

Genetic Control Of Embryonic Development ^[1]

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1995 Nobel Prize Medicine

Edward B. Lewis, Christiane Nüsslein-Volhard and Eric F. Wieschaus were named the 1995 Nobel Laureates in Physiology or Medicine for their discovery concerning the genetic control of embryonic development.

Lewis, Nüsslein-Volhard and Wieschaus were able to identify, localize and classify a small group of genes responsible for the control of early embryonic development of the fruit fly, *Drosophila melanogaster*. This small group of genes was shown to be responsible in determining the body plan and the formation of body segments in the embryonic fruit fly.

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The Winners

Edward B. Lewis was born on the 20th of May 1918 in Wilkes-Barre, Pennsylvania. He finished his early schooling in Meyers High School. He then received his B.A. degree in Biostatistics from the University of Minnesota in 1939 and his Ph.D. from the California Institute of Technology in 1942. He served the United States Army Air Force for three years as a meteorologist and oceanographer.

Lewis joined the Caltech faculty in 1946, appointed professor of Biology in 1956, and named Thomas Hunt Morgan professor of Biology in 1966. He received multiple awards including Gairdner Foundation International award in 1987, Wolf Foundation prize in medicine in 1989, Rosenstiel award in 1990, Albert Lasker Basic Medical Research Award in 1991, and Louisa Gross Horwitz prize in 1992. Most of his famous researches contributed a lot to the field of developmental genetics. He died on the 21st of July 2004.

Christiane Nüsslein-Volhard was born on the 20th of October 1942 in Magdeburg, Germany. She earned multiple degrees: biology, physics, and chemistry from Johann Wolfgang Goethe University in 1964. She then received her diploma in biochemistry from Eberhard Karls University in 1968.

In 1973 Nüsslein-Volhard earned her Ph.D. in biology and genetics from the University of Tübingen. She then received her first independent research position at the European Molecular Biology Laboratory in Heidelberg, Germany. She got acquainted with Eric F. Wieschaus who was also finishing his training. Because of their common interest in *Drosophila*, Nüsslein-Volhard and Wieschaus decided to work together to find out the mechanisms behind genetic control of embryonic development, such a challenging task for two newcomers in the field of developmental genetics. Eric F. Wieschaus was born on the 8th of June 1947 in South Bend, Indiana. He then enrolled at the University of Notre Dame for college. In his sophomore year at Notre Dame, he needed money and found a job preparing fly food in a *Drosophila* laboratory run by Professor Harvey Bender. In Bender's lab, he encountered his first fruit flies and learned basic genetics. He graduated magna cum laude with his bachelor's degree in biology from the University of Notre Dame in 1969 and his doctorate from Yale in 1974. His doctoral dissertation involved using genetic methods to label the progeny of single cells in fly embryos.

In 1978, Wieschaus moved to his first independent job at the European Molecular Biology Laboratory in Heidelberg. This gave him a chance to work with Christiane (Janni) Nüsslein-Volhard on the embryologic development of fruit flies. He then became an assistant professor of biology in Princeton University in 1981, associate professor of biology in 1983 and a professor in Princeton University in the year 1987.

The Discovery

Nüsslein-Volhard and Wieschaus started their research in the late 1970's. The pair wanted to find out how the newly fertilized *Drosophila* egg developed into a segmented embryo. They opted to use the fruit fly *Drosophila melanogaster* as their experimental system due to its extremely rapid embryologic development. The fruit fly only needs nine days to undergo complete development and they only have one set of genes that control development compared to the four sets that humans possess. Their main goal was to isolate specific genes that are responsible for the embryo's early development. Their first step was to damage the male flies' DNA. Then, they "knocked out" one gene from the fly and bred generations of fruit flies without this particular gene. By the use of this method, they were able to isolate particular genes and observe its effects on future mating. After which, these male flies mated with normal female flies which often produced dead and mutated fly embryos.

After testing approximately 20000 fly genes, they found 150 genes that were essential in the genetic control of embryonic development. Out of that 150, they found 15 genes that, if mutated, would cause defects in fruit fly segmentation. They even went further, classifying these genes into groups based on their effects on segmentation. First, gap genes control the body plan along the head-tail axis. Loss of gap gene results in a reduced number of body segments. Second, pair rule genes affect every second body segment. Loss of this gene known as "even-skipped" will result in an embryo consisting only of odd numbered segments. Lastly, segment polarity genes affect the head-to-tail polarity of individual segments.

On a completely separate laboratory, Lewis was conducting an independent research on the reasons behind the most common mutation in *Drosophila*, the development of an extra pair of wings instead of halteres, the fruit fly's organ of balance. By mutating fly embryos so that the flies developed extra pairs of wings, Lewis found that it was not only the wings that were

duplicated in the mutated flies, but the whole body segment that contained the wings.

Lewis found that the gene responsible for this development belong to a family of genes known as bithorax-complex that controls the segmentation of the fly along the longitudinal axis. He also found that the genes at the beginning of the gene complex controlled the development of an anterior body segment and the genes at the end of the gene complex controlled the development of a more posterior body part. This is the foundation of the colinearity principle. He also found that the body regions controlled by genes overlapped. This means that if a gene was knocked out, the genes that are proximal to it might take over its controlled region.

Clinical Correlations

The reason why this discovery had great impact in medicine was the fact that the genes discovered by Lewis, Nüsslein-Volhart and Wieschaus have their counterparts in higher organisms, especially in the genome of human. These counterpart genes in men performed similar functions during development. This discovery could help other scientists find genes that could explain birth defects in humans.

The applications of their research extend to in vitro fertilization, identifying congenital birth defects, and increased knowledge of substances that can endanger early stages of pregnancy. Because of our knowledge on the genetic control of embryonic development, we can also develop ways to treat patients with high risks of giving birth to babies with congenital defects.

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