Historical transformations

Master Control Genes in Development and Evolution: The Homeobox Story
by Walter J. Gehring
Yale University Press: 1999. 296 pp. $35, £25

William McGinnis and Peter A. Lawrence

" 'It's a poor sort of memory that only works backwards,' the Queen remarked" — *Through the Looking-Glass* by Lewis Carroll.

The past 20 years have seen embryology transformed into developmental biology: we no longer transplant bits of embryos but run gels, identify genes and try to think up catchy names for them. Walter Gehring has lived through this transition, and he and his co-workers have made many important discoveries on both sides of the divide. The most charismatic of these is the identification of the homeobox, a piece of DNA that encodes a protein motif, a signature written into some of the most illuminating genes ever defined.

In *Master Control Genes* Gehring writes clear and accessible prose, free of the acronyms and stilted jargon of most scientific text. He takes us on a roller-coaster ride, mainly down into the demanding depths of heavy-duty description, occasionally up to the entertaining heights of lyrical reminiscence, giving us a book that is part primer, part autobiography, part gossip. After a Swissocentric introduction that reviews how information is transferred from genes to proteins, the book introduces its central themes, homeotic genes and the homeobox.

With a sense of wonder, Gehring recounts the history of homeotic mutations that, for example, transform antenna into leg, and then shows how the homeobox became a window through which one could see that humans, bugs and worms are all sisters under the skin, all built and designed by the same genes. This window also showed us that invertebrates and vertebrates share, in part, an immemorial body plan — a grand surprise with evolutionary, even philosophical implications.

The homeobox has also proved to be an aid in picking out some of the special genes concerned in animal design, genes that embody instructions to single cells, directing their differentiation or, more significantly, acting in cell groups, telling them which parts of the body to make. Gehring conveys some of the excitement of the early homeobox era as unifying results were discovered and new models emerged. Indeed, he delights in reliving Ah Hah! moments of discovery, and also reveals a few scars lingering from defunct intellectual disputes. The book then hunkers down to basics, telling in textbook style how embryos are constructed at the cellular level, and how stripes of gene expression are generated. He next describes how homeotic proteins may work, and, in a particularly vivid section, how a "master control gene" specifying eye was discovered.

A homeotic nightmare

This beast is not the work of a mutated "master control gene" but rather of the German artist Thomas Grünfeld. Grünfeld lives and works in Cologne, where, over the past 10 years, he has specialized in taxidermy to produce a whole bestiary of misfits.

In "Misfit (COW)", the 1997 work pictured here, a bull's head is apparently seamlessly sewn onto an ostrich's body. It currently resides in the Saatchi Collection.

SAATCHI GALLERY LONDON. COURTESY KARSTEN SCHUBERT, LONDON. PHOTO: LOTHAR SCHNEPF

For the general reader, the book brings to life recent discoveries in developmental biology. Historical vignettes garnish the stories: most chapters begin with personal memories from Gehring's travels that relate to the scientific problems discussed. An interesting section describes how molecular biology was embraced by only a few embryologists like Gehring, who took up cloning with messianic fervour. Today it seems obvious to study both cells and gels, but it cannot have been so in the mid-1970s or more would have done it. Gehring was prescient in this and other decisions and one is at first impressed by his unerringly accurate predictions. But after a few of them, as he and his eager subordinates uncover one developmental secret after another, most readers will feel their amazement turning to incredulity. In one passage his predictive prowess takes wing in a time machine, as Gehring assures the reader "I would have predicted [that result]".

Readers will want to know exactly when, how and by whom the homeobox was discovered. First let's consider the method: DNA probes made from a homeotic gene were hybridized to gels carrying DNA from many genes. It was found that some probes hybridized to several places on the gel, showing that several genes shared at least a piece of sequence. This piece was the homeobox and turned out to encode about 60 amino acids. Now the history: in the front of the book there is a chronology, starting with *The Origin of Species* and including the homeobox discovery; the former is credited to Charles Darwin, the latter to Matthew Scott and Gehring himself. Indeed, the discovery was made independently at about the same time in the United States and Switzerland. However, when the key observations were made by Scott and Amy Weiner in Indiana, they were postdoc and graduate student in Thomas Kaufman's laboratory, and though it was, and is, common practice for lab chiefs to co-author the papers of postdocs and students, Kaufman generously did not insist on it. Kaufman had done fine work, identifying and describing the Antennapedia complex of homeotic genes, upon which Scott and Weiner's amazing discovery depended, so there is no doubt he deserves considerable credit for preparing the ground in Indiana, just as Gehring himself does in Basel.

Gehring's account of the discovery in Basel lacks detail and a consistent timeline, and is at odds with the records and recall of other participants. Gehring recollects that he alone saw the significance of his postdoc Rick Garber's hybridization with Antennapedia DNA. But participants at the meeting (early autumn of 1982) where this was discussed remember that there was an anomalous band in Garber's gel that could have led to the discovery. However, it was attributed to overloading of the gel, lumped into the 'uninterpretable results' category and not followed up. No one besides Gehring can know his thoughts at the time, but if the significance of this band were so obvious, it is a mystery why it was not chased up immediately.

When Bill McGinnis arrived in January 1983, he was not asked by Gehring to explore Antennapedia cross-homology. Instead, he worked on the *lethal giant larvae* gene with

Bernard Mechler, while looking around for other projects. Nothing homeobox-related was done until March 1983, when Michael Levine made the crucial suggestion that an Antennapedia probe be used on a blot with DNA from different species of the fruitfly *Drosophila* (McGinnis was intending to test for sequence conservation in the *lethal giant larvae* gene). This experiment lies at the heart of the discovery of the homeobox — they found that the Antennapedia probe hybridized to multiple bands in both *Drosophila melanogaster* and *D. hydei*, implying common sequences in other genes. As recounted in *The Making of a Fly: The Genetics of Animal Design* by P. A. Lawrence (Blackwell, 1992), Ernst Hafen, Atsushi Kuroiwa, Levine and McGinnis then followed this common sequence to its various sources in the *Drosophila* genome, finding that the sequence mapped to the chromosomal loci of two groups of homeotic genes, the Antennapedia and Bithorax complexes. Then, by hybridizing probes to tissue sections, they found that genes containing the sequence were expressed locally in the antero-posterior axis of embryos. Gehring received DNA from Pierre Spierer that included the Ultrabithorax transcription unit (another homeotic gene) and more cross-hybridization showed that Antennapedia and Ultrabithorax had the same common sequence, which then acquired the homeobox tag.

What about the discovery of homeoboxes in vertebrates? In the book Gehring credits himself and Eddy de Robertis with the decision "in a flare of boldness ... to begin looking for homeobox genes in vertebrates". But he also points out that there was an earlier "zooblot", which was done in June 1983. Now, this blot contained DNA from a Noah's Ark of animals, *including* vertebrates; it showed up homeobox bands in them all (see *The Making of a Fly*). This discovery made Gehring and De Robertis' search rather less adventurous than portrayed. It is, of course, a difficult task to write history when nearly all the participants are still alive. Gehring realizes this, stating that the book "represents my personal view and is therefore certainly biased". Those who have detailed knowledge of some of the events in the book will agree with him on this point.

At the beginning of the most famous autobiographical essay in modern biology, James Watson wrote that he had "never seen Francis Crick in a modest mood", and Watson goes on to describe events and people with unbridled candour. Gehring's autobiographical stories provide candour too, but unlike the *The Double Helix*, this book omits the fits and starts, the blind alleys pursued, the struggles with techniques and the endless doubts. It does not illustrate the part that timeliness and luck play in nearly every discovery. In sum, *Master Control Genes* contains a deeply personal view, told in a heroic style, of how a fruitful collision between embryology and molecular genetics of flies and other animals changed how we think about development and evolution. But some of the pictures painted in the book should be viewed through the looking-glass. □

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Different perspectives: as Lewis Carroll pointed out, your view depends on where you're standing.

Painting a picture of development

The Art of Genes: How Organisms Make Themselves
by Enrico Coen
Oxford University Press: 1999. 392 pp. £20

John Maynard Smith

"Over the past twenty years there has been a revolution in biology: for the first time we have begun to understand how organisms make themselves." These are the opening words of the preface to Enrico Coen's book, and I think they are true. In *The Art of Genes*, Coen tries to explain to readers with no special knowledge of biology or development what is happening in the world of genetics.

He does so by means of a protracted analogy with artistic creation; but this is not an attempt to obfuscate or mystify. Coen has himself contributed to the revolution that is under way and he is a mechanist at heart, with a passion for communicating. He uses the artistic analogy to emphasize the difference between the process of development and the fabrication of a machine by following a plan or blueprint. Before a painter starts painting a picture, he does not have an image in his mind of the completed picture. Instead, he reacts continuously to the pattern of paint already on the canvas.

Coen introduces the analogy by describing Curt Stern's 1956 study of the effects of the *scute* gene on bristle patterns in the fruitfly *Drosophila*. (One of the book's great merits is Coen's sense of the history of his subject, from debates between preformation and epigenesis to the premolecular era of developmental genetics.) Stern studied flies that were mosaics of genetically *scute* and normal tissue. He explained the resulting bristle patterns as arising from an interaction between what he called a 'prepattern' (corresponding roughly to what Lewis Wolpert later called positional information) and the competence of cells locally to respond to it. He found that the prepattern in *scute* flies was unchanged from the normal but cell competence to respond was impaired.

I remember being both excited and disappointed by Stern's paper — excited because it showed how genetics could be used to analyse development, but disappointed because the prepattern was unchanged. After all, it is the pattern, not the response, that is the exciting thing we want to understand. There is no longer any need to feel disappointed. Genetic analysis is also revealing how prepatterns are laid down, as Coen illustrates by describing, in some detail, the development of segmentation in *Drosophila* and of flower morphology.

Following the artistic analogy, prepattern is described in terms of regions of differing colour, eliciting different responses. Coen gives a detailed account of early *Drosophila* development along these lines, including a discussion of how colours spread, how some responses depend on the presence of two contrasting colours, and so on. At least the analogy helps him to avoid the clumsy terminology of *Drosophila* development, with its *bicoid* and *hedgehog*, *Notch* and *fushi-tarazu*, and to intersperse the geometric diagrams with pictures by Magritte, Escher, Picasso and Heath-Robinson.

I am delighted that one of the leading practitioners in the field should have taken time off from the lab to tell the rest of us what is going on. How far has the attempt succeeded? It does avoid any assumption of previous knowledge: there is nothing here you cannot understand if you want to. But it is not an easy read. If you want a book entitled "A Brief History of Development", to browse through for an hour, learning enough of the vocabulary to keep your end up in cocktail conversation, this is not for you.

But there is an alternative reader for whom the book is ideal. When I have