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In his 1894 book, *Materials for the Study of Variation*, William Bateson coined the term Homoeosis with the following prose:

*The case of the modification of the antenna of an insect into a foot, of the eye of a Crustacean into an antenna, of a petal into a stamen, and the like, are examples of the same kind.*

*It is desirable and indeed necessary that such Variations, which consist in the assumption by one member of a Meristic series, of the form or characters proper to other members of the series, should be recognized as constituting a distinct group of phenomena.*

*I therefore propose...the term HOMOEOSIS...; for the essential phenomenon is not that there has merely been a change, but that something has been changed into the likeness of something else.*

The book was intended as a listing of the kinds of naturally occurring variation that could act as a substrate for the evolutionary process and Bateson took his examples from collections, both private and in museums, of materials displaying morphological oddities. Interestingly the person who also coined the term “Genetics” proffered little in the way of speculation on the possible genetic underpinnings of these oddities. It wasn’t until the early part of the next century that these changes in meristic series were shown to be heritable.

As was the case for Bateson, the homeotic or Hox genes were first recognized by virtue of their striking mutant phenotypes in the fly *Drosophila melanogaster*. The seminal work of E.B. Lewis enlarged on these early discoveries and mapped a set of these mutations into a complex on the third chromosome that affected the segmental identity of the posterior thorax and the abdomen. Subsequently a separate complex controlling the identities of the anterior thorax and head was discovered. The anterior and posterior acting complexes were named after their most prominent member loci: *Antennapedia* (ANT-C) and *bithorax* (BX-C) respectively. The genetic mapping of lesions within each complex and the segments affected by those lesions revealed the fact that the left to right order of the homeotic loci within each complex and the domains of affect of each locus were colinear. The subsequent molecular characterization of
both complexes demonstrated that the expression domains of the genes were entirely consistent with the morphological results. The subsequent molecular characterization of the two complexes produced two other striking findings:

- The resident loci encoded transcription factors that contained a highly conserved motif termed the homeodomain
- The ANT-C contained loci that while encoding the homeodomain did not act as canonical Hox genes.

With molecular probes in hand it became possible to search for similar genes outside of the fly. It soon became apparent that not only are the Hox genes highly conserved, so is their residence in a complex and the rule of colinearity, with both characteristics extending to most animal phyla. Within the arthropods one can see excellent examples of this conservation despite rather divergent embryonic morphologies and types of embryonic development.

In the early days the discovery of the molecular character and ubiquity of the Hox genes led to a good deal of speculation on the function of the genes, their mode of action and the underlying reason(s) for the maintenance of the complex over a phylogenetic range including both the protostomes and deuterostomes. The period in the early 1980s to the mid 1990s when this speculation was rife has been referred to as the era of Homeomadness and was unfortunately characterized by what can be charitably called excessive behavior by some of the participants. Fortunately, as this book will attest, this period has mercifully ended and more measured analyses and conclusions now characterize the investigation of Hox gene function, genomic organization and evolution.

The book is divided into three major sections. The first four chapters cover aspects of the regulation of Hox gene expression (Chapters 2, 3 and 4) and the structure and function of the now justifiably well-known homeobox (Chapter 1). The second section offers insights and discussions of the sometimes contentious issues of the origin (Chapter 5) and evolution (Chapter 6) of the aforementioned Hox complexes. The two remaining chapters in this section (7 and 8) delve into the topic of the constraints on the conservation of the component loci of the complexes in animal phylogeny. In the third and last section the role of the resident loci in the specification of body plans and meristic identity (Chapters 9 and 10) of the arthropods is presented. The cases of Hox genes that have apparently gained novel functionality relative to their presumed ancestral roles in ontology are also noted. In addition to these discussions on segmental and tissue identity the role of the Hox genes in the specification of cellular identity in the nervous system is presented (Chapter 11). Finally the editor of the book shares his thoughts on the Hox genes and what constitutes inclusion as a member of this class of loci.

Wallace Arthur posits the following in his 2006 book, *Creatures of Accident: The Rise of the Animal Kingdom*, when noting the discovery of the homeobox:

> In the 1980s two groups ...made an important discovery. Actually this is putting it mildly: If I had to choose the most important biological discovery over the last half century, this would be it.
Actually, the Hox genes, their complexes and the homeobox represent only the tip of the genetic conservation iceberg. The majority of developmentally important genes are conserved across all animal phyla. This latter discovery coming on the heels of the homeobox revelation has now altered the landscape of evolutionary thought and research. One must now be concerned with explaining how an essentially common set of molecular paradigms have been used to produce the vast array of extant and fossil animals. The chapters presented here are excellent examples of the change in landscape, thinking and research.

Prof. Thom C. Kaufman
Department of Biology
Indiana University at Bloomington
Bloomington, Indiana
USA
PREFACE

Are the Hox genes so important? Frankly, it is but a rhetorical question. In my opinion, the answer is YES, without any doubt. Still, I found it the right place to ask this question at the beginning of the present book. My purpose is here to argue, and try to convince those who may not agree, that the Hox genes are indeed so important that their study will not end with the 20th century.

In fact, I do think that the discovery of the homeobox\textsuperscript{1,2} was one among the main scientific events in biology during the second half of the 20th century, together with the structure of the DNA molecule by Watson and Crick\textsuperscript{3} and the discovery by Lwoff, Jacob and Monod\textsuperscript{4} that the regulation of gene expression was itself genetically determined. I am old enough to remember the shocks that the discovery of the homeobox provoked a quarter of a century ago. Indeed, I can remember what our thoughts were at that time, and how much it changed our way of thinking, in molecular biology, developmental biology and evolutionary biology. In molecular biology, almost everybody at that time was convinced that each transcription factor had to be unique in both structure and sequence to accommodate its specific binding to DNA. Then came the Hox genes, and soon after the huge family of homeobox-containing transcription factors, contradicting this assumption. Similarly, although embryologists were familiar with the similarities in the development of mammals, and even between mammals and non-mammalian vertebrates, very few dared dream that studying a fly or a worm would bring deep insights to the knowledge of vertebrate development. Most biologists at that time were convinced that in order to make a fly different from a human being, despite clear homologies in the so-called ‘house-keeping’ genes, what would differ should be precisely developmental genes. Evolutionary biologists thought that evolution has produced new genes in order to achieve new body plans.\textsuperscript{5} The same year when it was discovered in \textit{Drosophila melanogaster}, the homeobox provided a means to retrieve homologous genes in other animals, including tetrapod vertebrates, mammalians and \textit{Homo sapiens}.\textsuperscript{6} In addition, it rapidly appeared that these homologous genes, now called ‘Hox’ genes, performed the same homeotic function in vertebrates as in flies.\textsuperscript{7} This similarity brought into revival Geoffroy Saint-Hilaire’s hypothesis of the “unity of design” throughout the whole animal kingdom,\textsuperscript{8} an idea that seemed refuted after its famous
dispute with Cuvier in 1830. Actually, it opened the door to a new discipline in biology, comparative developmental genetics, so-called ‘evo-devo’.

The molecular problem is now coined ‘the Hox paradox’: How can a series of transcription factors, so similar in their homeodomain, the part of the molecule that binds to DNA, achieve the function of the Hox genes, which is precisely to give specificity—even often called ‘identity’—to the domains in which they are expressed? This issue is not completely solved. Samir Merabet et al report the present-day answers and still-remaining questions in the first chapter of the present book.

The role of RNAs, including non-translated RNAs and microRNAs, in gene regulation has recently been brought into focus. Robert Maeda and François Karch examine the Bithorax-Complex (BX-C) of Hox genes in *Drosophila melanogaster* from this point of view and recall that Ed Lewis, who can be seen as the founder of ‘Hoxology’, included as ‘genes’ in his genetic description of this complex, regulatory elements that are now known to correspond to such RNAs, the precise mechanisms of activity of which is still under research.

Another now fashionable stream in current research on gene expression is ‘epigenetics’. In its modern meaning, epigenetics refers to the mechanisms by which gene expression is regulated without changes in the DNA sequence itself. Again, Hox genes provide a useful model. Indeed, expression of the Hox genes in Drosophila is maintained long after it has been initiated. Ed Lewis has studied the first known gene involved in Hox expression’s maintenance. These maintenance factors are, as well as the Hox genes themselves, preserved during metazoan evolution. In Chapter 3, Samantha Beck et al review the present knowledge about Hox genes’ expression maintenance.

Another brilliant finding by Ed Lewis was what he called ‘colinearity’. Indeed, he noticed that the genetic elements, genes and control elements, of the BX-C are arranged along the chromosome in the same order as their region of activity along the anterior to posterior (A-P) axis of the fly. This property is again conserved in most bilateral metazoans. Hox genes cluster in complexes along the chromosomes in most bilaterians. François Spitz reviews in Chapter 4 the recent discoveries in the mammalian Hox complexes of regulatory regions that could account at least in part for the still mysterious colinearity property.

The second part of the book is devoted to the evolution of Hox genes and Hox complexes, in relation to animal evolution. Recent genomic data show that Hox-like genes are present in Cnidaria, thus predating the bilaterian radiation. Still, as argued by Bernd Schierwater and Kai Kamm in Chapter 5, the ‘Hox system’, defined as a complex of Hox genes involved in specifying the identity of the body regions along an axis, is specific to the Bilateria. The authors give an account of the debate on the origin of Hox genes and gene complexes. Then in Chapter 6, David Ferrier reviews the evolution of Hox genes and complexes, from their origin in cnidarians, to their diversification in bilaterians through duplications and losses. The theme of loss is exemplified by the Nematode case in Chapter 7 by Aziz Aboobaker and Mark Blaxter, and that of duplications by the case of the so-called ‘posterior’ Hox genes in Deuterostomes by Rob Lanfear in Chapter 8.
Preface

The third part of the book is devoted to the function of the Hox genes at the organism level. Wim Damen reviews in Chapter 9 the typical role of Hox genes as ‘architect genes’ in the design and evolution of chelicerate body plans. In the ‘Origin of Species’ Darwin viewed the change of function of homologous organs during evolution as “so important”. Change of function was later theorized by Louis Cuénot as ‘preadaptation’ and by Stephen J. Gould and Elizabeth Vrba as ‘exaptation’. In the Hox field, exaptation is exemplified in Chapter 10 by Urs Schmidt-Ott et al. by the evolution of the Hox3/zen gene in Insects. In Chapter 11, Heinrich Reichert and Bruno Bello review the function of the Hox genes in the design of the Drosophila brain. In the last Chapter, I discuss the biological function of the Hox genes in the Bilateria, and suggest that their morphological function, resulting in homeosis when the Hox genes are altered, is derived from a primitive neurogenic function that arose with the constitution of a central nervous system organized along the A-P axis at the origin of the Bilateria.

Prof. Emer. Jean S. Deutsch
Developmental Biology, Pierre and Marie Curie University
Paris, France

REFERENCES

ABOUT THE EDITOR...

JEAN S. DEUTSCH, is a Professor Emeritus of Genetics and Animal Biology, Université Pierre et Marie Curie, Paris 6, Department (UMR 7622) “Biologie du Développement”. Under the supervision of Prof. P.P. Slonimski, he participated to the birth of mitochondrial genetics of the yeast *Saccharomyces cerevisiae*. During the ‘80s, he moved to the Institut Jacques Monod in Paris to study developmental genetics of *Drosophila melanogaster*, focusing on the genetics of the hormonal control of metamorphosis. In 1993, he was the first in France, together with André Adoutte, to undertake evo-devo studies, choosing the cirripedes, which have been Darwin’s favourite animals, as a model, because of their so peculiar body plan. In a second step, his team studied the developmental genetics of other arthropods, including scorpions and pycnogonids. He is author of a number of scientific publications in international journals, and of three textbooks in French on Drosophila and genetics.
PARTICIPANTS

Aziz Aboobaker  
Institute of Genetics  
The University of Nottingham  
Queen's Medical Centre  
Nottingham  
UK

Samantha Beck  
Molecular Epigenetics Group  
Department of Zoology  
Life Sciences Center  
University of British Columbia  
Vancouver, British Columbia  
Canada

Bruno Bello  
University of Basel  
Basel  
Switzerland

Mark Blaxter  
Institute of Evolutionary Biology  
University of Edinburgh  
Edinburgh  
UK

Hugh Brock  
Molecular Epigenetics Group  
Department of Zoology  
Life Sciences Center  
University of British Columbia  
Vancouver, British Columbia  
Canada

Wim G.M. Damen  
Department of Genetics  
Friedrich-Schiller-University Jena  
Jena  
Germany

Jean S. Deutsch  
Developmental Biology  
Pierre and Marie Curie University  
Paris  
France

Floria Faradjji  
Developmental Biology  
Pierre and Marie Curie University  
Paris  
France

David E.K. Ferrier  
The Scottish Oceans Institute  
University of St Andrews  
East Sands, St Andrews  
UK
Participants

Yacine Graba
Institute of Developmental Biology of Marseille Luminy
University of the Mediterranean
Marseille Cedex
France

Kai Kamm
ITZ, Ecology and Evolution
School of Veterinary Medicine
Hannover
Germany

François Karch
NCCR Frontiers in Genetics
and
Departement of Zoology and Animal Biology
University of Geneva
Geneva
France

Thom C. Kaufman
Department of Biology
Indiana University at Bloomington
Bloomington, Indiana
USA

Robert Lanfear
School of Botany and Zoology
Center for Macroevolution and Macroecology
Australian National University
Canberra
Australia

Steffen Lemke
Department of Organismal Biology and Anatomy
University of Chicago
Chicago, Illinois
USA

Robert K. Maeda
NCCR Frontiers in Genetics
and
Departement of Zoology and Animal Biology
University of Geneva
Geneva
Switzerland

Samir Merabet
Institute of Developmental Biology of Marseille Luminy
University of the Mediterranean
Marseille
France

Frédérique Peronnet
Developmental Biology
Pierre and Marie Curie University
Paris
France

Jacques Pradel
Institute of Developmental Biology of Marseille Luminy
University of the Mediterranean
Marseille
France

Ab. Matteen Rafiqi
Department of Organismal Biology and Anatomy
University of Chicago
Chicago, Illinois
USA

Heinrich Reichert
University of Basel
Basel
Switzerland