

Animal Anomalies

What Abnormal Anatomies Reveal about Normal Development

Among the offspring of humans and other animals are occasional individuals that are malformed in whole or in part. The most grossly abnormal of these have been referred to from ancient times as monsters, because their birth was thought to foretell doom; the less severely affected are usually known as anomalies. This volume digs deeply into the cellular and molecular processes of embryonic development that go awry in such exceptional situations. It focuses on the physical mechanisms of how genes instruct cells to build anatomy, as well as the underlying forces of evolution that shaped these mechanisms over eons of geologic time. The narrative is framed in a historical perspective that should help students trying to make sense of these complex subjects. Each chapter is written in the style of a Sherlock Holmes story, starting with the clues and ending with a solution to the mystery.

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Cambridge University Press
978-1-108-83470-4 — Animal Anomalies
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“Orthodoxy is so rife in science these days it is strangling originality. The spread of ‘best practice’ as well as the related belief that there is only one ideal way to understand and explain things has stifled both diversity and imagination. It is increasingly commonplace to explain a natural phenomenon by confusing the consensus view with the truth. There has been a growing dependence on a few model systems such as the mouse, *Drosophila*, and *C. elegans*; this pragmatic approach has proved successful, but it is also confining and a bit dull.

Lewis Held shows us there is another way – to look at the natural world open-mouthed and open-minded. We are taken on a lively ramble through myriad natural phenomena in countless species and the attempts of scientists to understand them. There is an infectious sense of the wonder and complexity of everything. There are innumerable nuggets to be found and it is fun. As Professor Held says in his introduction: ‘Tedium is the bane of textbooks, and I wanted to write a more whimsical opus.’ He has succeeded: his book sings like the descant in a choral rendition of a familiar hymn. I recommend it, but don’t try and read it all in one go!”

Peter A. Lawrence
University of Cambridge, UK

“With rigorous arguments presented in captivating prose and crystal-clear drawings so rich in information, this new masterpiece by Lewis Held is a unique introduction to the genetics of development. Here, monstrous and normal illuminate each other, as products of the same developmental logic. This book is full of inspiring insights, on a par with the works of the great developmental biologists highlighted in its pages.”

Alessandro Minelli, University of Padova, Italy, and author of
Understanding Development



Cyclopic male goat from a Boer goat breed stock, which was born in 2012 on a farm in Saint Lawrence (near Midland), Texas [1325]. This kid, which had a normal twin sister, is being held by Garry Batla, a son of Delmer Batla, the farm's owner. Delmer's granddaughter Kendra sent this picture to *Ripley's Believe It or Not!*, where it was published in the 10th edition of their annual book series. The Batlas fed the kid with an eyedropper because its mouth was too deformed to suckle, but despite their loving care it lived for only two weeks. They never gave it a name.

Cyclopia, which affects humans also, is normally a rare condition [221,309,1153], but on one occasion it occurred as an epidemic in a whole flock of sheep when they happened upon a meadow of toxic plants [112,686]. The plants contained a chemical that inhibits the Hedgehog pathway, which governs the midline of the vertebrate body [207]. That pathway is discussed in this book along with other modalities of intercellular communication.

In Homer's *Odyssey* a giant Cyclops held Odysseus and his men captive in his cave, and they seemed doomed until a strategy occurred to the great general that ultimately allowed him to defeat the Cyclops and liberate his soldiers. Another goal of this book is to recount the exploits of researchers in the field of developmental biology who have been as clever as Odysseus in the experiments they have designed and executed over the years. Their feats are no less heroic than the mythical deeds which Homer lauded so lyrically. Photo courtesy of Delmer Batla.

(A black and white version of this figure will appear in some formats. For the color version, please refer to the plate section.)

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UNIVERSITY PRESS

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[More Information](#)

CAMBRIDGE UNIVERSITY PRESS

University Printing House, Cambridge CB2 8BS, United Kingdom
One Liberty Plaza, 20th Floor, New York, NY 10006, USA
477 Williamstown Road, Port Melbourne, VIC 3207, Australia
314–321, 3rd Floor, Plot 3, Splendor Forum, Jasola District Centre, New Delhi – 110025, India
79 Anson Road, #06-04/06, Singapore 079906

Cambridge University Press is part of the University of Cambridge.

It furthers the University's mission by disseminating knowledge in the pursuit of education, learning, and research at the highest international levels of excellence.

www.cambridge.org

Information on this title: www.cambridge.org/9781108834704

DOI: 10.1017/9781108876612

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First published 2021

Printed in the United Kingdom by TJ Books Limited, Padstow Cornwall

A catalogue record for this publication is available from the British Library.

ISBN 978-1-108-83470-4 Hardback

ISBN 978-1-108-81974-9 Paperback

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Foreword

Developmental biology can be seen as going through a golden age: our understanding of thirty years of work on developmental molecular genetics is enabling us to explore in ever greater detail three important areas. These are the developmental basis of evolutionary change (evo-devo), the regulation of stem-cell development, and the mode of operation of the complex networks that drive developmental change. The result is, on the one hand, a stream of rather technical papers and reviews that developmental biologists are duty-bound to read and, on the other, a range of necessarily simplified books that are aimed at the general public.

What is missing are books for working biologists who want to stand back from the bench and sit down with a good read about their subject, one that reminds them of why they enjoy being biologists. Lewis Held's *Animal Anomalies* may be what they have been looking for! It brings together information on developmental anomalies from across the animal world and provides the molecular and developmental context in which to appreciate them. Although some are well known, many are not, but all pose intriguing problems, many of which remain to be solved.

Lewis Held has spent many months investigating the obscurer corners of the biological literature and has brought back to life an area of developmental biology that today seems mainly to have slipped through the cracks. The result is a fascinating investigation of how embryogenesis can take wrong turnings. Every developmental biologist will know some of these examples, but may not have appreciated how they are now explained; very few, however, will be aware of most of the abnormalities that Held has uncovered.

These heritable curiosities have an additional significance: because they show us the outer reaches of developmental potential, they provide tests for standard theory. Perhaps more important, they can force us to go beyond our current thinking to produce novel explanations and experimental tests for what is going on. The classic example here is the set of homeotic mutants in *Drosophila*, first discovered by Bridges in 1915. It took more than sixty years for the underlying homeobox genes and their mutations to be identified, but only a few more years before their role in anterior–posterior patterning in embryos across the phyla was revealed. Who knows what further Nobel-Prize-winning discoveries lurk in the unexplained molecular thickets of those anomalies yet to be explored?

The book should have a wider resonance. Molecular biologists who focus on simple eukaryotes and the prokaryotic world will find this book to be an intriguing

way into the molecular complexities that keep developmental biologists awake at night. Geneticists should enjoy this exploration of a molecular complexity that the founding fathers of their subject could never have imagined. Perhaps more important, however, is that everyone who teaches in the general area of development will find here a host of fascinating topics and anecdotes that will engage their student audiences, even on a hot Friday afternoon in summer.

Jonathan Bard
Oxford

Preface

Each of us started life as a single cell. Inside that egg's DNA there must have existed some sort of instruction manual for how to assemble our body, but the exact nature of that guidebook has eluded embryologists for centuries. Only recently have we succeeded in deciphering those plans by researching how simpler animals develop, and most of our understanding has come from aberrant individuals that manifest heritable defects.

Although we seek to understand the events occurring in normal embryonic development, it is the bizarre mistakes made by the developing organism, either spontaneously or in response to experimental manipulations, that are most instructive. [163]

One of the most informative such mutants was the four-winged “bithorax” fly, the investigation of which led to the discovery of the Hox Complex and its widespread role in constructing both vertebrates and invertebrates. The bithorax phenotype exemplifies the phenomenon of “homeosis” wherein one body part transforms into another. That term was coined by William Bateson, who cataloged hundreds of naturally occurring anatomical abnormalities in his 1894 tome *Materials for the Study of Variation* [80]. Many of the unusual specimens he collected were likely due to mutations, while others must have arisen through congenital (non-genetic) errors.

Bateson pursued his collection not as an end in itself, but to promote a hypothesis explicitly enunciated in the remainder of his book's title: ... *Treated with Especial Regard to Discontinuity in the Origin of Species*. In contrast to Darwin, who thought that new species diverge from old ones by a gradual process of incremental change, Bateson supposed that new species could arise *discontinuously*, via the sorts of anomalous “sports” in his catalog [1017]. Richard Goldschmidt later extended Bateson's argument in a monograph of his own whose title – *The Material Basis of Evolution* – pays homage to Bateson's classic [447].

Goldschmidt thought that deviants could found new species under the right environmental conditions – whence the term “hopeful monsters” (see Fig. 11.2) [305,307], but few, if any, of the variants in *Animal Anomalies* meet that expectation. The focus of this book is more on development than on evolution [1346]. The field of developmental biology is experiencing a renaissance, thanks in part to the burgeoning of “-omics” and stem-cell innovations [1194].

The most exciting time in the history of developmental biology is right now. Fueled both by new technologies and by new thought from other fields, we are exploding old notions and opening fantastic new horizons in embryology. The only problem we face is a problem of perception.

How do we – as a *community* – convey this excitement to others? Since storytelling is the most fundamentally human activity, I think we start by telling our stories. [1346]

Animal Anomalies celebrates some major triumphs of this field by recounting key scientific experiments that yielded pithy insights. It uses a case-study approach where each chapter follows a simple rubric: a puzzling anomaly leads to a search for the phenotype's etiology. As the detective story unfolds, take-home lessons emerge about how animal development works, with further examples (“tangents”) added to explore those general principles (“GPs”) in detail. The GPs are numbered to enable cross-referencing.

More comprehensive treatments of these same axioms can be found in the Embryo Project Encyclopedia (<https://embryo.asu.edu>), Lewis Wolpert *et al.*'s *Principles of Development* [1405], Gilbert and Barresi's *Developmental Biology* [433], and Alberts *et al.*'s *Molecular Biology of the Cell* (4th ed., Chapter 21) [17]. The best primer in this genre remains Sean Carroll's *Endless Forms Most Beautiful* [187].

Ideally, Carroll's book should be read before trying to digest mine because I dive right into the narrative instead of ramping up slowly with a lot of introductory material. Tedium is the bane of textbooks, and I wanted to write a more whimsical opus. Yes, there is a lot of jargon to absorb, but I've opted to define the technical terms when they're needed to grasp the stories at hand, rather than risk losing readers by force-feeding them preambles about the history, theory, or vocabulary of the embryological concepts.

A similar approach was used in a different venue by another Carroll. Lewis Carroll exalted the wonders of what has been called “recreational mathematics” through his Alice books [46,184]. Like those books, *Animal Anomalies* was written more for amusement than edification, in a spirit of “recreational embryology” (e.g., trying to decipher zebra stripes and leopard spots in Chapter 10). Despite my attempts to soft-pedal the pedagogy, the text remains regrettably ponderous, especially in the early chapters. However, for readers who stick with it there is one reward awaiting them near the end: the chapters progressively get shorter or, as the Gryphon said to Alice, “That's the reason they're called *lessons* – because they lessen from day to day.”

Many outstanding treatises discuss anomalous humans [1039], including a voluminous compendium called *Anomalies and Curiosities of Medicine* published two years after Bateson's classic volume [463], Armand Leroi's *Mutants* [777], Mark Blumberg's *Freaks of Nature* [127], and a host of medical genetics textbooks. Such works extend the didactic tradition of the *Wunderkammer* cabinets of curiosities, popular in the seventeenth century [475], but which devolved into the voyeurism of P. T. Barnum's freak shows in the nineteenth century and the hucksterism of Ripley's *Believe It or Not!* in the twentieth [737]. The latter exploitations led me to feature *non-human* anomalies instead, but it would be silly to try to avoid human

topics entirely, because animal models have helped to solve clinical syndromes [654,1389,1398]. Hence, human cases do appear here as well, albeit sparingly.

Why focus on frogs, flies, dogs, and cats? Frogs and flies have been two of the model organisms employed by embryologists for the past century, and much of our understanding of developmental mechanics has come from these two groups. Dogs and cats have been subjected to artificial selection for millennia, based on fortuitous peculiarities that happened to appeal to their human handlers, so they also offer a rich reservoir of traits that depart from the norm of wild ancestors. Now is a good time to revisit those traits, because many have recently been demystified through genomic surveys.

The internet abounds with pictures of freaky animals, but many are fakes. All of the pictures in this book have been fully authenticated, and all of the sources have been thoroughly investigated.

For example, the notion of a frog with eyes in its mouth (Chapter 1) seems incredible, but I corresponded with the herpetologist, Jim Bogart, who personally examined this specimen. This frog was pictured on the cover of the 1995 book *Phenotypes* by David Rollo [1078], and David was helpful in referring me to Jim, as well as to Scott Gardner, who shot the picture. Although I never inspected this individual myself, I was involved, directly or indirectly, with the other oddities discussed in Part I. Chapter 1 explores two key phenomena: induction and morphogenesis.

Chapter 2 recounts the research done by John Gerhart [413], my PhD advisor at the University of California, Berkeley. Before I graduated in 1977, John had voiced skepticism about an old experiment on the “gray crescent.” His hunch turned out to be correct [416], and his revised interpretation, based on work done with students who came after me, revealed an unsuspected mechanism of cytoplasmic reorganization [665]. This chapter also delves into Falkenberg’s rule, a puzzle posed in 1919, which concerns the orientation of the left–right axis in conjoined twins. When such twins share a thorax, the left member of the pair looks normal, while the right one has its internal organs reversed half of the time. Why? The mystery was solved in 1996 by a team of researchers studying chick embryos [783], with further insights added in 2017 by a different team studying frogs [1285].

Chapter 3 discusses Bateson’s rule – a riddle even older than Falkenberg’s rule – about the symmetries of extra legs in a variety of insects, crustaceans, and vertebrates. After brainstorming with Stan Sessions, the world expert on such defects in frogs, the two of us submitted our conjecture to the *Journal of Experimental Zoology*, which published it [564]. Hence, there is much overlap between this chapter and that article. Whether or not our hypothesis turns out to be right, this project closed a circle for me, since my first book, published in 1992, was based on Bateson’s book [553].

Flies have provided the preferred model system in genetics for more than a century, so they offer an opportunity to explore the underworld of gene regulation which drives development, and that is an understatement. Little did I realize when I chose the fly’s second-leg *basitarsus* for my doctoral research in 1974 that it would

turn out to be a microcosm of animal embryology in general [547]. The ~1800 cells on that leg segment employ all of the cardinal signaling pathways of metazoans to build a cuticular pattern [555]: the Dpp, Wg, and Hh pathways fix the axes (Fig. 3.10) [554], the Notch pathway pinpoints the bristles (Fig. 6.10) [550,562], the PCP pathway orients them [566], and the EGFR pathway induces the bracts (Fig. 1.4) [556]. To paraphrase William Blake, it feels in hindsight like I was seeing the world in a 300- μ m-long cylinder of prickly cuticle. The patterning mechanisms employed by flies are surveyed in Part II (Chapters 4–6) [561].

Regrettably, those devices cannot be explained without a host of gene names as alien as the toves and borogoves of *Jabberwocky*, but fear not! There is a frabjous way around this frumious impasse. The names of fly genes turn out to be quite charming once you know how they were coined, and the etymologies are all available at Tom Brody's *Interactive Fly* website. Google it, and you'll see.

Chapter 4 continues the theme of obdurate old conundrums. As in Chapters 2 and 3, Chapter 4 presents a mystery that was first uncovered by my own research team in 1986 [566]. It concerns a polarity-modifying mutation that causes fly tarsi to have twice as many joints as normal, with each of the extra joints being upside-down. Why? This riddle has basically been solved, but many questions remain.

Chapter 5 begins with the most famous mutant ever described – the four-winged “bithorax” fly. Its discovery in 1915 was as fortuitous as Howard Carter's finding of Tut's tomb seven years later. By delving into the etiology of the mutant's four-wing phenotype, Ed Lewis (1918–2004) stumbled upon a cluster of genes that has been organizing the head-to-tail axis of animals for the past 600 million years [774,804]. This “Hox Complex” has furnished a goldmine of insights into how genes construct anatomy. One tangent that I discuss is the frog leg, whose extra tibia and fibula arose by the tweaking of Hox gene expression. This same trait arose in two jumping mammals (tarsiers and galagos) [560]. Given the billions of people on earth, it is surprising that this anomaly has never shown up in a human. Basketball teams would surely love to have players with this sort of catapulting superpower.

Chapter 6 investigates a gene cluster – the Achaete-Scute Complex – that offers some useful contrasts with the Hox Complex. Disabling its main genes causes virtually all bristles to vanish, making the fly virtually bald. This nude syndrome resembles our own species insofar as humans are what Desmond Morris aptly called the only “naked ape.” Some years ago I wrote a review on the genetics of human hairlessness [558], and I adapt that essay here by permission of Springer Nature (2010). Also adapted for this chapter is material from *Imaginal Discs* (2002) [555], whose contents needed updating based on insights unearthed in the interim. The goal of that book – and this chapter – was to probe how genes represent anatomy in DNA language [198,840].

Dogs have been guinea pigs, so to speak, in a global experiment spanning millennia. The original goal was to domesticate wolves to do the bidding of their human masters, but as the descendants of those progenitors proliferated, mutants emerged that people found useful or beautiful or comical. By mating those

exceptions together and subjecting their offspring to selective breeding, generation after generation, dog fanciers sculpted the sundry varieties that we know today [11]. Darwin realized the power of artificial selection to modify morphology, and he used it as an analogy for the process of natural selection in his *Origin of Species*, though he employed pigeons as his cardinal example, rather than dogs [68,359]. The mottled coat patterns we see in dogs are thought to have arisen as a result of the domestication process itself [1392,1393], but if so, then it seems strange that humans do not show similar splotches [1004], since we are thought to have *self*-domesticated over the eons [864]. Geneticists have recently been digging into the dog genome [951,982,995,1124], and some choice nuggets are featured in Part III (Chapters 7–9) of the present book.

Shaggy dog stories that were omitted but are still worth mentioning [1212] include how the Dachshund got its short legs (answer: an *Fgf4* retrogene that causes chondrodysplasia) [996], how the Borzoi got its long snout (answer: an odd ratio of tandem-repeat glutamines to alanines in the *Runx2* gene) [1312], how the Dalmatian got its spots (answer: a deviant allele at the *Mitf* color locus plus a second-site mutation) [675], how the bulldog got its underbite (answer: a missense mutation in the bone-promoting *BMP3* gene) [841,1125], how the Siberian Husky got its blue eyes (answer: a 99 kb duplication upstream of the homeobox gene *Alx4*) [287], how the Bearded Collie got its beard (answer: a combination of *Fgf5* and *R-spondin2* alleles) [170], how the Mexican Hairless lost its hair (answer: a frameshift mutation in the *FoxI3* gene) [324], why Labrador retrievers collapse when they exercise (answer: an error in the *dynammin* gene *DNM1*) [891], and why dogs are so affectionate in general (answer: they carry the hypersociality alleles of Williams syndrome “leprechauns”) [775,1341,1425].

It is worth pausing to note that readers who are not geneticists may have still been able to get the gist of the last paragraph despite not being familiar with the arcane verbiage, in the same way that Catholics and Jews can benefit from their respective services without knowing Latin or Hebrew. The reason for bringing this point up is that this whole book had to face this dilemma. It ended up being written for an ecumenical audience without being “dumbed down,” so it is up to readers to judge whether its technical terms are a deal-breaker.

Chapter 7 examines a Chinese dog breed with rumpled skin called the Shar-Pei. This deformity has been traced to a mutation that causes a polysaccharide – hyaluronic acid – to perfume the dermis so as to loosen the skin. Similar phenotypes exist in cats, humans, and flies, and some of them can be understood on the same basis. Surprisingly, hyaluronic acid also helps carve the convolutions of the human brain, and we delve into how our big brain evolved – an issue I’ve covered before [557]. Fingerprints likewise exhibit labyrinthine patterns, and we assess their genetic basis by reviewing some old forensic studies of the Dionne quintuplets. The take-home lesson from this excursion is that some patterns organize themselves “under the radar” of the genome, based on physical forces that are subject to stochastic vagaries – like a herd of cattle that is spooked to stampede in unpredictable directions. The idea that physics shapes anatomy was

the central thesis of D’Arcy Thompson’s classic monograph *On Growth and Form* [1280]. The question of determinate growth remains one of the most profound mysteries in developmental biology [893,1336,1338], and it figures prominently in the next two chapters.

Chapter 8 begins with the Bully Whippet, a stocky breed whose double-muscling trait is due to a mutation in the *myostatin* gene. Strikingly similar phenotypes and etiologies have arisen in various species of livestock [9], and a single human case has been documented as well [1129]. Other organs aside from muscles do not appear to use dedicated inhibitors like myostatin: there is simply no equivalent “osteostatin,” “neurostatin,” or “colostatin” to limit the growth of bones, nerves, or intestines for example. Rather, most other tissues (e.g., the liver) rely upon a generic (Hippo) signaling pathway for this function. A separate (insulin) pathway is utilized by organs to amplify their growth beyond that of the body as a whole (e.g., deer antlers). Several of these case studies could lead to breakthroughs in solving clinical problems.

Chapter 9 offers a history lesson for the younger crop of developmental biologists, who may be a bit too glib about all the glitzy genomic tools at their disposal [1205]. They should heed the haunting homily of the elf queen Galadriel in the prologue of the first *Lord of the Rings* movie: “Much that once was is lost, for none now live who remember it.” Some of us *are* old enough to remember the pioneers who blazed our trails, not with technical trickery but with mental wizardry. They were keen thinkers who tackled daunting phenomena and solved knotty mysteries [611] – for example, John Gerhart’s exegesis of cortical rotation (Fig. 2.2), William Bateson’s synopsis of limb symmetries (Fig. 3.3), and Curt Stern’s analysis of genetic mosaics (Fig. 6.9). Here I highlight the work of Pere Alberch and Jonathan Cooke, who are relatively unsung heroes from that earlier epoch, though Alberch’s ideas have recently been revived by Rui Diogo [306,307,309]. Alberch had the acuity to see subtle constraints in the hind paws of his parent’s pet dog, and Cooke had the temerity to claim that Wolpert’s popular model of morphogen gradients was full of holes, which he proceeded to plug with Alan Turing’s reaction–diffusion tenets [232]. The chapter’s theme is polydactyly – a symptom in more than 300 human syndromes [109,1309,1330].

Only one mammal group other than ours has had a Broadway musical all to itself. *Cats* celebrates cats in a way that is inconceivable for any counterpart *Dogs* production. There is something ineffable about how cats behave that gives them a unique “purrview.” They are clearly too smart for their own good, and they know better than to look up to us. Dogs obey us, but cats exploit us. They even got the Egyptians to worship them as gods! Supercilious behavior and superior intelligence aside, however, cats cannot measure up to dogs in two respects. They are all about the same size, and they are all about the same shape [473]. Where they tend to vary is in their coat patterns – at least as much, if not more so than dogs [340,663]. Consequently, cats portray how mammal skin gets “painted” while dogs exemplify how mammal bodies get sculpted [323]. Part IV (Chapters 10–12) takes advantage of this fact to probe how three odd coat patterns arise.

Chapter 10 starts with a tale of two cats – one little and one big. The little one is the domestic tabby, and the big one is the cheetah, known for its speed but also for its spots. There is a mutation in cheetahs that turns their spots into stripes and irregular blotches, and it so happens that virtually the same mutation makes tabbies blotched as well. In one case (the tabby) we go from tiger-like *stripes* to blotches, and in the other (the cheetah) from *spots* to blotches. How curious! This riddle prompts us to ask deep questions, like the languid Caterpillar interrogating Alice, about the nature of spots and stripes in general. Here Turing’s model helps us realize (with apologies to Joni Mitchell) that we never really knew stripes or spots at all. They are both visible manifestations of invisible machinations at the cellular level that we are only now beginning to grasp. Along the way we will ponder the coat patterns of zebras, giraffes, and leopards. Our tour of the zoo will be informed by clever analyses of insects and fish, including a classic experiment by another titan from an earlier age [758]: Sir Vincent Wigglesworth was a superb researcher whose feats deserve wider appreciation [337,338,761]. He was the insect physiologist who trained Peter Lawrence [757], the patriarch of developmental genetics who in turn trained Gary Struhl [1331], whose contributions to the field are legendary. The chapter ends with a fish story from the lab of Shigeru Kondo, another luminary, who solved the riddle of how the fish gets its stripes. Kondo apprenticed with Walter Gehring, a co-discoverer of the homeobox (Chapter 5) [1388], who in turn was trained by Ernst Hadorn, the discoverer of transdetermination [503]. The field of developmental biology boasts an illustrious genealogy indeed.

Chapter 11 concerns the Siamese cat, which, like many breeds, is named for the part of the world where the originating mutation arose – in this case Siam, the country we now call Thailand. The same mutation that causes its distinctive coloration also causes it to cross its eyes [851,1362], and the story of how that correlation was deciphered is told in a charming essay entitled “Serendipity and the Siamese cat: the discovery that genes for coat and eye pigment affect the brain” [662]. Bateson was the first to notice the similarity between Siamese cats and Himalayan rabbits [81,617], and since that time (1909) analogous mutations have been found in other mammals, including humans. In all of these cases the outside temperature affects the mutated tyrosinase enzyme, resulting in dark extremities. Some species of butterflies and mammals have evolved a reliance on outside temperature as a means of giving them different phenotypes in different seasons of the year, and some species of reptiles have incorporated it into their sex-determining mechanisms. Other species use other environmental influences such as nutrition, crowding, or social interactions as a way of creating alternative anatomies, especially various insect castes. How evolution wired animal genomes to utilize these external cues remains a mystery.

The narrative closes with Chapter 12, which uses the calico cat as a springboard for diving into the phenomenon of mosaicism in general. The potential of genetic mosaics for investigating gene function (in lieu of tissue transplantation) was first realized by Curt Stern (1902–1981), one of whose experiments was discussed in

Chapter 6. His *Genetic Mosaics and Other Essays* [1203] was one of my favorite books in graduate school at Berkeley, where I was privileged to meet the great man himself before Parkinson's disease forced him to retire [1291]. Stern was an illustrious member of Morgan's fly lab [717], but there were so many stars in that firmament that it is hard to rank their luminosities. Even so, no story about mosaics would be complete without discussing gynandromorphs, and no account of those half-male, half-female creatures would be complete without recounting how they were harnessed to construct fate maps by another of Morgan's disciples, Alfred Sturtevant. It was not my intention to write a history book, but as my own career nears its end, it is hard to resist one last glance at the totem pole of giants on whose shoulders I have been honored to stand.

Abbreviations include ECM (extracellular matrix), EGFR (epidermal growth factor receptor), Fgf (fibroblast growth factor), GOF (gain of function), GP (general principle), GTPase (guanosine triphosphatase), LOF (loss of function), and PCP (planar cell polarity). Gene names are italicized, as per convention in fly genetics, and protein names are capitalized. Capitals are used for genes when the originally isolated mutation was dominant – e.g., *Serrate* (gene) and Serrate (protein) – vs. cases in which the originally isolated mutation was recessive – e.g., *achaete* (gene) and Achaete (protein). Names can denote what a gene does, as for growth factors, but often they reflect the phenotype when the gene malfunctions – e.g., a serrated wing or a bristleless (“a-chaete”) cuticle. Numbers in brackets are citations of sources listed in the *References*, which can steer readers to related research in the literature.

Constructive critiques of the book proposal and of draft chapters were kindly provided by Richard Campbell, Jane Maienschein, Cliff Tabin, and Adam Wilkins. Many colleagues provided pictures, and they are acknowledged in the relevant figure legends. Dominic Lewis, my editor at Cambridge, was steadfast in his support of the project; Hugh Brazier, my copy-editor for this third book in a row, wielded his scalpel as deftly as a neurosurgeon; and my “coaches” all along were my sister Linda Wren and my friend Sam Braudt. Even Scott Gilbert, author of the most widely used developmental textbook of all time [433], gave his blessing to this more casual approach when I discussed it with him at the outset.

The educational strategy used here was modeled after my favorite professor at MIT, Seymour Papert, who exhorted all of us undergraduates to look for big ideas, which he called “general powerful principles” (distilled here to “GPs”), that we could use as heuristic tools to build conceptual frameworks in whatever field we chose to pursue [991]. In keeping with Papert's didactics, GPs should be applied to other cases as soon as they are abstracted from a particular case so as to affirm their generality. That means going off on tangents, at least briefly, after each GP is formulated, which is the rubric I've adopted.

In an essay for *Newsweek* entitled “How life begins,” Sharon Begley extolled the grandeur of human embryogenesis from egg to baby: “It is as if a single dab of white paint turned into the multicolored splendor of the Sistine Ceiling” [91]. The majesty of development has long been shrouded in mystery, but many of the tricks

behind the magic have now been deciphered, thanks largely to the analyses of anomalies. The underlying mechanisms possess an esthetic all their own [966], but readers will have to plow through a lot of complexities before they can reap the full bounty of the beauty.

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Lubbock, Texas
July 2020

Cambridge University Press
978-1-108-83470-4 — Animal Anomalies
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Frontmatter
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