The flies that brought Walter Gehring world fame were far from ordinary. Aside from the usual two compound eyes on their head, these fruit flies (Drosophila melanogaster) sported up to twelve additional eyes distributed on their wings, legs and antennae. The sensational creatures, unveiled by Walter Gehring and his team in the journal Science in 1995, astounded the scientific community – and struck fear into the hearts of the general public.

Walter Gehring designed the experiment to confirm a prediction he had made. He had postulated that a single genetic switch, a master control gene, is responsible for activating an entire cascade of genes that then work together to form a new organ. It turns out that this master control gene can trigger the formation of an eye in many different tissue types.

When it became clear that this master control gene, known as Pax6, is almost identical in a number of different animals – from worms and flies to mice and humans – the textbooks had to be rewritten. Until then, the accepted wisdom had been that eyes arose independently between 40 and 60 times in the course of evolution. In fact, Walter Gehring was guilty of perpetuating this error in his own textbook, he admitted at the time with a laugh.

Walter Gehring was originally from Zurich, where he graduated from high school before studying zoology at university. He had been fascinated by birds since his school years, but turned his attention to smaller winged creatures when he began working under Ernst Hadorn, a renowned developmental geneticist and fly researcher at the University of Zurich. Walter Gehring once said that he always sought out the best teachers as they were the ones he could learn the most from. As a doctoral researcher, he came across a remarkable mutant fly in Hadorn’s lab; in place of antennae, the insect had two legs growing from its head. He named the creature “Nasobemia” – a reference to the poem “Das Nasobem” by Christian Morgenstern about an imaginary creature able to walk on its noses. He spent the subsequent years in search of the gene that had caused this mutation.

He acquired the necessary knowledge as a postdoc at Yale University in New Haven, where he also became a professor. After five years in the US, he returned to Switzerland and established a group of his own at the Biozentrum. His choice of team members could hardly have been better, as he was fond of saying – after all, two of them went on to win Nobel Prizes.

In 1984, Walter Gehring and his team finally identified the Antennapedia gene, which can cause flies to grow legs from their head instead of antennae if the gene is mutated. The discovery was a long time in the making. To begin with, Gehring created Europe’s first Drosophila gene library. To this end, his group cloned all of the fruit fly’s genes. The researchers then searched this gene library for genes that controlled the flies’ development. When Gehring and his colleagues eventually succeeded in characterizing the Antennapedia gene, a conspicuous gene sequence helped them to discover related developmental control genes. This special gene section, known as the homeobox, opened up a broad range of possibilities for developmental biologists in one fell swoop. The special thing about this sequence is that it is conserved in numerous control genes, allowing the researchers to use it as a probe to extract these genes from the gene library in a very short time. To their surprise, they observed that these homeobox sequences are also present in analogous genes in mice, frogs or humans. Walter Gehring and his team had discovered a universal principle of nature.

The final proof consisted in modifying the Antennapedia gene in fruit flies, ultimately causing the insects to grow legs from their head. In doing so, Gehring had succeeded in deliberately reproducing in the lab the chance mutation he had observed as a doctoral researcher. In the course of these experiments, the team stumbled across another interesting Drosophila gene resembling the Pax6 gene involved in the development of eyes in mice. It was this discovery that led to the many-eyed flies that caused such a stir in 1995. Incidentally, the extra organs were in fact capable of detecting light.

His fascination with the developmental biology of Drosophila notwithstanding, Walter Gehring also remained a dedicated zoologist. Of all the Biozentrum researchers, he was probably the one with the greatest knowledge of animals, he once claimed with some satisfaction. His hobby was marine biology, acquired during a visit to Banyuls-sur-Mer in southern France as a student. Later, he would lead excursions for his own students there. During these trips they had the opportunity to experiment on marine animals at the renowned Institute for Marine Biology.
“It was an incredibly exciting time” Interview with Professor emeritus Renato Paro, former director of the D-BSSE and a Gehring alumnus: Anja Fossgreen

Professor Paro, you studied at the Biozentrum from 1974 to 1978. What was it like?

Paro — It was an incredibly exciting time. At the Biozentrum, we could study the fledgling research field of molecular biology. This was a groundbreaking opportunity in Europe. What is more, biology had just been rocked by a revolutionary development: It had become possible to selectively cut up and replicate an organism’s genetic material – to recombine DNA, in other words.

In 1978 you took your final exams at the Biozentrum...

Paro — The final oral exam in microbiology was a special experience – one of the two examiners was Werner Arber. He had found out two days earlier that he was going to receive the Nobel Prize. He just calmly performed his duties as if nothing had happened.

After that you researched under Walter Gehring. He had a reputation for only taking on the very best graduates. What did you learn from the experience?

Paro — Walter Gehring was one of those young professors who had worked in the US – there were a few of them at the Biozentrum. This was one of the reasons for the special pioneering spirit that characterized the Biozentrum back then. During that time, I learned to sometimes work through the night if a particular experiment demanded it. That said, the group would often go out for a beer together as well.

Walter Gehring was considered a pioneer in various fields. Why?

Paro — Walter Gehring was actually a zoologist. He was a consummate early adopter of new technologies and research areas. For example, he was the first person in Europe to establish a gene library for the fruit fly Drosophila melanogaster using recombinant DNA.

Which you also worked with...

Paro — Yes, at the time diploma students like me had the opportunity to research where particular genes were located within the fly’s genome. This worked well in my project, so he offered to supervise my doctorate as well.

You have had an impressive career: You did research in Scotland and California, you were a group leader and professor at the Center for Molecular Biology in Heidelberg, and ended up back in Basel, where you established the Department of Biosystems Science and Engineering (D-BSSE) of the ETH Zurich. Did you stay in touch with Walter Gehring?

Paro — Yes, I did, and after he retired in 2009 he used the high-throughput sequencing technology that we set up at the D-BSSE. With this technology it was possible to very quickly analyze the entirety of an organism’s genetic information.

What was Walter Gehring working on at the D-BSSE?

Paro — He was studying the genetic make-up of cyanobacteria, as they have light-sensitive receptors. Walter Gehring had previously shown that the eye did not evolve multiple times as previously thought, but just once. Now he wanted to look at whether genes similar to those that influence the development of eyes in higher life forms were also present in basic organisms like cyanobacteria. He didn’t have enough time for that, however. Sadly, he died far too soon.

How two Nobel laureates started out at the Biozentrum

Eric Wieschaus (born 1947) had already worked with Professor Walter Gehring at Yale University. When Gehring moved to the Biozentrum in Basel in 1972, Wieschaus went with him as his first doctoral student. After completing his doctoral thesis in 1974, Wieschaus took up a research position at the University of Zurich, but continued to work with members of Gehring’s research group. This is how he met Christiane Nüsslein-Volhard (born 1942), a postdoc who worked with Walter Gehring from 1975 to 1977. The biologist was instantly fascinated by the work with fruit flies. Specifically, she studied the flies’ eggs in search of factors that influence the insects’ development.

In Walter Gehring’s lab, Eric Wieschaus was working on imaginal discs – structures in fly larvae that develop into organs and body parts such as wings or legs after metamorphosis.

Eric Wieschaus and Christiane Nüsslein-Volhard, who always discussed their projects with each other at great length, subsequently received an invitation from the European Molecular Biology Laboratory (EMBL) in Heidelberg to create a research group together to investigate which genes are involved in the embryonic development of flies. By systematically analyzing countless mutant flies, the pair succeeded in showing how body patterns develop. In this process they found a large group of genes that specify the body axis – the fact that one end of the embryo will become the fly’s head, and the other end the tail. These genes also determine the ventral and dorsal side. They also observed that the embryo is divided into segments that assume a particular position along the head-to-tail axis.

The genetic principles in embryonic development discovered by Eric Wieschaus and Christiane Nüsslein-Volhard were later also found in other animals and in humans, suggesting that the mechanisms were conserved by evolution. In recognition of their pioneering work, Nüsslein-Volhard and Wieschaus received the Nobel Prize for Physiology or Medicine in 1995.