WALTER JAKOB GEHRING
20 March 1939—29 May 2014
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Walter Jakob Gehring was one of the most influential developmental biologists of the last 50 years. First as a student with Professor Ernst Hadorn in Zurich, later as a postdoc in Yale and finally as group leader in Basel, he was involved in a number of major discoveries that had a profound impact in the understanding of the genetic and molecular mechanisms of animal development, not only for the fruit fly *Drosophila* but for the whole animal kingdom.

Throughout his career Gehring demonstrated an outstanding ability to recognize key problems and then to push experimental work on these problems with great energy. Gehring pioneered the application of molecular techniques to developmental problems, an approach that was at the root of many of his contributions. His laboratory was involved in a number of key findings: the first cloning of a Hox gene, the discovery of the homeobox, the enhancer trap method, and the remarkable conservation of features of the visual system in metazoans.

He was an excellent speaker, with special ability to emphasize the relevant aspects of his work and to draw conclusions of general interest. This attracted a number of gifted students and postdocs who were key for the success of his research group.

Passionately interested in science, he was also very excited about other scientific disciplines; he was an accomplished bird watcher and was also fascinated by marine life. But he also had non-scientific interests, too; he claimed to be an excellent football player and frequently commented that he had had to decide whether to be a scientist or a professional footballer. He decided on the former, but one wonders if he might have been a Swiss version of Messi or Ronaldo.

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Biographical Memoirs

Early days and education

Walter Jakob Gehring was born in Zurich on 20 March 1939, to Marcelle Rembann and Jakob Gehring. His father was a capable and humorous mechanical engineer at the former MFO engineering works in Oerlikon. Gehring was the second child in the family; he had two sisters with whom he got along very well. He was especially fond of his younger sister, whom he took around on his bicycle and protected against others. When Walter Gehring was still a boy, his uncle sent him a cardboard box filled with butterfly pupae. He stored the box and, to his delight, beautiful butterflies emerged from the pupae in spring. Later, whenever he told this story, you could still see the excitement in his eyes and would certainly believe him saying that this event shaped his interest in animals and their development. It also inspired him to start collecting butterflies himself, a hobby he continued to cherish over his entire life. Walter also started to trap insects while he was at elementary school and brought them home to observe them. Even after becoming a famous scientist, he would still catch Drosophila specimens in the garden of his house in Therwil, close to Basel. He would immediately anaesthetize them with ether and look at them under the microscope, trying to find out whether he had just discovered a new mutant fly, and, even if that was not the case, to establish a new wild-type stock to be maintained in the lab. Over the years, this resulted in the isolation of many ‘Therwil’ strains, which he carefully maintained in the lab himself!

From 1952 to 1958, Walter went to the Realgymnasium (Science High School) in Zurich, which he finished with the Matura (High School Certificate) in 1958. During that time, Walter often went on excursions with his friend Walter Leuthold and others in the vicinity of Zurich, most of the time on bicycles, recording birds resting or breeding in wetland areas and counting birds migrating over the nearby hills. According to Walter Leuthold, these ornithological activities continued beyond high school, as both of them started studying zoology at the University of Zurich in 1958 and they became members of a young ornithologists group formed in 1960 to promote studies of the avifauna around Zurich and also in the Rhine Delta at the eastern end of the Bodensee (Lake Constance). In the autumn they would set up observation posts on several hills to record migrating birds in a coordinated effort.

University studies

1963: Diploma in zoology

Not surprisingly, considering his ornithological interests, Walter’s Master’s thesis (‘Radar studies on bird migration’) dealt with the biology of birds and the fascinating phenomenon of bird migration, a seasonal large-scale movement of many species of birds of the northern hemisphere between their breeding and wintering sites. The study made use of radar as a major tool. Hans Briegel, one of his companion students, remembers:

The daily/nightly work on radar screens of Swissair’s air navigation services in Kloten inspired us both. During the day, Walti (as Walter was called by most of his close friends) took care of all the analyses of the chronological photographs, which yielded very beautiful and innovative image results and pioneering evidence on the subject. For control purposes we often drove on his scooter to selected observation points at early or late dawn.
Figure 1. Walter Gehring in the company of Ginés Morata (ForMemRS 2017) during one of the visits to the Coto Doñana in southwest Spain, where they spent many hours observing wintering ducks and geese and other species of predatory birds. (Online version in colour.)

This work accentuated his interest in ornithology and had a long-term influence on Walter. For the rest of his life, he was interested in many aspects of bird life and travelled to many places to observe birds (figures 1 and 2).

1963–1967: PhD thesis

After his diploma, Walter started his PhD work in the laboratory of Professor Ernst Hadorn. Hadorn was a famous Swiss developmental biologist, arguably the father of what has been called the Swiss School of Developmental Biology, which included Gehring, Nöthiger, Schubiger, Ursprung and also foreign associates such as the Spaniard Antonio Garcia-Bellido (ForMemRS 1986).

In Hadorn’s laboratory they used the fruit fly *Drosophila* as a model system. Walter became fascinated by the little creature, a fascination unabated until his death. The work with
Hadorn had a definitive effect on Walter’s career, and he used *Drosophila* as his favourite experimental model system for the rest of his life. Even though he was working very hard on his thesis project, he also managed sometimes to go on ornithological excursions around Zurich (figure 3).

From 1965 to 1967, Walter remained in Zurich and worked as an assistant with Ernst Hadorn. Walter was already being paid as an assistant from 1963 onwards, which allowed him to buy a Lambretta and go on excursions with his friends on the back seat, or go around town with his girlfriend Elsbeth Lott, who became his wife in 1964. They had two sons, Stephan (born in 1965) and Thomas (born in 1970).

His friend Hans Briegel notes:

In those times (in Hadorn laboratory), I got to know another, ultimately more important person: Elsbeth Lott. At first occasionally, but then soon more regularly, we met the couple over lunchtime in the quiet university grounds, and soon Elsbeth was a welcome lab guest, be it for tea or to pick up Walter at the end of the day. In the mornings, Walti regularly set the pan for the morning coffee or tea water on the Bunsen burner. But as soon as he sat down at his binocular microscope to prepare the flies, he forgot his tea for hours and then lamented on his cold tea—at the amusement of Elsbeth and everyone in the group!

In 1965, Walter finished his PhD degree on ‘Transdetermination of antennal imaginal discs in *Drosophila*’. It was an important work, which deserves some description. In Hadorn’s laboratory, they used *Drosophila* imaginal discs as the focus of research. These are sac-like
structures present in the larvae and contain the precursor cells of the adult cuticular structures; they are named after the adult structures they will eventually form: eye imaginal disc, wing imaginal disc, leg imaginal disc and so forth. During larval development, the imaginal discs grow floating idle in the haemolymph without performing any function related with larval life; they simply use the larvae as culture medium.

The imaginal discs turned out to be a very convenient model tissue to study the problem of cell specification in development. A key feature is that they retain their specific developmental fate (e.g. generating wing, leg or eye tissue) even after long periods of in vivo culture, upon transplantation into female hosts, a method originally developed by Beadle & Ephrussi (1935). This meant that mature discs attained a specific and stable ‘state of determination’. The elaboration of the concept of determination—the commitment of a group of cells to
differentiate into a particular structure before actual differentiation takes place—is one of the principal contributions of the Swiss school.

Even though the state of determination of imaginal discs is usually stable, Hadorn and colleagues had found that after long-time culture, disc cells would occasionally modify their determination state. For example, some leg cells would suddenly change and become determined to differentiate wing structures. They called this phenomenon ‘transdetermination’, a change in the developmental programme of the cells. The study of transdetermination became central in the research of the group. For his PhD work, Walter analysed the levels and directions of transdetermination in the antennal disc, a study evaluated with summa cum laude.

Following on the issue of transdetermination, Walter made an intriguing observation whose significance took years to be appreciated. He found (1)* that transdetermination was not a clonal event, as most people would have expected (a change in the determination of an individual cell, which transmitted the new state to its progeny), a very sensible view, but his experiments indicated something very different: that the change in determination had occurred simultaneously in a group of cells—it was a group decision. This provided the first indication that developmental decisions may be taken by groups of cells, likely through local interactions. Later, the ‘community effect’ reported by Gurdon (1988) during muscle specification in Xenopus, but especially the work by the Garcia-Bellido group in Madrid on the compartmentalization process in imaginal discs (Garcia-Bellido et al. 1973), confirmed the existence of group decisions during development. It is of interest that 60 years after the original report by Walter there is still no understanding of the molecular mechanism underlying group decisions.

It was during his time in the Hadorn laboratory that Walter was shown a strange mutant fly in which the antenna had the appearance of a leg. He termed the mutation causing this phenotype ‘Nasobemia’ after a creature able to walk on its nose. It was later found that this mutation affects the function of a Hox gene of the Antennapedia class. This fortuitous encounter started a life-long association with Antp mutations, with important consequences later in Walter’s career.

**POST-DOCTORAL PERIOD: Yale**

After the completion of his thesis in Hadorn’s laboratory in 1967, Walter went to Yale University to work with Alan Garen, a well-known molecular biologist who had discovered suppressor mutations for transfer RNA. Garen was not a developmental biologist, nor did he have any experience in working with fruit flies; Walter must have been the odd person in the group.

Although at the time Walter had little experience in biochemistry and molecular biology, his stay in Yale had a profound effect in his career, as it convinced him that understanding the molecular mechanisms of development was of utmost importance. He stayed in Yale until 1972, having published a series of articles in *Proceedings of the National Academy of Sciences* that gained him an assistant professorship in Yale and eventually a professorship in Basel.

While in Garen’s lab, Walter supervised the work of a graduate student, L.-N. Chan, whom he trained in the transplantation methods he had mastered in Zurich. The result was a very

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* Numbers in this form refer to the bibliography at the end of the text.
interesting paper showing that anterior blastoderm cells retain the anterior specification after mixing with cells from other regions (2). It was a major finding, because it showed that even though blastoderm cells look alike and show no signs of differentiation, they have already acquired distinct developmental programmes. He later explored this idea further through the work of his own first graduate student, which we elaborate on in the next section.

**Development of his research group in Basel**

After his time in Yale, at the early age of 32, Walter was appointed professor at the newly opened Biozentrum of the University of Basel, Switzerland, in 1972, where he established his own research group. He remained in Basel for the rest of his career, and it was here where his laboratory generated a number of very significant discoveries that shaped the field of developmental biology.

Following his interest in early development, he proposed to his first PhD student Eric Wieschaus (later to become Nobel laureate in 1995) that he study cell determination in early embryogenesis. The method they used was clonal analysis, a key technique in developmental biology consisting of labelling a particular cell with an indelible mark at a particular moment in development. The mark expressed by the original ‘mother’ cell would be transmitted to the progeny, which would appear as a marked clone in the final structure. The existence in *Drosophila* of marker mutations that affect the differentiation of cuticular structures such as bristles or hairs greatly facilitated such clonal analyses. The mutations used are usually recessive: heterozygous flies have a normal phenotype, but in those flies it is possible to generate homozygous clones by inducing recombination of sister chromatids during the G2 period of the cell division cycle, and such clones express the mutant marker phenotype. The experiment that Wieschaus performed consisted of inducing marked clones very early in development, at the blastoderm stage, and then examining the extent to which those clones contributed to adult tissues. At that early stage, all cells (with the exception of the pole cells, the precursors of the gametes) look alike; the embryo appears to be made up of a monotonous monolayer of seemingly identical cells. Yet the important observation by Wieschaus and Gehring was that the progeny of marked blastoderm cells was always restricted within one segment of the adult. The implication was that even though all cells look alike in the blastoderm, they are in fact subdivided into groups of cells with distinct segmental determination; the *Drosophila* embryo is segmented well before segment boundaries are visible. These important results were published in 1976 (3). Work from Lawrence & Morata (1977) some months later confirmed the original observation and added that blastoderm segments are further subdivided into anterior and posterior compartments.

**Beginning of molecular analysis of Drosophila development**

It was in the late seventies/early eighties that the methods of molecular cloning became available in flies, and naturally Walter jumped into this emerging field. He realized the importance of accumulating cloned sequences—gene banks he called them—as a step towards efficient cloning and molecular analysis of *Drosophila* genes. Walter always insisted on using the term gene ‘bank’ rather than gene ‘library’; after all, the work had been done in Switzerland, and it had to be possible to generate the best gene banks in this particular country! In collaboration with the lab of Alfred Tissières in Geneva, the Gehring group
cloned the *Drosophila* heat shock genes (4), work that later inspired the use of heat shock promoters to manipulate gene expression and function; it was with this system that the Gehring group reported for the first time the consequences of ectopic expression of a homeotic gene, *Antennapedia* (*Antp*) (9). The important conclusion was that just forcing the expression of the *Antp* protein in the antenna was sufficient to induce leg development, thus establishing the major developmental role of the *Antp* gene. Walter used the term ‘master regulatory genes’ to designate genes that are at the top of a particular developmental programme. Additionally, and very importantly, the accessibility to *Drosophila* gene banks was instrumental for one of the major contributions of the Gehring laboratory: the discovery of the homeobox.

To understand the huge significance of the discovery of the homeobox, it is important to review briefly the function and structure of the homeotic genes as they were understood in the 1980s (the term ‘Hox’ to refer to these genes was introduced later). In *Drosophila*, there are two major groups of homeotic genes, clustered in two complexes: the *Antp* complex (ANT-C), which includes the *Antp* gene itself plus *Sex comb reduced* (*Scr*), *Deformed* (*Dfd*), *labial* (*lab*) and *proboscipedia* (*pb*), and the bithorax complex (BX-C), which only contains three genes, *Ultrabithorax* (*Ubx*), *abdominal-A* (*abd-A*) and *Abdominal-B* (*abd-B*). The clustering of these genes already suggested a common evolutionary origin, arising by tandem duplications. The genes of these complexes perform a crucial developmental role, for in their absence *Drosophila* embryos, larvae and adults lose all morphological diversity: all cephalic, thoracic and abdominal segments develop alike into a ground pattern that resembles a mixture of first and second thoracic features. The importance of the function of homeotic genes cannot be overemphasized: they determine the specific developmental programmes of the different body parts.

How they perform such general functions was not clear, but it was obvious that a single gene function could not account for the development of all features of an entire body segment. The hypothesis was that, somehow, homeotic genes must regulate the activity of subsidiary genes responsible for the specific features of the segment in question.

The key finding by the Gehring laboratory (7), simultaneously reported by Matt Scott’s group (Scott & Weiner 1984), was that *Antp* (which had been cloned in Gehring’s lab) and other homeotic genes had in common a short stretch of 180 base pairs that the Gehring laboratory termed ‘homeobox’. The discovery of the homeobox had consequences of enormous impact. In the first place, it confirmed the common evolutionary origin of these genes, for they most likely derive from a common ancestor containing this sequence. In the second place, it turned out that the homeobox encodes a DNA binding protein domain, already providing a molecular mechanism of homeotic function: the Hox genes encode master regulatory elements that regulate the transcription of subsidiary genes responsible for the individual features of the various developmental pathways. In a very fruitful collaboration with Kurt Wüthrich’s laboratory in Zurich (11), the three-dimensional structure of the homeobox was determined. These results paved the way for a new avenue of research on homeotic function.

The identification of the homeobox provided a molecular probe to search for Hox genes in organisms in which these genes could not be identified by conventional genetic methods, for example in mammals. It was immediately found in the Gehring lab that the Hox genes are present in all metazoans (5,6); that is, they represent a universal feature of the animal kingdom. And not only are the Hox genes present in all animals, but the whole structure of the complex is conserved to a very large degree: in most animals the ancestral Hox clustering
is preserved. In mammals there are four copies of the complex, and the clustering within each copy is conserved.

Partially obscured by the discovery of the homeobox, the development of the enhancer trap method (8, 10, 12) represents another major contribution of Walter’s laboratory. In *Drosophila*, as in any other organism, there are some genetic elements, termed transposons, that have the ability to insert themselves into foreign DNA, with the help of some specific sequences they carry along. A well-studied case is the P element; inserted P elements are generally stable but can be excised by the activity of a particular protein, a transposase. Forcing transposase function in flies results in the excision and subsequent re-insertion of the P element in other parts of the genome—a mobilization of the transposon. O’Kane and Gehring demonstrated that this mobilization and re-insertion property, when combined with a marker gene under a weak promoter, allowed them to identify new gene expression patterns in the *Drosophila* genome (8). Essentially, they constructed a modified P element carrying the coding sequence of the *lacZ* gene, which encodes β-galactosidase. This P element will, after mobilization, insert into a new gene, and in many cases the enhancers of this gene will control the expression of the *lacZ* gene. Thus, *LacZ* distribution (which can easily be visualized with histochemical methods) will mimic that of the gene where the P element has inserted. Massive use of this method provided a whole inventory of novel expression patterns, which allowed the identification and subsequent cloning of many genes of interest (10, 12). With the development of the enhancer trap method, the Gehring laboratory provided a hugely useful genetic tool to the *Drosophila* community.

A late major contribution from the Gehring team was the identification of some of the key genetic elements of the photoreceptor mechanism: a finding that significantly changed the understanding of the evolutionary history of the visual system. A *Drosophila* mutation first described in detail as early as 1922 (Richards & Furrow 1922), in the early days of *Drosophila* genetics, is called *eyeless*. As its name suggests, the mutant flies either lack eyes or their size is much reduced.

In 1967 a mouse dominant mutation called *Small eye* was reported (Roberts 1967) that caused, in heterozygous condition, considerable size reduction of the lens and optic cup. It results in small eyes, hence the name given to the mutation. Although *Small eye* mutations are homozygous lethal, some embryos develop fully before death, and they show complete absence of eyes and nasal cavities. In humans, a mutation called aniridia (lack of iris) had been reported (Hodgson & Saunders 1980) that causes eye defects: it also showed phenotypic similarities with the *Small eye* mutations in mice.

During the 1980s many developmental genes were cloned and eventually sequenced. As mentioned above, many of them contain a homeobox, but several other conserved motifs were also discovered. One of them was the ‘Paired/Pax’ box—it took the name from the *Drosophila* gene where the motif was originally found (Bopp et al. 1986). Further characterization of the Pax motifs in *Drosophila* and other species indicated that it is a multimember family comprising several classes of Pax boxes. Interestingly, it was found that both the mouse *Small eye* and the human aniridia genes belong to the Pax-6 class of homeobox genes (Hill et al. 1991), suggesting structural and functional similarity.

Then, in 1994, the Gehring group reported that the *eyeless* gene of *Drosophila* also contained a Pax-6 box and was homologous to *Small eye* and to aniridia (13). Furthermore, they reported (14) that ectopic expression of the *eyeless* gene in imaginal discs could induce eye formation in many different parts of the fly, such as in legs, wings, antennae (figure 4).
This suggested that \textit{eyeless} is a ‘master regulatory gene’ whose function is to specify eye morphogenesis. Moreover, and importantly, they showed that forcing expression of the mouse Pax-6 gene in \textit{Drosophila} also caused the formation of ectopic fly eyes, indicating the conserved function of the Pax-6 gene family among the animal kingdom.

These were very important findings; here you have essentially the same gene performing a similar function in three evolutionary distant species. At least in one case, the role of specifying eye development had been clearly established. Following this, it was immediately found that homologous Pax-6 genes are present in many other animal species, including ascidians, cephalopods, nemerteans and many more.

All of this suggested that the development of the \textit{Drosophila} composite eyes, the lens-containing eyes of vertebrates and those of octopuses is initiated by the same genetic event. The implication was that the eyes of metazoans have a common evolutionary origin: a common ancestor of Pax-6 was already involved in the development of a primitive visual system. It was a heterodox view, because insect and vertebrate eyes are structurally and functionally very different and it was hard to think they have a common evolutionary origin. In fact, it had been proposed that eyes have appeared many times during evolution; for example, Salvini-Plawen \textit{et al.} (1977) suggested that photoreceptor systems have appeared between 40 and 65 times independently.

The work on the genetics and evolution of the visual system was Walter’s last major service to science: work that was recognized as very significant and for which he received important distinctions, such as the Kyoto Prize (2000).

It was with consternation when, in May 2014, we learned that Walter had died from the consequences of a car accident in Greece, a country he loved. He was 75 years old but intellectually he was in his prime. Two months before his death, many of his collaborators and friends attended a special symposium on the occasion of his seventy-fifth birthday, and
there he was in his usual ebullient mood, full of energy and making plans, scientific and non-scientific, for the years to come (figure 5).

In sum, Walter Gehring was a most successful scientist; his name will always be associated with discoveries that shaped the field of developmental biology in the second half of the twentieth century. He was man of strong personality and tremendous self-confidence. One of his catch phrases about a new discovery, ‘I predicted it’, often annoyed his colleagues. He could be difficult on occasions, which created tension with some of his collaborators; however, Walter also loved to spend time with his many friends and former lab members (figure 6), and most of them remember him as a great colleague. Everybody agrees that his lab in Basel was the site where many new ideas and techniques germinated. Without these contributions, developmental biology would not be as it is today.

**Personal reminiscences**

Additional reminiscences from his colleagues and friends can be found as online supplementary material entitled Walter Gehring—Personal Reminiscences. These contributions are by: Ernst Hafen, Georg Halder, Cahir O’Kane, Hugo Bellen, Eddy de Robertis, Denis Doboule, Debra Wolgemuth, Ginés Morata and Markus Affolter.
Figure 6. Walter in the company of Markus Affolter and some friends, obviously having a great time. Walter always enjoyed a good meal with friends and colleagues. (Online version in colour.)

**MAJOR PRIZES AND DISTINCTIONS**

1986  Foreign member of the USA National Academy of Sciences  
1987  Gairdner Foundation International Award  
1987  Louis-Jeantet Prize for Medicine  
1997  March of Dimes Prize in Developmental Biology  
1997  Foreign member of the Royal Society  
2000  Kyoto Prize for Basic Science  
2002  Balzan Prize for Developmental Biology

**ACKNOWLEDGEMENTS**

We wish to acknowledge Walter’s many friends and colleagues for their comments, which were of great help to build a picture of his complex personality. Thanks in particular to those that appeared cited in the text and to those that sent reminiscences of their experiences with him.

The frontispiece portrait photograph was taken by Prudence Cuming Associates in 1997 and is © the Royal Society. All other photographs are from the Gehring family collection.

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