*) tended to develop portions of an extra pair of wings. In normal flies the second segment of the thorax carries a pair of wings while the third thoracic segment has a pair of balancers, or halteres, attached to it. *Bithorax* flies have the normal pair of wings all right; but in addition, the front half of each haltere is replaced by a half-wing. The transformation stands out because halteres are tiny compared to wings and the juxtaposition of the mismatched halves presents a strange sight (Fig-

ure 1). Such a phenomenon, where a segment, or a portion of a segment, gets replaced by another segment, is known as homeosis.

Lewis identified a whole series of homeotic genes in what came to be known as the *Bithorax complex*. A number of important conclusions emerged from Lewis's study of homeotic mutants. Let us denote the segments of the body by the symbols *H* (for head), T_1, T_2, T_3 (for the three segments of the thorax) and A_1, A_2, \dots, A_8 (for the eight segments of the abdomen; see Figure 2). First of all, mutations in two genes, *bx* and *pbx*, cause a $T_3 \rightarrow T_2$ switch. Therefore, in the normal fly, the genes in question must be needed to make T_3 develop differently from T_2 . One says that the action of *bx* and *pbx* confers segmental identity to T_3 . The same thing can be said in different words: the wild-type gene breaks an underlying sym-

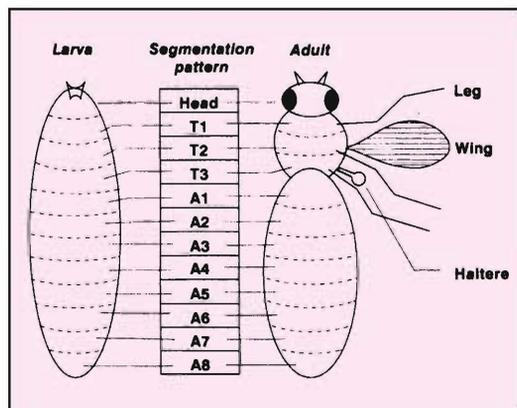


Figure 2 A diagrammatic representation of segmentation in *Drosophila*. The worm-like pattern seen in the larva is retained in the adult fly. T_1 - T_3 are thoracic segments, A_1 to A_8 are abdominal segments. Drawn using a computer (based on Gilbert 1988).

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metry between T_2 and T_3 . On the other hand, the double *bx pbx* mutant reveals the existence of the symmetry. Similarly, other genes of the *Bithorax complex* are responsible for breaking the symmetry between A_1 and T_3 , between A_2 and A_1 , and so on. The deepest symmetry of all is unveiled when the entire complex is deleted, because in that condition all segments posterior to T_2 look like T_2 . As Lewis pointed out, both single gene mutations and the deletion of the complex appeared to evoke traces of the fly's evolutionary ancestors, four-winged insects like dragonflies and worms. However, the mutants are not *true* throwbacks to an ancestral form; the four-winged fly cannot fly and the $H-T_1-T_2-T_2- \dots -T_2$ larva dies very early. This means that other genes must also have evolved in the course of the evolution from worms to flies. As you must have noticed, the *Bithorax complex* does not seem to be required in H , T_1 and T_2 . It turns out that these segments depend on the activity of another set of homeotic genes, also constituting a complex, known as *Antennapedia*. Genes such as those of the *Bithorax complex* have been called master genes or control genes for the specification of body pattern.

Nüsslein-Volhard and Wieschaus are responsible for identifying three families of other master genes which regulate body pattern well before the *Bithorax complex* becomes active.

(They do so soon after fertilization, and in some cases even before the embryo has become subdivided into cells.) The two of them treated fly embryos with a chemical mutagen and with the aid of standard but extremely tedious procedures, set about looking for as many genes as possible that could influence body patterning along the anterior-posterior axis. The results were astonishing in two respects. Firstly, the total number of candidate genes turned out to be unexpectedly small, just 15 in all. Today, 16 years later, the number still remains small. (It would not have been considered strange if hundreds of genes had participated in the major decision-making steps necessary for the specification of the body plan.) Secondly, the genes fell naturally into three families. Within each family, mutations had striking but distinct effects.

- The first class of genes were named *gap* genes. When mutated so that their function was lost, they gave rise to larvae with gaps of varying extent in the segmental pattern.
- Next were the *pair-rule* genes, and they caused the most surprise when people first heard about them. Mutations in these genes cause the elimination of portions of the body pattern in a periodic fashion. The strange thing was that the period did not correspond

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to the length of one segment, as might have been expected, but to that of *two* segments. By skipping alternate segments, the pair-rule genes point to an underlying periodicity in the body plan with two segments as the unit.

- Finally, there were the *segment polarity* genes. When mutated they led to the disappearance of a portion of each segment and its replacement by the remaining portion. However, the replacement has its polarity inverted, meaning that the duplicated portion is a mirror image replica of the undisturbed part.

This report of Nüsslein-Volhard and Wieschaus was so illuminating that it led to an explosive burst of activity on the part of researchers all over the world. Thanks to it we can today begin to build a model of how genes specify the body plan of *Drosophila*. The basic idea seems to be that there is a hierarchical order to genetic activity. Genes that are higher in the hierarchy specify gross features of the body plan and genes that are lower down in the hierarchy sharpen the specification further.

What I have described is the barest outline of what we know about how genes regulate the fly's body pattern. Even so, it is apparent that the picture we are beginning to glimpse is one of both order and complexity. Further research is going on in an attempt to decipher

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the details, especially the molecular details, of the working of these 'master' genes. The achievements of Lewis, Nüsslein-Volhard and Wieschaus constitute a striking vindication of the power of formal genetic analysis in the study of development. "Look for the genes behind the phenomenon" has turned out to be a successful philosophy. Their work needed very little by way of sophisticated equipment; perhaps a good dissecting microscope, but that is all. Why then did no one attempt it earlier?

Suggested Reading

- S F Gilbert. *Developmental Biology*. (Second Edition) Sinauer Associates Inc., Sunderland, Massachusetts. 1988.
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- P A Lawrence. *The Making of a Fly - The Genetics of Animal Design*. Blackwell Scientific Publications, Oxford. 1992.

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