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Ernst Hadorn, a Pioneer of Developmental Genetics

ROLF NÖTHIGER*

Zoological Institute, University of Zurich-Irchel, Switzerland

During his lifetime and beyond, Ernst Hadorn was probably the best known and most influential developmental biologist of Switzerland, with a high international reputation. And we, his students, used his name like a magic formula that opened the doors to scientists, laboratories and congresses. We were accepted without further questions. Ernst Hadorn has given much to all of us: as a scientist, he set the standard which was to be attained; as a teacher, he gave an example of how it should be done. When necessary, he did not hesitate to guide us, to modify our plans and to direct our future. He was a man who assumed responsibilty and exercised leadership.

Hadorn's career started at the very bottom and ended, rung by rung, at the very top. He was born in 1902 as the son of a modest farmer in Forst, a small village near the majestic Alps of the Bernese Oberland. When Hadorn died in 1976, the telephone directory of Forst listed only 61 names, 19 of which read HADORN. At that time, most of these Hadorns were still farmers who were born, lived and died in Forst. Ernst Hadorn was one of the few who left the village, but he was always very proud of his rural roots.

It was on the farm of his parents where Hadorn's curiosity and interest for nature awoke. He was fascinated by the sprouting and growing of a bean seed and by the miraculous processes that transformed the hundreds of little black eggs inside a jelly mass into swimming tadpoles and frogs. These wonderful phenomena left deep impressions on him, and it was almost natural and logical for him to become a biologist. For financial reasons, he first worked as a teacher at the elementary school of a nearby village. When he had saved enough money, he registered at the University of Berne to study biology with the renowned Professor Fritz Baltzer (see article by R. Weber in the present issue, pp. 15-22). After his Ph. D. in 1931, Hadorn returned to teaching, this time at the secondary level. He built himself a small laboratory in the basement of his apartment. There, he spent all his free time experimenting with amphibia. The results impressed Baltzer so much that he encouraged Hadorn to enter a research career. In 1937, Hadorn applied for a Rockefeller fellowship and spent a year at Rochester University where he met Curt Stern and *Drosophila*, – a truly decisive encounter. After his return to Switzerland, he went back to teaching, this time at the college level. Two years later, he accepted a position as Professor of Zoology at the University of Zurich. Despite several tempting offers from prestigious universities, he remained in Zurich until he retired in 1972.

In 1942, Hadorn became Director of the Zoological Institute which at that time was small and almost unknown. It was Hadorn's inspiring personality and the quality of his work that attracted many students so that the institute steadily grew to several times its initial size. Ernst Hadorn was a devoted experimentalist who enjoyed spending long hours at the bench during his entire career, without much respect for weekends or holidays. He was a scientist who knew to ask a clear question that could be approached by simple experiments, and he was a gifted teacher who gave lectures that were a pleasure to attend. In addition to his full schedule as a professor, he also served the University as Dean and as Rector, and for many years he was a member of the *Wissenschaftsrat*, the top committee of the Swiss National Science Foundation.

Hadorn's scientific work can be grouped into three parts, all of which addressed the same basic question: what are the mechanisms that govern development, and what are the roles of the nucleus with its genes on the one hand, and of the surrounding cytoplasm on the other? He was a pioneer of developmental genetics who recognized the analytical power of genetic mosaics, i.e. animals in which cells with different genetic information are confronted. The main technique

***Address correspondence to:** Dr. Rolf Nöthiger. Zoological Institute, University of Zurich-Irchel, Winterthurerstr. 190, CH-8057 Zurich, Switzerland.
Fax: +41-1635-6823. e-mail: Rolnot@Zool.unizh.ch

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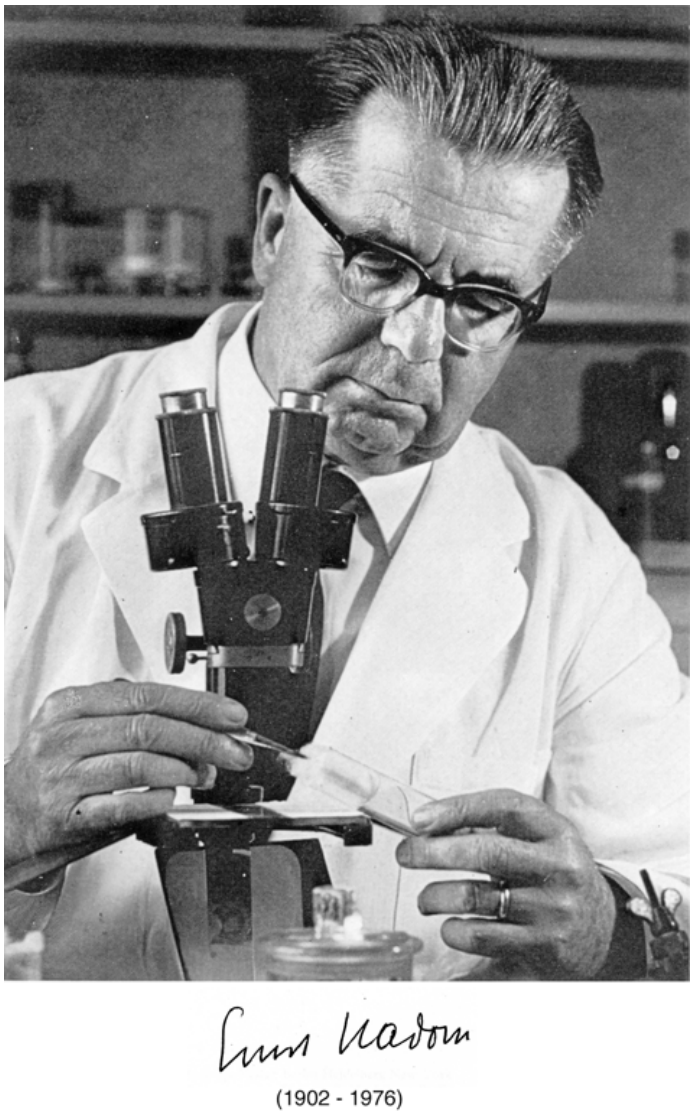

Fig. 1. Ernst Hadorn *working at his old and beloved stereomicroscope, about 1965. (Foto W. E.Böhm).*

Hadorn used was organ transplantation. By transplanting mutant tissues into wildtype hosts, and vice versa, he could see whether a tissue was affected autonomously or non-autonomously by a certain mutation. This technique enabled him to determine the focus of a gene's activity, i.e. to identify the tissue in which the function of the gene was essential. Today, genetic mosaics are widely and very successfully used again to study gene function and cell interaction. However, the techniques have become much more sophisticated and effective. Using transgenes that induce mitotic recombination at a given time and in a given tissue (Chou and Perrimon, 1992), it is now easy to generate in an animal, clones of mutant cells in which a specific gene is knocked out or ectopically activated (Basler and Struhl, 1994).

Initially, Hadorn worked with amphibia. His doctoral thesis, carried out under Fritz Baltzer, and especially his later work on nuclear-cytoplasmic interactions, established Hadorn as a skillful and original scientist. After his return from Rockefeller University, however, he must have realized that the long generation time of amphibia and the absence of mutations rendered these animals unsuitable for an analysis of the problems that interested him most. It is typical of Hadorn that in a clear and quick decision, he left the amphibia and turned to *Drosophila* with which he then worked for the rest of his life. Here was the animal of choice with a wealth of genetic information which was just waiting to be applied to problems of development.

The first mutant Hadorn put his hands on was *lgl, lethal giant larvae*. He told us how in 1937 he went to George Beadle and asked him for a mutation that was lethal and arrested development at a specific stage. Was it sheer luck, or was it the gift to a man who asked a clear and specific question? In a few months, Hadorn had found that the mutant was defective in its hormone metabolism and that the affected organ was the ring gland. Others had seen the ring gland before, but failed to discover its function. The discovery of this organ, later rewarded with an honorary doctor's degree, is characteristic of Hadorn as a sharp observer. It gave a tremendous impetus to the whole field of insect hormone physiology. For Hadorn himself, it marked the beginning of his analysis of lethal factors. This work, together with results obtained by others, led to the important insight that genes are called into action progressively during development (Fig. 2), and that different genes are active in different tissues. A series of solid papers appeared during the next 15 years, culminating in 1955 in a comprehensive textbook, *Developmental Genetics and Lethal Factors* (English translation, 1961). This publication earned him the highest Swiss distinction, the Marcel Benoist Prize. The book is still interesting for students of developmental genetics, not just for historical reasons, but because it is a rich source of information that is still valid today. Through his papers and his textbook, Hadorn won worldwide recognition as a developmental geneticist, a fact that became reflected in his election as President of the XI International Congress of Genetics in 1963 in Den Haag (Netherlands).

While still working with lethal factors, Hadorn entered his third and most successful field: imaginal disks. Imaginal disks are ordered assemblies of small cells that derive from the embryonic epidermis and occupy fixed positions in the larva. They grow by cell division and gradually acquire the capacity to differentiate, during metamorphosis, defined structures of the adult insect. *"The choice of the object was perfect"*, wrote Dietrich Bodenstein in his preface to *The Biology of Imaginal Disks,* a book dedicated to Ernst Hadorn by his students on the occasion of his 70th birthday.

Hadorn began his work on imaginal disks in 1945. For many years, he and his collaborators were practically alone, almost unnoticed by the rest of the world who, spellbound, watched the glamour and success of the rising molecular biology. Patiently and systematically, they worked out the basic features of the development of imaginal disks, without any spectacular results for almost 20 years. They established that each disk was determined to give rise to a specific part of the adult body; and by cutting a disk reproducibly into defined fragments, they constructed fate maps which revealed that also small regions within a disk (Fig. 3), or even individual cells after dissociation and reaggregation, remained determined for region-specific structures. Thus, the disks became the prototype of a rigidly determined developmental system.

This view was so dominating that it prevented the discovery of the regenerative capacity of specific disk fragments for years. Only much later was it found that a certain fragment of these disks could regenerate the rest of the disk and differentiate all the structures normally produced by this disk. This discovery led to the fashion-

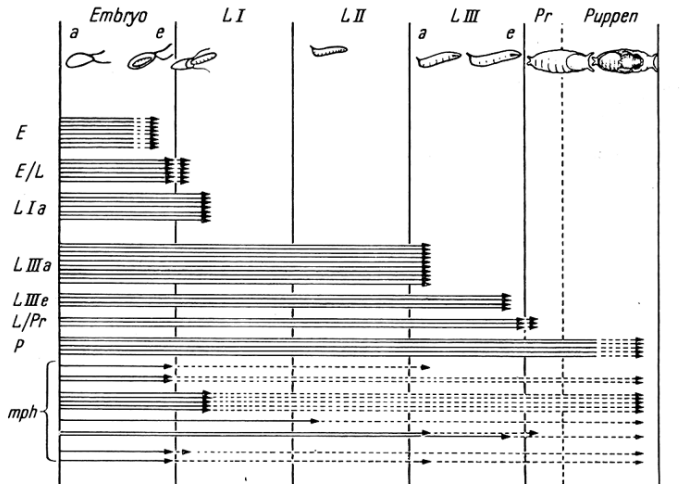

Fig. 2. Phase-specific lethality caused by various lethal mutations located on the 2. chromosome of *Drosophila melanogaster*. *Abbreviations:* a, *beginning;* e, *end of a stage;* E, *embryo;* L I, L II, L III, *first, second, third larval instar;* P, *pupae;* Pr, *prepupae;* mph, *multiple phases of lethality. (Modified from E. Hadorn: Letalfaktoren, Georg Thieme Verlag, Stuttgart, 1955).*

able "polar coordinate model" (for review see Bryant *et al.*, 1981) which, however, remained an abstract formulation and failed to show the way to a mechanistic or even molecular analysis of the phenomena.

Much earlier, in 1963, Hadorn and his collaborators had already discovered the phenomenon of transdetermination (for review see Hadorn, 1978). Fragments of disks were cultured *in vivo* for weeks and months by injecting them repeatedly into abdomens of adult females where they could grow by cell division, but due to the absence of molting hormone were prevented from metamorphosis. Under these experimental conditions, they underwent abrupt changes in determination. Cells that derived from a genital disc, e.g. now differentiated structures of the antennal or leg disk when subjected to metamorphosis after transplantation into a larval host (Fig. 4). Almost over night, the disks became a "hot" and fashionable topic of research. Developmental biologists, geneticists, biochemists, molecular biologists and theoreticians became interested in imaginal disks and started to work with them. Such a development represents undoubtedly the highest recognition an individual scientist can hope to receive. On the negative side, it brought to an end the "romantic" period of imaginal disk research, characterized by a friendly atmosphere and free exchange of information. Now, a growing number of people and laboratories began to produce an ever increasing flood of publications; the field became competitive, and the run for priorities set in. Hadorn's merits remained above this turmoil. With the imaginal disks, he provided biologists with the object which allowed them to study development with some hope of understanding its principles in genetic terms.

This hope has since experienced a formidable fulfilment. Hadorn was still alive when the genetic approach of Antonio Garcia-Bellido and his students in 1973 revealed that, during development, imaginal discs became progressively subdivided into sharply defined realms, the compartments, in which homeotic genes played their determining roles (for review see Garcia-Bellido *et al.*, 1979). And even pattern formation, the old *"pièce de résistance"*, has yielded to a genetic and molecular analysis, providing deep mechanistic insights into this formerly mysterious process (Basler and Struhl, 1994).

The relation between transdetermination and homeotic mutations was obvious. It was also obvious that the abrupt changes in determination that occurred in transdetermination, e.g. from genitalia to leg, from leg to wing, reflected changes in gene activities. But just what happened here? Hadorn had developed a hypothesis which proposed that the additional cell divisions forced upon the disks during continued culture led to a dilution of "carriers of determination". But this hypothesis was too vague and not really helpful because it lacked a heuristic value, not suggesting meaningful new experiments.

In 1972, Hadorn organized an international conference at Boldern, a rural site just South of Zurich. It was one of the first meetings sponsored by the young EMBO (European Molecular Biology Organization). Ernst Hadorn had a dream: he wanted to build a bridge and bring together developmental genetics and molecular biology. He believed that developmental phenomena, in his case determination and transdetermination in imaginal disks, must ultimately be explained, and will become explainable, in genetic and molecular terms. To this end, he selected and invited an illustrious group of some 15 molecular biologists plus an equal number of "Drosophilists" from all over the world, truly *"the best and the brightest"*. And the names read like a list from the Hall of Fame: François Jacob, Gerald Edelman, Manfred Eigen, Francis Crick, Charles Weissmann, Max Birnstiel, Sol Spiegelman, Sydney Brenner, Boris Ephrussi, Peter Lawrence, Antonio Garcia-Bellido, Klaus Sander, John Gurdon, Conrad Waddington, Jean Brachet, Tuneo Yamada, and many others (Fig. 5).

Hadorn's ambitious goal was not reached and for him remained a dream. François Jacob later commented about the conference: *"Each team told its own story, trying to be simple and to be understood by the other. Between these groups, however, a large gap remained."* This is a euphemistic version of saying that the attempt had failed and that there was no way the two fields could join

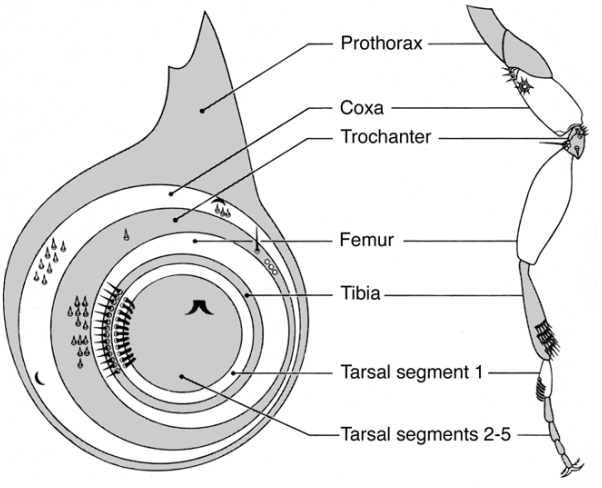

Fig. 3. Fate map of the male foreleg disk. *The map shows the regional organization within the disk and was obtained by cutting the disk into defined fragments and subjecting these to immediate metamorphosis by transplanting them into larvae ready to pupate. Each fragment produces a defined part of the adult male foreleg. (Modified from H. R. Wildermuth (1972). Determination and transdetermination in cells of the fruitfly.* Sci. Prog. Oxf. *58: 329-358).*

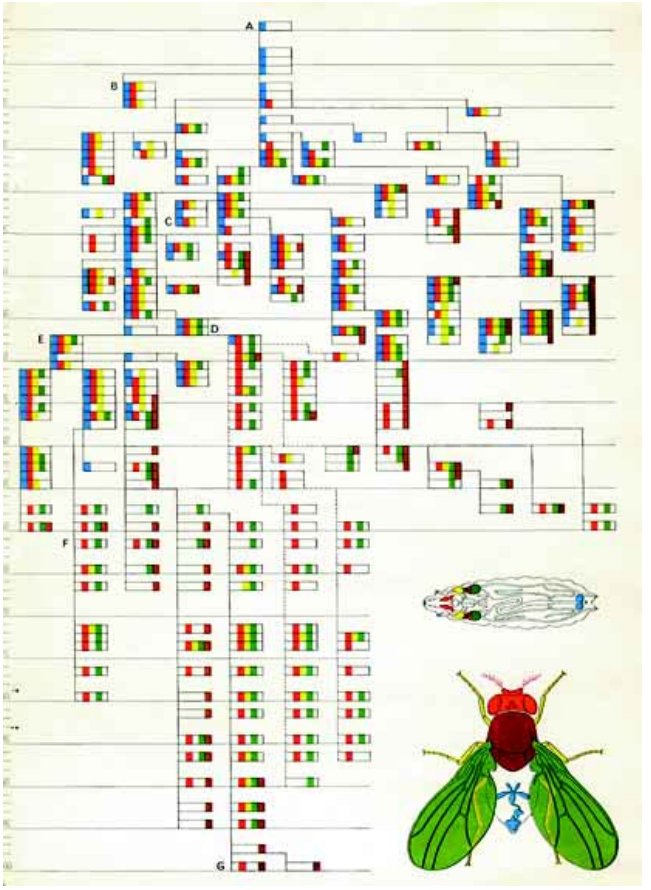

Fig. 4. "Pedigree" of transdetermination. *Beginning with a fragment of the male genital disk (blue, top), prolonged and repeated culture in the abdomens of adult females led to extensive growth and then to changes in the state of determination, which resulted in differentiation of structures of different body segments. The different colours represent the different imaginal disks, programmed to produce different regions of the adult fly. The time axis runs from top to bottom and indicates the number of transfer generations in abdomens of adult females. One hundred transfer generations are shown in the figure; they correspond to approximately 2 years of culture* in vivo. *From E. Hadorn (1968). Transdetermination in cells. Sci. Amer. 219 (Nov): 110-118.*

their efforts. This was before the arrival of cloning and transgenic techniques. Now, in 2001, the results and insights obtained since then have surpassed our boldest hopes of those years. We are now able to visualize the activity of specific genes *in situ*, confirming the conclusion reached by developmental genetics that genes are active at specific times in specific cells; we can manipulate genes, knocking them out at will or expressing them out of temporal or spatial context. We can now claim, without much exaggeration, that we understand the principles of development in genetic and molecular terms. I have often tried to imagine how Hadorn would react if he could return and see all the fantastic progress; that we can isolate a gene, put it under a different control, change its sequence *in vitro*, bring it back into an animal of the same or even of a different species, and observe its expression and the developmental consequences in the transgenic animal! How amazed or even shocked would he be, and how long would it take him to understand what has happened in only 25 years since his death in 1976?

Hadorn was an objective, self-critical and open-minded man. I remember his reaction when I informed him about my new results with dissociated and reaggregated cells of imaginal disks. These results suggested an interpretation that was contrary to Hadorn's own and published view. He looked at me, and then the professor replied to the student: *"That's fine; let the experiments decide. I am not married with my hypotheses."*

Hadorn was never concerned about the practical consequences of his research and its applicability to humans and medicine. For him, research was a human activity of higher order that belonged to *Homo sapiens* like literature, music, painting or philosophy. No further legitimation is needed; curiosity and the desire to know are specifically human and of divine origin. The ever deeper penetration of the human mind into the secrets of nature created no conflict for Hadorn. Natural science and religion were no contradiction for him, but rather represented complementary human approaches. In a lecture just a few weeks before he died, he defended reductionism and asked: *"Kann nicht das ergriffene Staunen auch dann bleiben, wenn wir noch viel mehr von den ewigen Naturgesetzen verstünden? Und was hindert uns daran, die Universalität, die im Naturgesetz verwirklicht ist, als letzten Sinn einer nicht von uns geschaffenen Ordnung zu verehren, einer Ordnung, in die wir selbst eingefügt sind und in der wir unser Dasein als Aufgabe und Verantwortung erleben?" ("Cannot our deep wonder and amazement remain, also if we understood much more of the eternal laws of nature? And why should we not accept and revere a system of a higher order, not created by us, but a system in which we are embedded and in which we have a duty and a responsiblity?").*

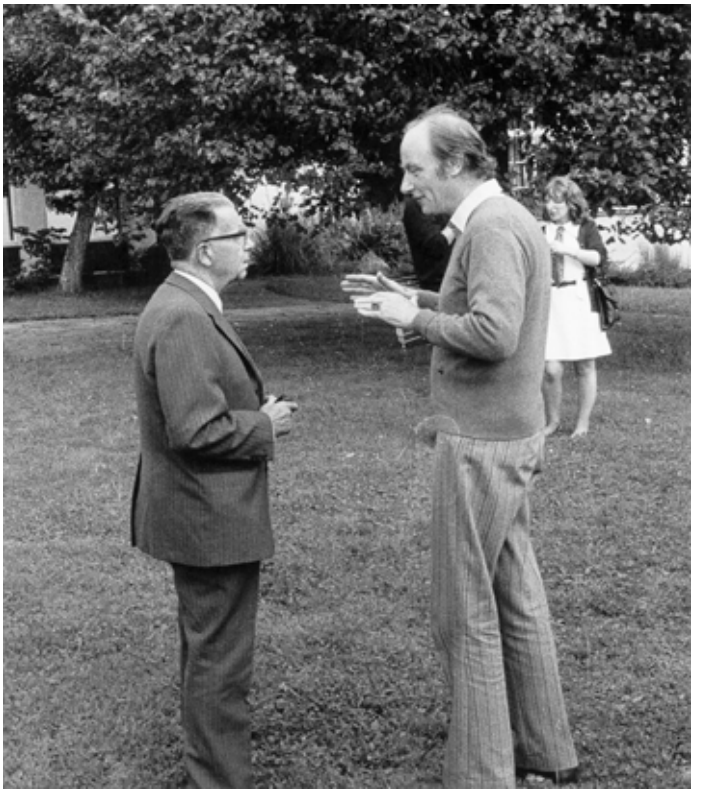

Fig. 5. Ernst Hadorn (left) and Francis Crick *at the Boldern Conference in 1972.*

As a scientist, Hadorn received many academic awards. Among the highest and most appreciated by him were his election to the National Academy of Sciences (USA) and the *"Ehrenzeichen für Kunst und Wissenschaft"*, handed over to him by the President of the Republic of Austria. He accepted these distinctions with pride and delight, but without conceit. He was aware of the ephemeral character of these phenomena, and he knew that they belonged to his soma. More important to him was his intellectual germ line. He produced a large number of students who occupied positions at all Swiss Universities and at many abroad, including the USA. Through his students, he exerted an intellectual impact that was far more important, reaching farther and lasting longer than any of the many honours he received. His students carry on his ideas and his credo, and through them he continues to influence biology in schools, universities and industry.

Let us end by quoting again Dietrich Bodenstein: *"Perhaps the most distinctive characteristics of Hadorn's personality are his absolute devotion to and infectious enthusiasm for his work, as well as his relentless energy. He is an inspiring teacher and a superb lecturer, an understanding and stimulating colleague, and a good man."*

Summary

This article gives a short and personal portrait of Ernst Hadorn (1902 - 1976), one of the most influential developmental biologists in Europe. Hadorn initially worked with amphibia, but then soon turned to *Drosophila* where he very successfully studied lethal factors and the development of imaginal disks.

KEY WORDS: *Hadorn, Drosophila, developmental genetics, genetic mosaics, transdetermination*

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