

## From egg to organism

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The embryo is a remarkable self-assembly machine. From a single cell, the fertilized egg, arises all of the differentiated cell types of the body. Embryos unfold in an elegantly choreographed manner that we strive to understand by observing the process, dissecting it into smaller bits, and mucking up the works by expressing too much or too little of some protein. Yet the mystery remains and, as knowledge and technology advance, we understand more about the depth of its complexity than about the process itself.

Given the beauty and intricacy of the developing embryo, it is a lofty challenge to put the current state of information in a form that is both understandable and captures the imagination of students of biology at the undergraduate and graduate level. Scott Gilbert has met this dual challenge in the latest edition of *Developmental Biology*. He has caught the excitement of the field in a remarkably lucid way. The book starts by building from first principles and defining concepts, and then moves toward the details of morphogenetic processes themselves and what is known about their molecular bases. This book is worth investing in because it has been nicely expanded and updated over the previous versions, and also has much improved graphics.

Although developmental biology has historically deep roots, some of the seminal work of the past is often ignored. Gilbert is keenly aware of this and does a wonderful job of putting the study of developmental biology in historical context. He describes the importance of development for understanding evolution, and discusses how it influenced Darwin's discovery of the origin of the species. He frequently refers to the work of individuals who pioneered different aspects of experimental embryology and made pivotal discoveries that still influence thinking today. He also

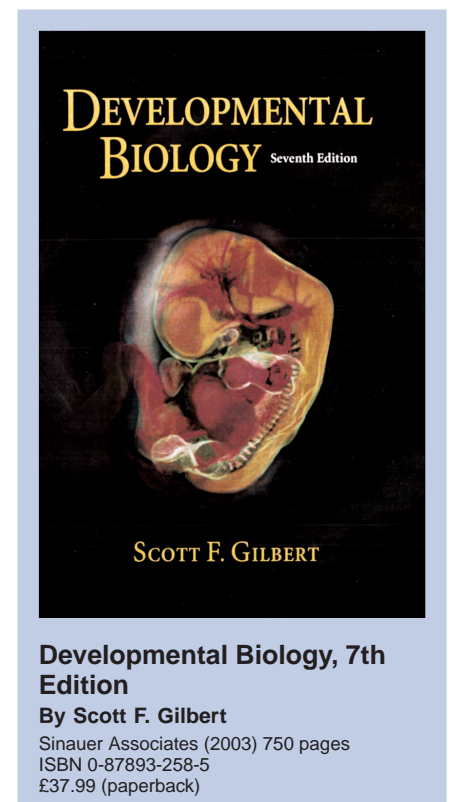
discusses the interesting interface between embryology and genetics, two fields that once were thought of as different disciplines, but that clearly have become integral to one another and are nearly indistinguishable today.

The book does a very nice job of looking at the developing embryo at many levels, from the submicroscopic to the macroscopic. Given the importance of regulatory and coding regions of the genome, and the proteins that they encode, Gilbert provides an excellent introduction into the fundamentals of differential gene expression. He explains basic concepts in cell biology and genetics, particularly those that are integral for developmental biology, such as cell interactions and cell signaling. Furthermore, there is a broad introduction to many different organisms so that the book does not seem too 'vertebrate-centric'. Of course, there is more detail and attention given to the better characterized 'model' organisms, but not at the expense of keeping a broad perspective. Sprinkled throughout the text are excellent illustrations that help the reader visualize the processes under study.

The book is organized into four large sections, each of which is subdivided into chapters. The first section presents the background information that is essential to understanding the concepts of biology, both historically and scientifically. The second section discusses early events in development, starting with fertilization and proceeding to axis formation. The third section deals with particular types of tissues, ranging from the formation of the nervous system to the limb. Finally, the book ends with a discussion of the medical implications of developmental biology and how development can instruct our understanding of evolution and vice versa. This section also includes a nice chapter, contributed by

Susan Singer, that provides an overview of plant development. For those whose primary interest is plant developmental biology, this section may seem to provide too little coverage of this topic and to come too late in the book. It is safe to say that the book is mostly one on animal developmental biology.

In conclusion, I highly recommend Gilbert's *Developmental Biology* to students at both the university and post-graduate level. For that matter, it's a very good read for more advanced investigators as well, and is a good resource for checking up on the latest research in an area that is outside of your own. It is up-to-date and is written in an engaging style that captures the excitement of developmental biology today.



## Liz and Norbert at the movies

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As most of us are aware, today's primary school, high school and undergraduate biology programs are struggling to incorporate even a fraction of the 'molecular revolution' of biological knowledge and technologies that surround us. In the first term alone, life science and biology classes of the new millennia routinely cover condensed versions of the year-long classes taught in the 60s, 70s and 80s. Teachers no longer have the luxury of spending half a year presenting Mendel and his peas.

As many of us appreciate, fruit flies offer a superb means to illustrate basic Mendelian principles to kids as young as primary school age. Among model organisms used in research, the fruit fly is one of the most thoroughly analyzed, and it is appreciated by geneticists, neurobiologists and developmental biologists alike. In addition, flies are a practical choice of school and undergraduate teachers because of their relative ease of handling, their small size, their rapid generation time and, not least, because of their rich array of easily scored and provocative mutant phenotypes.

### Play

However, imagine yourself, if you will, surrounded by 22 eager [read: impatient], inquisitive [read: demanding] and communicative [read: shouting] eleven-year-olds, whilst simultaneously hearing: 'Is this fly a girl or boy?', 'Are these specks pupae or larvae?', 'Is this fly poop?', 'My flies are escaping. Are they going to bite me?', 'But Mendel used peas, right?', 'Teacher, Sandy's gonna be sick!'

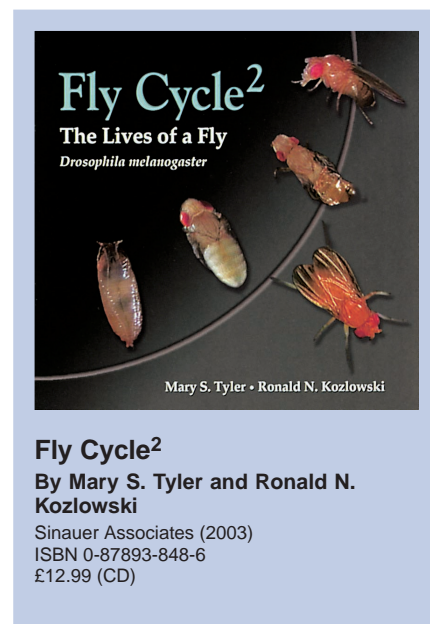
### Stop. Rewind... Play

Now imagine yourself in total control of those same 22 eleven-year-olds while all 44 eyes are glued to the tube [more than likely their favorite activity], with each

of the above mentioned questions answered in living color during a 40-minute educational and entertaining CD-ROM entitled *Fly Cycle<sup>2</sup>*. Joy!

### *Fly Cycle<sup>2</sup>*: the movie

For these reasons, among others, the 40-minute CD-ROM created by Mary Tyler and Ronald Kozlowski, with contributions from Rachel Fink, Shinya Inoue, Dan Kiehart, Eric Wieschaus and Paul Young, should become a welcome and familiar tool for students in biology and genetics classes at primary school and high school, and at undergraduate and even graduate levels.



*Fly Cycle<sup>2</sup>* introduces the viewer to the life cycle of the fly from several perspectives. First, a section on reproduction provides clear and detailed footage of adult courting behaviors and mating [teaching aid: tell the kids it's for adults only]. Second, *Fly Cycle<sup>2</sup>* illustrates beautifully the various stages of embryonic development, larval growth and metamorphosis. Third, a

number of the mutant phenotypes commonly used in introductory *Drosophila* genetics courses are described.

This is not all, the CD-ROM also includes two text files: one that annotates the movie, and a 40-page booklet with additional materials related to *Drosophila* research, instructions for laboratory studies, a glossary and links to online study questions. The movie combined with the 40-page booklet will be particularly useful in undergraduate genetics laboratories. It will not only supplement the student's materials but will help teachers design laboratory exercises that will complement the movie. Undoubtedly, teachers will be able to come up with other creative ways to use and present the information provided in *Fly Cycle<sup>2</sup>*. Overall the movie is a wonderful contribution to the field, and will be appealing and useful to a wide audience from primary school kids to postdoctoral fellows. However, there is room for improvement, with the main drawback being that it provides too little or too much depending on the viewer's level of knowledge. For students just being introduced to the fly, some parts of the movie are too detailed and their attention spans will be tested (e.g. the level of detail on the first 13 embryonic cell cycles will be too much for them). However, this same footage would be highly interesting to advanced students. Likewise, the advanced student will smile at the more basic footage (e.g. how to distinguish a male from a female), whereas younger students will find this most informative.

The target audiences of *FlyCycle<sup>2</sup>* are as diverse as the field of *Drosophila* genetics that it addresses. When making the movie, the authors must have struggled with what to include and what to leave out. For example, oogenesis, so intensely studied today, is not included

in the current version, nor is there presented a practical way to handle and perform genetic crosses.

Perhaps one way to sufficiently address the needs of each target audience is to think of the next step: what will *Fly Cycle*<sup>3</sup> look like? Our suggestion would be to divide future *Fly Cycle*<sup>3</sup> content into sections targeting each audience level. *Fly Cycle*<sup>3</sup> Part 1 could target younger students and fly novices, and could describe the *Drosophila* life cycle, sex differences and mating behaviors, as well as explaining salivary gland chromosomes and showing common

genetic mutations. *Fly Cycle*<sup>3</sup> Part 2 could target more advanced students (those taking lab classes), and could include basic genetic information like how to pick virgins, how to make and follow simple F<sub>1</sub> and F<sub>2</sub> crosses, and how to clone a gene. Finally, *Fly Cycle*<sup>3</sup> Part 3, for the most advanced students, could describe novel visualization methods using green fluorescence proteins to follow specific developmental processes, and could include descriptions of various genetic technologies used in research today.

Stylistically, the movie could be

improved with a more energetic narrative and, particularly desirable, pauses between sentences and subjects, as well as more pointers/arrows to direct the viewer's attention to the structures being described. Finally, although there is a terrific introduction in the movie, the ending is too abrupt and a summary would be helpful.

Nevertheless, we give *Fly Cycle*<sup>2</sup> two thumbs up, we highly recommend it and we look forward to *Fly Cycle*<sup>3</sup>. As far as we are concerned, this educational tool should be promoted, made widely available and developed further.

## Spineless culture

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Invertebrate animals span a huge biological realm of form and function, and have evolved many unique characteristics. The wealth of variety within this diverse group not only contributes to the health of the ecosystem, but also provides a virtually unlimited potential for biological discovery. Models for basic research originally included a large number of invertebrates. However, over the past few decades, most research has focused on a limited number of systems, such as flies and worms, for which molecular genetic technology is easily available. Nevertheless, two things have recently changed this focus: the development of RNA interference (RNAi) techniques to perturb gene expression in diverse organisms and a renewed interest in the evolution of developmental mechanisms. One main caveat to being interested in diverse organisms is the comparable paucity of technical information regarding the handling of tissues and cells from these organisms. Knowing where to begin with any new animal system requires a bit of patience, a certain amount of stubbornness, and, now thanks to Mitsuhashi, a good road map to plan your way through this new unknown.

For scientists initiating tissue culture projects, *Invertebrate Tissue Culture Methods* starts with a detailed introduction into the necessary and suggested equipment needed to properly equip facilities for invertebrate culture research. General principles for establishing and maintaining cultures are discussed, with an emphasis upon those areas most likely to delay the progress of establishing a viable culture. Although media selection can partly depend upon empirical determination, several successful culture solutions are described in the text, which may serve as a template to customize media selection for animals of a specific phyla. In addition, several suggested media additives are described to maintain the proper nutrition and growth of the culture. Once a culture media has been selected, contamination of the culture must be avoided; to this end, frequent sources of contamination are outlined in this book, such as food and bacteria in the gut, as well as from the incompletely sterilized external surfaces of the animal. Avoiding an excess of unwanted blood, which will oxidize to toxic metabolites, including melanin, is another recurring theme in the initial establishment of a healthy invertebrate tissue culture.

Tissues of interest are usually best identified through careful dissection and consultation of available anatomical information. *Invertebrate Tissue Culture Methods* offers a comprehensive array of figures, many of which are focused on the proper identification and removal of a variety of specific tissues from a wide range of invertebrate phyla: Insecta, Prochordata, Echinodermata, Mollusca, Annelida, Nematoda, Platyhelminthes, Coelenterata, Porifera, and various non-insect arthropods. Although the emphasis of the text is on previously reported culture methods for representative members of these invertebrate phyla, one can also extrapolate these methods to new tissue types and organisms. An equally broad portion of the book is devoted to the establishment of whole-organ culture for selected tissues from the above phyla, and this section usefully focuses on those tissues that have been successfully maintained. Techniques for studying developmental processes in embryonic tissues, as well as in imaginal discs and gonadal tissue, are outlined for most phyla, although any given species may not be covered in great depth. Most major organ systems are represented, and are discussed from both a

developmental and a functional perspective, including the nervous system, the circulatory system and hemocytes, intestinal tissues, and species-specific exocrine tissues (such as silk and pheromone glands). Once the appropriate tissues have been removed, there are a number of general methods in cell culture described that can be applied to fit individual experimental design, including protocols for cellular dissociation, subculture and the induction of cell growth.

The concluding portion of *Invertebrate Tissue Culture Methods* focuses on related techniques for the study of cells in culture. These instructive chapters offer general directions for the characterization and manipulation of viable tissue culture. Broadly, these chapters describe the genetic identification of cell lines, methods to evaluate and document cell growth and viability, techniques for optimal photography, and tips for creating large-scale invertebrate tissue cultures. This final section offers a concise compilation of several modern and traditional approaches to the

characterization of cell culture, and is outlined in a protocol-driven style that is accessible and easily followed. An appendix is provided to the main text, listing the various formulations of media, as well as media suppliers, together with an anthology of previously reported continuously cultured cell lines.

There are a number of places where this book could have been improved. While an outline of basic cell culture and sterile techniques will prove useful to the uninitiated researcher, in reality, this introductory section could have been replaced with a reference to any of a number of standard cell culture handbooks. In addition, the section on organ culture could have been expanded to focus on the techniques that currently apply to flies, as the myriad of techniques developed for flies will equally apply for other organisms. Even a table of references for additional fly organ culture protocols would have been useful. Also, the book was short on descriptions of molecular technologies, and this aspect could have been developed to cover techniques such as in

situ hybridization and, in particular, the use of RNAi. However, overall this book will prove to be an essential companion to any laboratory wishing to research non-standard invertebrates.

One of the most exciting features of this book is the new opportunity for discovery that will accompany the reading of this text, and while it could certainly be used as a teaching device in a formal laboratory setting, it is also suited for hands-on use in any invertebrate research lab. As scientific questions of developmental and evolutionary interest continue to probe invertebrate systems, researchers are likely to continue to require a broad source of species-relevant information, and, to this end, *Invertebrate Tissue Culture Methods* provides an excellent resource.

### **Invertebrate Tissue Culture Methods**

**By Jun Mitsuhashi**

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## **Molecules take center stage**

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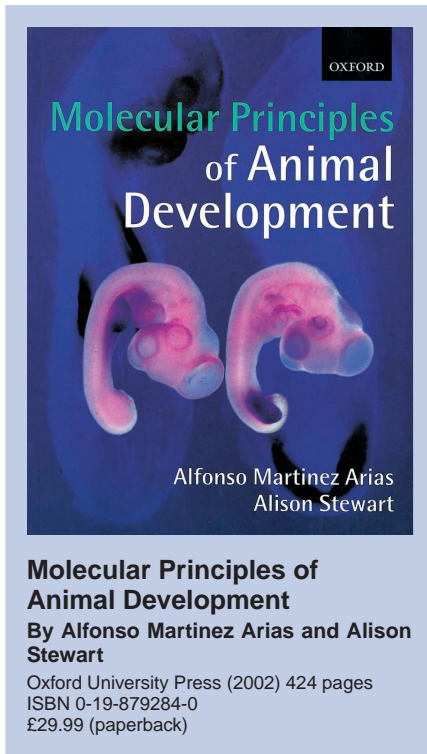
All animals, including humans, begin life as a single cell. During the first few hours of development, that initial cell and its progeny make a series of crucial decisions that ultimately lead to the formation of organs and structures of the adult organism. The principal aim of developmental biology is to understand how these amazing processes occur.

In the past two decades, the explosion of information and novel techniques in molecular biology and genetics has armed modern embryologists with powerful tools with which to dissect the molecular basis of development. Recent studies have illustrated a remarkable conservation of molecular and cellular developmental strategies among embryos of different species. The future of

developmental biology therefore relies on a comparative approach, especially in the post-genome era.

*Molecular Principles of Animal Development* stands perfectly within this context. Martinez Arias and Stewart's rationale is to approach developmental biology, primarily from a molecular perspective. Thus far, traditional textbooks have begun with a description of developmental processes (such as axis formation, gastrulation and organogenesis) in different model systems. Molecular explanations were subsequently provided along the way. In *Molecular Principles of Developmental Biology*, however, molecules take center stage rather than the embryo or its constituent parts.

The book is split into three sections. After a general introduction about the fundamental questions of developmental biology over the past few centuries, chapters 2-5 provide a basic course of molecular biology surveying topics such as transcription, signaling molecules and receptors, signaling pathways, and networks. These four chapters should give the reader the tools to understand the molecular mechanisms underlying developmental events. It is hard to predict, however, if this general overview is rigorous enough to teach a molecular understanding of development to a reader lacking any previous background in molecular biology or genetics. The next section, chapters 6-9, describes the integration of basic molecular



mechanisms into cellular and developmental processes such as cell adhesion, polarity, movement, cell divisions or cell death. Finally, the last three chapters focus on selected topics: how specific cell types are generated (e.g. myogenesis, neurogenesis); and then how specific cell types become organized in two- or three-dimensional patterns (e.g. development of the *C. elegans* vulva, vertebrate limb development, patterning and growth of the *Drosophila* wing).

The final challenging aim of the book, which is very valid, argues for the need to re-interpret all the developmental processes within a molecular framework. The amateur embryologist, however, might be better served with a broader view of events that gradually focuses at the molecular level. For example, it is useless to build up a gene map of embryos without having a clear concept of the fate map and the

ability to correlate gene expression with the spatiotemporal coordinates of the embryo. The Wnt signaling pathway, for example, can exert opposite effects depending on where and when the embryo is exposed to it.

In conclusion, this textbook should be considered as a companion to more traditional texts about developmental biology, and it is clearly useful for advanced graduate students and teachers who already have a background of embryology. Readers will further benefit from the figures and suggested readings. Ultimately, however, we should leave the embryo on the center stage and build up the molecular networks around it. What matters at the end, is not only the understanding of the molecular components, but the overall strategies that an embryo uses to guide its own development.

## Watering down vertebrate development

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Zebrafish are easy and inexpensive to maintain, their embryos are transparent, and their genetics tractable. Thus, they have become a powerful model with which to investigate an enormous variety of problems in biology and medicine. As an example of their increasing popularity, over the past decade the number of zebrafish papers listed on PubMed has increased by over tenfold. With increased popularity comes increased diversity in the organ systems and cell biological processes under study. Until now, to obtain a comprehensive view of zebrafish biology the only sources were: the scientific literature, which is vast and not easily traversed without expert guidance; *The Zebrafish Book*, which needs updating; and the Company of Biologists Zebrafish CD ROM, which is permanently stuck in 1996.

Fortunately, there is hope in the form of a new book, *Pattern Formation in Zebrafish*, which goes a long way towards helping the uninitiated to understand why zebrafish have made such great strides. The editor, Lilianna Solnica-Krezel, was instrumental in the identification of many of the mutations described in the book. She has enlisted some of the top names in the zebrafish community to contribute their perspectives on zebrafish development. Although the book largely focuses on the control of early development, it also features discussions on the development of several key organ systems.

There is something here for everyone. For the embryologist, the first half of the book is a real treat, giving up the secrets of the molecular events underlying axis specification, germ layer identity and

gastrulation movements. Each chapter provides explanation in clear accessible terminology with the salient points reiterated by the various authors, so that the reader will remember what *one-eyed pinhead* is (for example), what it does, and why that name is appropriate and helpful. For the neurobiologist, the relative simplicity of neurogenesis, tract and commissure formation, and neural crest diversification makes it easier to understand the homologous events in higher vertebrates. For the cardiovascular aficionado, mysteries such as the complex morphogenetic movements underlying heart formation, the physiology of heartbeat and the specification of venous versus arterial fates all become more understandable. There is much more and all of it is good. In general, the reduction of complex processes to the molecular detail make for exciting reading.

I found three aspects of the book lacking, however. First, I feel the price is far too high. This is likely to limit sales of what is otherwise an excellent book. Graduate students, who would benefit most from the book, will probably find it unaffordable. Second, there are some notable absences in the book. The recent genetic work on ear development in zebrafish has uncovered new aspects of the mechanical basis of hair-cell function

but it is not discussed at all. My personal favourite embryonic structure, the notochord, is essential for vertebrate development but is only mentioned in passing and then only in the context of other systems. Finally, I found the index to be incomplete and thus not very useful. There are many examples of gene or mutant names where only a few of the citations are listed in the index. These minor criticisms aside, I think the book is

extremely helpful and expect most zebrafish laboratories will want to have a copy close at hand.

### Pattern Formation in Zebrafish

Edited by Lilianna Solnica-Krezel

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## What you didn't know about evo-devo

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The field of evolutionary developmental (evo-devo) biology is populated with scientists from diverse disciplines who are seeking the answers to questions that have been asked for millennia: why do organisms look different, how are these organisms built, are there common themes to how they are built, are there rules governing the evolution of organismal form? The surprise of evo-devo over the last few decades is that a reductionist approach, molecular developmental genetics, has repeatedly determined that the same genes are involved in building divergent organisms. One might decide therefore that morphological evolution is now understood: it is 'simply' the evolution of regulation of a conserved 'tool box' of genes combined with rare but important events like gene duplication and changes in protein function. It is easy to get caught up in recent progress towards explaining diversity at the molecular level, and to forget, therefore, how much of diversity remains unexplained and how instead of answering many questions about biological diversity we have simply failed to recognize them as problems.

We should therefore welcome attempts to bring our attention to broader themes and overlooked issues. This is just what Alessandro Minelli attempts to do for macro-evolutionary questions in his

recent book *The Development of Animal Form: Ontogeny, Morphology, and Evolution*. Minelli seeks a unification of evolutionary and developmental biology, and believes that this requires a philosophical shift by participants in evo-devo. He encourages workers to view the entire life cycle as development, not just the embryonic patterning phases, and to keep in mind that selection acts upon all these stages, not just upon the final adult form. This is a truism for evolutionary biologists, but perhaps a novel perspective for some developmental biologists. Minelli also questions the prevalence of what he calls 'finalism' in developmental biology, or the idea that all of development is directed towards the goal of producing the adult form. He points out that we long ago shed the notion that animals evolve inexorably towards 'higher' forms. Why haven't developmental biologists recognized, therefore, that development is not goal directed? I'm not convinced that this analogy is apt and I'm also not convinced that such finalism is common in developmental biology. Open the pages of any developmental biology journal more or less at random and you will find research delving into the details of developmental mechanisms, often with little concern for the consequences for the adult phenotype. There may, however, be a grain of truth in Minelli's criticism. Evo-

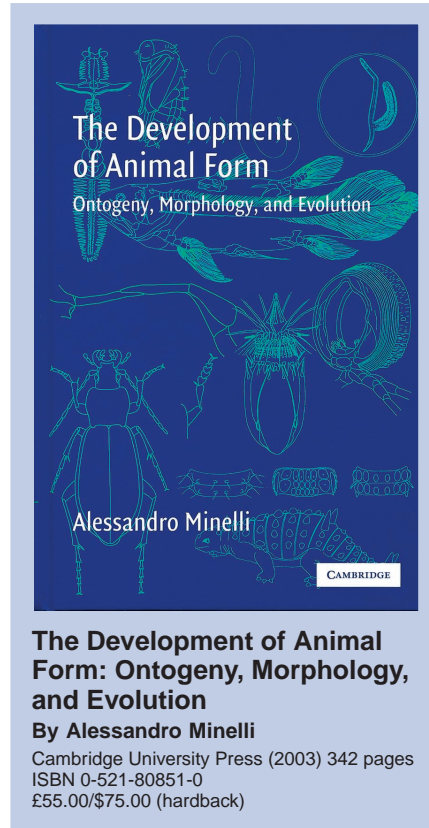
devo workers have been quick to infer organ homology from a few embryonic gene expression patterns. It is now clear that such comparisons, even when they involve more than just a few expression patterns, are fraught with difficulty, particularly when they are performed in the absence of phylogenetic information.

Minelli is also concerned that most of the experimental knowledge used to address evo-devo questions is derived from studies of a handful of model systems. There is, however, every indication that investigators will continue to expand the list of animals under study and that tools are being developed for functional assays in 'non-model' organisms. So I view Minelli's concern as a short-term issue. Nonetheless, he points out a number of unusual phenomena in little-studied animals and these 'exceptions' may provide key insights into the 'rules' of evo-devo.

Minelli revisits several subjects he has published on elsewhere, including paramorphism (the idea that limbs are in some way homologous to the main anteroposterior body axis), and various concepts related to segmentation, including the idea that segments are not only made in different ways between taxa but also within a species. I found

the chapter on segmentation the most frustrating because I could not get a clear grasp of how Minelli's concepts differed from our current understanding of segmentation in *Drosophila* and vertebrates. Minelli introduces the concepts of holomeric segmentation, which produces 'true' segments (eosegments), and meromeric segmentation, which produces segmentation within an eosegment. However, Minelli writes 'This is not the place for reviewing in detail the mechanisms by which segments are made in annelids, arthropods, and vertebrates' (p. 195). Where is the place, then? What precisely is the relationship between the *Drosophila* segmentation cascade, and eosegments and merosegments? This is an extreme example of Minelli's conversational tone. Those who already understand the molecular genetics of segmentation and the terminology associated with segmentation in comparative morphology may find gems in this chapter. The rest of us are left out in the cold. If Minelli wants evo-devo biologists – who traditionally have either a strong background in development or in evolutionary biology – to sit up and take notice, then he needs to make the connections more clearly.

This is not a text for undergraduates, and I suspect that many readers, particularly those with poor training in either developmental biology or comparative zoology, will be lost in places. For example, Minelli refuses to explain



many of the developmental arguments that require a thorough prior understanding of the contemporary development literature. He writes 'There is no need to...explain the concept of the Hox code...or to discuss colinearity' (p. 47). Although most students trained in developmental biology won't need this explanation, most trained in evolutionary biology will. The reverse may be true for the comparative

morphology terminology scattered throughout the book, although I fear that most students trained in contemporary evolutionary biology will be more familiar with models of linkage disequilibrium than with the terminology of comparative morphology (I speak from experience). The figures are poorly labeled and will confound those with a limited training in comparative morphology. I found a number of errors of citation for the literature I know, which made me wary of the remaining citations.

My overall impression of the book is that it is like having a conversation with the author. He touches upon many issues that he has clearly thought about deeply and scatters provocative ideas throughout the text. Every time I started getting lost in the ideas, he threw in a fascinating example; every time I lost track of the examples, he threw in a surprising idea. These ideas and examples are not always clearly connected and the arguments are not tightly argued, but the book wraps up with a satisfactory summary that, in my view, should have been the introduction. The book raises far more questions than it answers (I'm not sure it answers any), but that appears to have been Minelli's goal. For the prepared mind, and the mind prepared to focus on essentially macro-evolutionary issues, this is a worthwhile conversation with Minelli.

## Vertebrate patterning: how to cross-stitch an embryo

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'Life forms illogical patterns. It is haphazard and full of beauties which I try to catch as they fly by, for who knows whether any of them will ever return?'

I doubt the dancer Margot Fonteyn was ever a student of developmental biology; however, if she was, she would have

appreciated that vertebrate embryonic development is a truly mesmerizing and beautiful process.

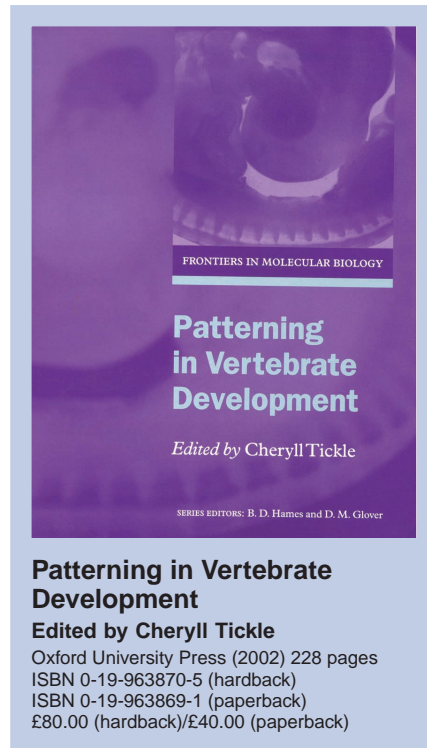
In *Patterning in Vertebrate Development*, Cheryl Tickle has compiled a comprehensive account, contributed by well-known developmental biologists,

that provides a fascinating insight into the complexity of vertebrate development and the consequences of patterning gone awry. Each chapter focuses on several species and emphasizes the recent genetic discoveries that underpin the molecular basis of vertebrate patterning. Patterning is the mechanism

that coordinates cell position, proliferation and differentiation during embryogenesis, and is mediated by cell signaling interactions, of which morphogen gradients are of key importance. This complex mechanism ensures that characteristic features such as the head, limbs, nervous system, organs, and even individual cartilage and bone elements, such as the vertebrae, develop in the correct location with the appropriate size and shape.

One of the major questions in developmental biology is how cells acquire positional information. It is therefore very fitting that the opening chapter of the book introduces us to morphogen gradients and the concept that cells acquire positional information based on their abilities to respond to differential levels or thresholds of a signaling gradient. This provides the perfect introduction to the chapters that follow, which can be broadly categorized into three themes: (1) body axis and mesoderm patterning; (2) central and peripheral nervous system development; and (3) limb and evolutionary development.

What is clear in each section is the underlying importance of morphogen gradients and the reiteration of similar signaling pathways in quite distinct developmental processes. For example, the second chapter describes establishing the vertebrate body plan and highlights the fact that despite the significantly distinct geometry and morphology that exists between frogs, fish, mice and birds, the determination of polarity and the process of gastrulation are remarkably similar. It was Lewis Wolpert who famously and appropriately said, 'it is not birth, marriage, or death, but gastrulation, which is truly the most important time of your life'. To any embryo, the failure to gastrulate properly is terminal. Following on from gastrulation, the mesoderm theme continues with the exploration of somite and axial development, and in particular discusses how a genetic oscillator patterns unsegmented mesoderm into somite blocks. We also learn how somites differentiate to give rise to a reiterated pattern of vertebrae and muscles and how these are specified in an



anteroposterior fashion primarily by the Hox genes.

By far the largest section of the book describes the patterning of the nervous system. The importance of a coordinated integration of positional information is no better illustrated than in the complex development of the adult central and peripheral nervous systems. Beginning with a chapter on neural competence and neural plate induction, we then discover how the neural plate becomes regionalized both anteroposteriorly and dorsoventrally in response to local signaling gradients. This is augmented by a discussion of the mechanisms that control axon guidance, which ultimately provides the essential scaffolding upon which the elaborate cytoarchitecture of the brain and spinal cord are superimposed.

The remaining one-third of the book, which I particularly enjoyed, covers the migration and patterning of neural crest cells, as well as limb patterning, and is rounded off by a final chapter that describes the importance of these tissues in vertebrate evolution. Neural crest cells give rise to an enormous number of cell types, tissues and organs during vertebrate develop-

ment, and are synonymous with craniofacial evolution and the transition from a sessile to a predatory lifestyle. Similarly, the formation of paired fins and tetrapod limbs helped to usher the vertebrate invasion of land, and we are beginning to understand the genetic basis of the distinction between forelimbs and hindlimbs. Fittingly, the final chapter on the evolution of vertebrate patterning describes these major evolutionary transitions and reinforces many of the ideas that arise in the preceding chapters on neural crest cell and limb development. This chapter also touches on distant extant vertebrate relatives, such as amphioxus, lampreys and ascidians, all of which have contributed enormously to the understanding of vertebrate evolution through studies of comparative genetics and anatomy.

The trouble with any book these days is that the field of developmental biology is moving so rapidly that many ideas become outdated or surpassed very quickly. For example, there appears to be increasing evidence that a link might exist between the oscillator or somite-clock mechanism and Hox gene patterning, which might facilitate the coordination of body plan segmentation with anteroposterior patterning. This recently emerged topic is discussed only briefly in this book. Similarly, the field of neural crest cell and craniofacial development has hotly debated whether cranial neural crest cells act cell autonomously or are plastic and responsive to the environment; the current consensus is that both mechanisms play important roles. This debate is also only briefly touched upon in this book, as the neural crest chapter mainly covers the development of the trunk neural crest. Overall, however, this book provides a concise yet comprehensive insight into the major events that occur during vertebrate embryonic patterning and should prove to be a valuable resource for researchers and the more advanced students of developmental biology.



## Building a better brain

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A six-layered cerebral cortex is a uniquely mammalian structure and is the center of cognitive function. The processes and genetic controls that govern its development are subjects of intensive study and have captured the attention of many developmental biologists. One major goal in this field is the identification of the factors and pathways that control the generation of precise numbers of the principal cell types within the cerebral cortex: neurons, oligodendrocytes and astrocytes. A second major goal is to understand how these building blocks are targeted to the different structures within the cortex, and how they are interconnected to establish functional networks.

The understanding of the ontogeny of the cerebral cortex requires us to understand not only how this structure is built in a step-by-step fashion, but also how this innate program is designed to interact with environmental influences to promote plasticity. Although this is an immense challenge, we need to have a full understanding of the developmental program of the cortex in order to gain an appreciation of how we think. To borrow a commonly used phrase, understanding the cortex is to understand how we understand.

*Cortical Development. From Specification to Differentiation* presents a concise description of several of the key steps that occur during the development of the cortex. This is the first volume to be published in a two-volume set and concentrates on 'early' events in ontogeny – issues relating to cortical cell generation/specification, migration and early differentiation. In this volume, Hohmann has selected a cross-section of what she and many in the field would consider to be the most pertinent and exciting areas in current research on cortical ontogeny.

The book is divided into eight chapters, which have been written by different experts in the field and build upon different themes following a more-or-less temporal course through cortical development. Richard Nowakowski et al. beautifully summarize years of collaborative work on the developmental dynamics of cell proliferation in the cortex. This work led to several key advances in the field, including the description of cell cycle regulation in the generation of cortical cells. Mark Mehler, in the first of two chapters that he contributes, focuses on mechanisms of lineage diversity and the role of the bone morphogenetic proteins, fibroblast growth factors (particularly FGF2), sonic hedgehog and basic helix-loop-helix molecules in this process. In his second chapter, he studies regional patterning and neural subtype specification under both morphogen and transcriptional regulation. These mechanisms serve to create the numerous distinct types of cells that constitute the cortex, and we learn of the relationship of these pathways to neurodegenerative diseases.

Later events in cortical development are covered in the subsequent chapters. For example, Bernd Sutor discusses gap junctions and their possible role in establishing early neuronal circuits, while Marcin Gierdalski and Sharon Juliano provide an overview of neuron-glia interactions and their role in neuronal migration. This chapter also covers the reeler pathway (in which reelin is secreted from a small group of cells and influences migration of most or all neurons arriving in the cortex), as well as the authors' own work on the methylazoxymethanol (MAM) model of cortical dysplasia, and its relevance to the reeler pathway. Several of these chapters also discuss the processes and molecules that are important for synaptic development and cortical plasticity. For example, A. Kimberly McAllister

discusses neurotrophins and their role in dendritic growth and synaptic plasticity, and Alvin Lyckman and Mriganka Sur discuss neuronal re-wiring plasticity in a fascinating model in which the visual input fibers of a ferret are re-routed to the auditory processing centers. In this model, ferrets are capable of using the re-wired auditory cortex to respond to light as a visual, rather than as an auditory, stimulus. The molecular characterization of this model and its future downstream applications, such as strategies to identify differential gene expression, are discussed. The relevance of the immediate-early genes [such as activin, NARP (neuronal activity regulated pentraxin) and homer], which are activated by an initial cascade of gene expression that is triggered by an extracellular signal, are also discussed in the context of synaptic development and cortical plasticity by Katrin Andreasson and Walter Kaufmann.

Increasingly, successful inquiry in the neurosciences depends on strongly interdisciplinary approaches. The interdisciplinary nature of the chapters is one of the great strengths of this book. However, there is little inter-relatedness or synergy developed between many of this book's chapters, despite there being much repetition between many of them. That said, each individual chapter does stand alone and provide a detailed view of the role of each of the highlighted molecules and pathways in the construction of the cerebral cortex. Neurodevelopmental biologists may also notice that there is a paucity of loss-of-function data that is customarily used to support the types of

### **Cortical Development. From Specification to Differentiation**

Edited by Christine F. Hohman

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£76.50/\$129.00 (hardback)

arguments that are presented in this text. An uninitiated developmental biologist might therefore choose a textbook that provides a broader view of these events. In addition, the emphasis on synaptic plasticity in the later chapters does not dovetail well with the issues of

embryogenesis that are presented in the book's earlier chapters.

These minor criticisms aside, this book helps fill a void in developmental neurobiology by providing a starting point for researchers and for other more

advanced students who are in search of an update by authorities of the field of cortical development. It will also help to educate the reader on a number of different specialties that are key to understanding the pathways that underlie the building of the brain.

## Embryos at the core of life

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Writing a textbook on developmental biology is, today, a dangerous task. The amount of data being produced in labs all over the world overwhelms every effort to be up to date, or to be fair to every developmental biologist in the business. Today, the study of developmental biology entails a vast array of conceptual frameworks, methodologies and exploration tools, making it all but impossible to cover ad extenso the sources, applications and directions of research. As a result, textbooks on developmental biology, while trying to cover as much ground as possible, have to focus on some specific issues. The convergence of genetics and embryology on the key problems faced by developmental biologists makes both disciplines absolutely necessary in an entry-level book such as this one. A winning book also has to look at mechanisms that bridge genetics and embryology to show how regulatory gene networks relate to cell biology, hint at the relationship between development and evolution, and demonstrate the richness of the interface between development and other sciences, such as mathematical modeling.

This is the case with *Principles of Development*. The first striking aspect of this book is its impressive list of authors – scientists who have all been instrumental in shaping the basic research and fundamental findings that comprise the core of developmental biology today. Equally impressive is the lengthy and astonishingly authoritative list of chapter editors, although, as Lewis Wolpert admitted, “I did all the writing”, while his co-authors were in

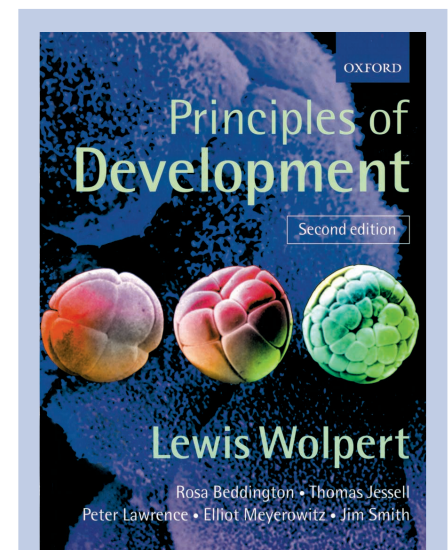
“permanent consultation”. The present book is a second edition (the first edition was published in 1998) that includes some crucial findings from the past five years. Needless to say, the first edition, along with the now classic *Developmental Biology* by Scott Gilbert (Sinauer Associates), has played a fundamental role in introducing college students to the difficult issues and problems that face our science.

### Content of the book

The structure of the book is logical, much like the acute mind of its main author, as those who are lucky enough to know Lewis are well aware. It moves effortlessly from the general to the specific and back to the general, reminiscent of the harmonious deployment of a Mahler symphony. *Principles of Development* is divided into 15 chapters. Opening with a short history on the beginnings of the field, it then delves into the vertebrate, invertebrate and plant model systems that are used in everyday research, and provides a short introduction into gene identification protocols. Next come chapters dedicated to early pattern formation events in vertebrates (particularly frogs, chicks and mice); Chapter 3 takes us through body axes and the formation of the three metazoan embryonic layers, endoderm, mesoderm and ectoderm, and Chapter 4 digs a bit deeper into mesoderm patterning events and the formation of the neural system. Chapters 5 and 6 are devoted to invertebrate embryogenesis, and review the most important model systems: the almighty *Drosophila*

*melanogaster* (which has been given, and no doubt deserves, the whole of Chapter 5 as a result of its fundamental role in helping to attain our present knowledge of developmental processes) and those other heroes of experimental lore, nematode worms, sea urchins, ascidian tunicates and slime molds. Chapter 7 outlines the exciting world of *Arabidopsis thaliana* and plant development in a concise, albeit very pedagogic, manner.

An excellent entry point into the generic processes of development is provided by



### Principles of Development, 2nd Edition

By Lewis Wolpert, Rosa Beddington, Thomas Jessell, Peter Lawrence, Elliot Meyerowitz and Jim Smith

Oxford University Press (2001) 568 pages  
ISBN 0-19-879291-3  
£31.99 (paperback)

Chapters 8 and 9, which discuss the morphogenetic processes and cell dynamics that generate form and cell differentiation, and the molecular mechanisms that underpin cell specialization in the embryo. In Chapters 10 and 11, the book moves on to the specifics of structure formation in chick limbs, the nematode vulva, insect wings and legs, and internal vertebrate organs, such as the heart, lungs, kidneys and nervous system. Chapter 12 describes the formation of germ cells and the mechanisms of sex determination, as well as the details of fertilization events (one wonders why this chapter is almost at the end of the book!). Chapters 13 and 14 deal with the important issues of regeneration and growth, issues that, today, touch upon the very hot topic of stem cell research. The closing chapter attempts to bring together two often-separated issues in modern biology: development and evolution. However, this last topic could have been covered more extensively to explain to students how development can help in explaining the origination of novel features in evolution, which is the last bone of contention used by creationists to criticize evolutionary theory.

In summary, this excellent book covers most of the recent findings and general knowledge of current developmental biology. Perhaps a whole chapter dedicated to theoretical concepts and mathematical modeling could have been added, as this would have provided an entry point to those rare, but much needed, students who want to venture into cross-disciplinary roads. Subjects such as bioinformatics, tissue engineering, and mathematical modeling of regulatory gene networks and cellular dynamics would also have very much enriched the contents of the book.

### The principles of development

An interesting paradox lies at the heart of the discipline of developmental biology. On the one hand, there is an emphasis on genes as the controlling operators of development. On the other hand, there is an explicit recognition that cells are the actual 'units of development' and that cell behavior provides the crucial link between genes and development. Wolpert introduces the concept of 'luxury' proteins as those

that are specific for cell types, but how does a knowledge of these proteins further our understanding of embryogenesis? By focusing our attention on these genes and proteins we reduce the whole of developmental biology to 'differentiation', a narrow path indeed. Instead, the truly important question we must ask in development is about generic cell behavior. How do genes and proteins affect cell proliferation, cell growth, cell migration, cell adhesion and cell death? From here, the next bridge to cross is that of the generic properties of embryonic tissues. How does cell behavior determine the making of epithelia, of mesenchyme, of sheets, of tubes or of vesicles? Only then can we begin to understand how organisms develop.

Wolpert, along with his high-profile editors, certainly recognizes these issues. *Principles of Development* tries hard to provide an array of specific answers to all of these issues, but sometimes from questions that are too genocentric. Development is not only about how the genotype controls the phenotype, but also about how information deploys and increases from rather meager information units, such as genes, into the rich complexity of a developing embryo. Despite an explicit definition of developmental biology as a discipline that "*deals with the process by which the genes in the fertilized egg control cell behavior in the embryo and so determine its pattern, its form, and much of its behavior*", Wolpert's scientific career has been built upon the recognition that many interacting forces are at play during development and that the emergence of new levels of complexity act together to shape the organism.

For example, Wolpert's positional information and gradient formation model can be found several times throughout the book as it applies to different scenarios (e.g. the response of ectodermal cells to activin, the development of anterior structures in *Drosophila* as a response to bicoid, or the formation of compartment boundaries, to mention just a few). The establishment of these gradients depends upon many interacting factors involving the cell and its environment. It

is the appearance of these and many other complex interactions that prevents development from being treated in a genotype-specifies-phenotype fashion.

Thus, the introductory chapter warns against taking genes as the ultimate cause of development, and on page 15 we find the following illuminating comment:

"...gene expression is only the first step in a cascade of cellular processes that lead via protein synthesis to changes in cell behavior and so direct the course of embryonic development. To think only in terms of genes is to ignore crucial aspects of cell biology, such as change in cell shape, that may be initiated at many steps removed from gene activity."

Indeed this is the case: much must happen from the moment a gene is expressed to the actual formation of an organ. Inside the cell cytoplasm, molecular interactions exhibit complex dynamics, including positive and negative feedback loops, oscillatory phenomena and cooperative enzymatic actions. Most importantly, cells act together and in coordination to exhibit emergent behaviors that cannot be deduced from the molecular interactions of the individual cells. Again, Wolpert is not taken off-guard, a great deal of these fascinating issues are delivered in Chapters 8 and 9, with an emphasis in linking morphogenetic processes to intracellular molecular interactions. The old search for how the linear information encoded in DNA specifies a three-dimensional organism needs to be transformed into a search for how the linear information of DNA is translated, reprocessed and spatio-temporally deployed across network levels (molecules, cells, tissues, organs, the whole embryo) into a three-dimensional organism. Textbooks about developmental biology need to emphasize this if we want to educate a new generation of developmental biologists that are able to bring more integrative views to our science.

### Textbooks a thing of the past?

If writing a textbook these days is a dangerous task, then reading it, and poring over its sections and subsections, headings and definitions is an act of love.

It strikes us as something from a past, romantic era – hardly 5 years ago – when RAM memory was still expensive, when bringing home a 1 Ghz computer was possible only for rich students, and when high-speed Internet access was only a dream. If there is a class of people that knows how to use computers and browse the Internet, it is undoubtedly college students. The future of academia lies

within the Internet. The possibilities are endless: simulations, virtual rooms with virtual three-dimensional reconstructions, pages and pages of illustrations, and almost infinite cross-hyperlinks between different sources. We are sure that publishers have the same vision of gathering academic data in places where everyone, regardless of geographic situation, can visit and use it at leisure.

Indeed, *Principles of Development* can be visited at the Oxford University Press website, where some of the text and all of the book's pictures have been made available to the public. We welcome this initiative as well as Lewis Wolpert's effort in bringing this unique updated version of the core of development to the biology classroom.

## All at the tip of a needle

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I remember my excitement at opening the first edition of *Manipulating the Mouse Embryo* in 1986. I had just established my own transgenic mouse colony in Boston and was struggling with problematic animal-housing arrangements, cumbersome genotyping techniques and a skeptical reviewer of our first paper on the subject (“this study merely confirms in vivo what the authors have already demonstrated in cell culture”, the curmudgeon wrote). The technology was still in its infancy, and far from routine for an aspiring transcription factor jock like myself, but this book provided detailed instructions on how to address all the burning questions I had about mouse development, and validated my tentative plans to extend my previous studies of gene regulation using recombinant DNA technology. The secrets of mammalian embryogenesis were finally accessible to molecular biology, no matter what my grumpy reviewer thought.

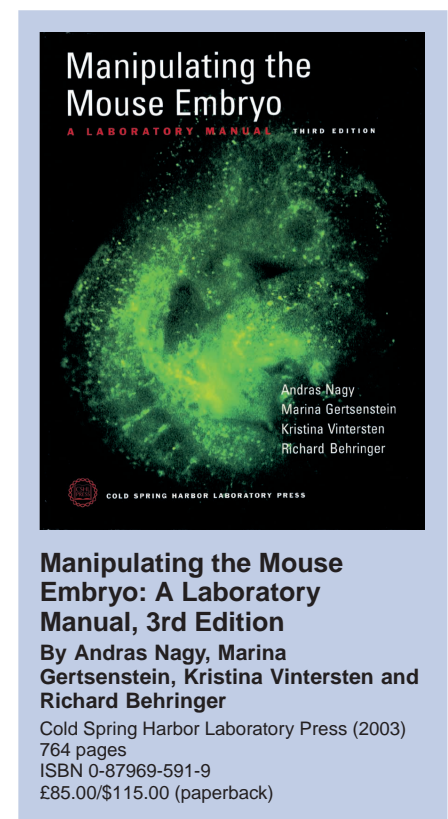
The Year of the Mouse Genome, 2003, is an auspicious launch date for the latest edition of this inspirational laboratory resource. Long regarded as a living bible of mammalian embryonic manipulation techniques, the updated third edition fulfills this mandate. It has been completely reorganized and expanded in the talented hands of the new authors, all leaders in the fields of mouse development and genetic manipulation. Andras Nagy and Marina Gertsenstein have championed chimeric analysis in

mouse embryogenesis, and are known for their collective expertise in conditional regulation of the mouse genome. As former head of the mouse transgenic core facility at EMBL, Kristina Vintersten has years of hands-on experience, and is a trusted authority on the nuts and bolts of mouse manipulation. And Richard Behringer, a renowned mouse geneticist, adds his profound knowledge of mammalian development to the mix. It's a great team.

At 764 pages, this tome is half again the size of its predecessor, and is bursting with fascinating concepts and clever techniques. The excellent historical background chapter has been retained and updated, as has the one on mouse development. Chapters covering the basics of transgenic mouse production, embryonic stem cell handling and genetic manipulation have been expanded, and state-of-the-art protocols are presented in an accessible style with more extensive troubleshooting sections. For fields in which significant advances have been made, such as in imprinting, the sections have been extended accordingly. The chapter on chimeras has been broadened and makes the technique seem readily accessible. My lab has never made a chimera but, as I read, I found myself thinking of the many ways I could use this approach.

An impressive amount of new material has been added as well. Explanatory text

and figures reveal the trade secrets of mouse cloning, assisted reproduction strategies (including intracytoplasmic sperm injection and in vitro fertilization) and whole embryo culture systems. Other novel features include DNA electroporation and reporter gene expression in living embryos, the uses of plastic casting to capture morphological anomalies, and other techniques for



visualizing gene products, cells, tissues and organ systems. On the molecular side, the section on vector design (Chapter 9) presents the latest conditional and inducible gene strategies, the ins and outs of BAC and YAC cloning, and novel reporters. Although I found the icons used to denote the DNA manipulations too small and hard to follow, an exhaustive array of gene expression tips and pitfalls makes this section a definitive resource and teaching tool. There's even a companion website with supplier links and information, Medline-linked references, and links to other databases of value to scientists working in this field, which has the advantage that supplementary information can be added after the book is published.

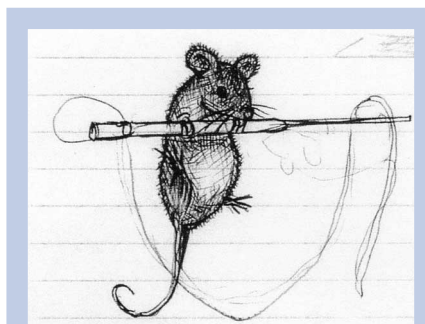
Reorganization of the book was necessary, given the amount of new content, and has made this third edition more practical. Easy-to-find references have been collated at the end of each chapter. A glossary of the mouse genome in the second edition was rather inadequate and has been omitted – it's a field in itself by now – and surgical techniques have been grouped together in one very helpful chapter. However, there are some confusing aspects to the new order. Whereas the misleadingly named Chapter 3 (Production of Transgenic and Chimeric Mice: General Issues) is primarily about establishing transgenic mouse colonies, Chapter 7 (Production of Transgenic Mice) is more technical, with important molecular information and detailed protocols. In all fairness to the authors, such a complex package makes it hard to know which should come first, the chicken (sic) or the egg.

There are some practical additions, such as a detailed 'how to...' section on setting up your own micromanipulation lab that will be of great value to scientists just starting out, and to established research groups switching to the mouse model. There is also a cautionary appendix that expounds the dangers of hazardous materials used in the protocols. Of particular relevance in this time of exploding mouse colony sizes, escalating animal costs and

limiting housing space, when getting mice off the shelf is becoming an increasingly pressing priority, is the section on embryo and gamete cryopreservation and re-derivation. There is even an informative discussion of mouse colony trends (we've come a long way since 1986!).

The book looks classier too. Many of the cartoons, including fate maps of early mouse embryogenesis by the incomparable artist/scientist Rosa Beddington (an original author of this manual, see Fig. 1) have been retained; however, other diagrams have been redrawn to illustrate the techniques more clearly. New colour photographs show real-life results of current genetic strategies. Alas, the old ring-book format is gone, presumably a casualty of the volume's increased girth, but the sturdy spine of the current paper edition will hopefully stand up to the constant thumbing and flattening on the lab bench that have dog-eared my two previous editions.

So what's wrong with this edition? Not much. But well, let's see, there's no heart development in the embryology section. This subject mysteriously didn't rate in the second edition either. Call me biased (alright, I admit I work on heart development), but the lateral mesoderm gives rise to more than the kidneys. The heart is the first organ to form and function in mammalian development, and its prominent and easily visible position during mouse embryogenesis makes it a very helpful signpost.



**Fig. 1.** Sketch by Rosa Beddington. Courtesy of NIMR (London, UK).

I would have also liked to see a compendium of protocols listed somewhere in the book, and a bit more cross-referencing would have been useful. For example, Protocol 1 on p. 435 (Electroporating DNA into ES cells and selection methods) is related in subject matter to Protocol 1 on p. 469 (Preparation of ES cells for injection). While we are on the subject of cross-referencing, the index is regrettably uneven. I will forgive the absence of cardiovascular terms (the words heart, cardiogenesis, circulation and vasculogenesis, didn't even make it into the index, and I checked, heart-brokenly). Omission of the term 'gene knockout', on the other hand, is a more serious oversight, particularly as none of the chapter headings lead the uninitiated reader to the appropriate pages (knockouts are discussed in Chapter 9, 'Vector design for ES cell-based transgenesis and genomic alterations', for those of you who were wondering).

In the greater scheme of things these are trifling concerns, especially considering the breadth of scope and depth of coverage the authors have achieved. I agree with the Cold Spring Harbor Laboratory Press promotional blurb that this book is the "premier authoritative and comprehensive source of technical and theoretical guidance for mouse developmental biologists and geneticists". It is helpful whether you are tempted to start your own mouse facility, or merely interested in making a single transgenic or knockout animal. It includes a marvelous summary of our current understanding of mouse development, and offers students and teachers alike an updated approach to mammalian genetic manipulation. It is brimming with useful and exciting information for the adventurous postdoc who is ready to embark on the generation of a conditional mutation, and it is a one-stop shop for the seasoned developmental geneticist looking for the latest tricks of the trade. But the best thing about this book is the sense of exuberance that these authors convey about their subject. You can feel their enthusiasm radiating up at you as you read. It is a tremendous time to be a mouse biologist. I am still as excited as I was in 1986.