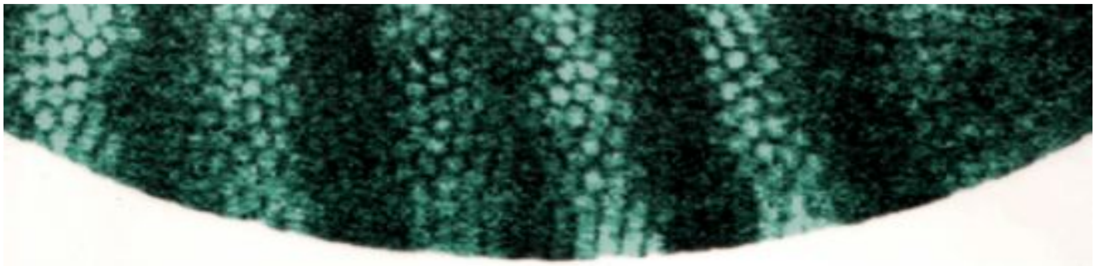
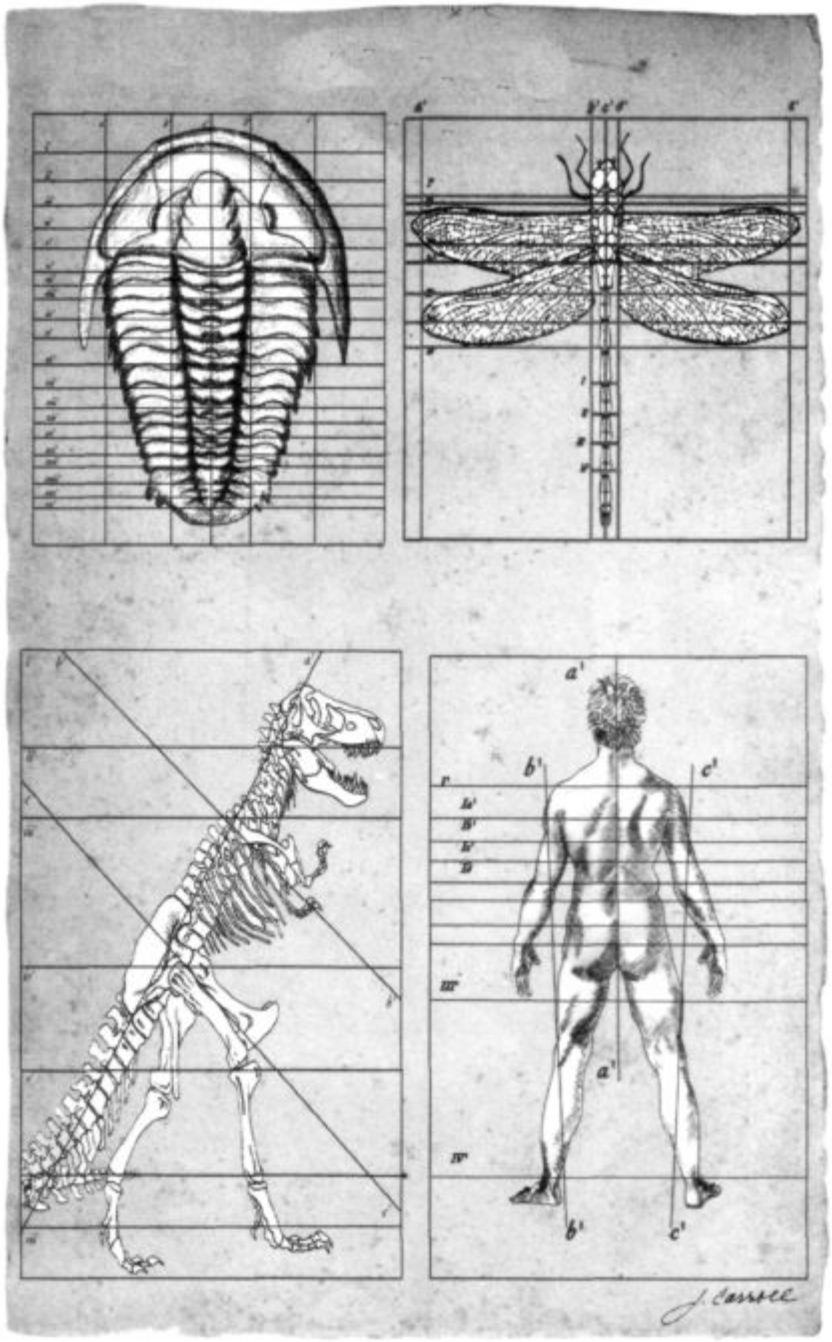


THE NEW SCIENCE
OF EVO DEVO

# ENDLESS FORMS MOST BEAUTIFUL

SEAN B. CARROLL



# Endless Forms Most Beautiful

*The New Science of Evo Devo*

and the Making of the Animal Kingdom

# Sean B. Carroll

WITH ILLUSTRATIONS BY

*Jamie W. Carroll * Josh P. Klaiss * Leanne M. Olds*



ISBN 0393060160

*For Jamie, Will, Patrick, Chris, and Josh*

# Contents

# *Preface*

# Revolution #3

You say you want a revolution

Well, you know

we all want to change the world.

You tell me that it's evolution,

Well, you know

we all want to change the world . . .

You say you got a real solution

Well, you know

we'd all love to see the plan. . . .

— John Lennon and Paul McCartney "Revolution 1" (1968)

The physicist and n□bel laureate Jean Perrin once stated that the key to any scientific advance is to be able "to explain the complex visible by some simple invisible." The two greatest revolutions in biology, those in evolution and genetics, were driven by such insights. Darwin explained the parade of species in the fossil record

and the diversity of living organisms as products of natural selection over eons of time. Molecular biology explained how the basis of heredity in all species is encoded in molecules of DNA made of just four basic constituents. As powerful as these insights were, in terms of explaining the origin of complex visible *forms,* from the bodies of ancient trilobites to the beaks of Galapagos finches, they were incomplete. Neither natural selection nor DNA directly explains *how* individual forms are made or how they evolved.

The key to understanding form is *development,* the process through which a single-celled egg gives rise to a complex, multi-billion-celled animal. This amazing spectacle stood as one of the great unsolved mysteries of biology for nearly two centuries. And development is intimately connected to evolution because it is through changes in embryos that changes in form arise. Over the past two decades, a new revolution has unfolded in biology. Advances in developmental biology and evolutionary developmental biology (dubbed "Evo Devo") have revealed a great deal about the invisible genes and some simple rules that shape animal form and evolution. Much of what we have learned has been so stunning and unexpected that it has profoundly reshaped our picture of how evolution works. Not a single biologist, for example, ever anticipated that the same genes that control the making of an insect's body and organs also control the making of our bodies.

This book tells the story of this new revolution and its insights into how the animal kingdom has evolved. My goal is to reveal a vivid picture of the process of making animals and how various kinds of changes in that process have molded the different kinds of animals we know today and those from the fossil record.

I wrote the book with several kinds of readers in mind. First, for anyone interested in nature and natural history who takes delight in animals of the rain forest, reef, savannah, or fossil beds, there will be much said about the making and evolution of some of the most fascinating animals of the past and present. Second, for physical scientists, engineers, computer scientists, and others interested in the origins of complexity, this book tells the story of the enormous diversity that has been created from combining a small number of common ingredients. Third, for students and educators, I firmly believe that the new insights from Evo Devo bring the evolutionary process alive and offer a more gripping and illuminating picture of evolution than has typically been taught and discussed. And fourth, for anyone who may ponder the question "Where did I come from?," this book is also about our history, both the journey we have all made from egg to adult, and the long trek from the origin of animals to the very recent origin of our species.

Drawing by Christopher Herr, age ten (Eagle School, Madison, Wisconsin)

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*Introduction*

# Butterflies, Zebras, and Embryos

Well she's walking through the clouds With a circus mind that's running round Butterflies and zebras And moonbeams and fairy tales, That's all she ever thinks about. . . .

—Jimi Hendrix, "Little Wing" (1967)

On a recent visit to my kids' elementary school, I was enjoying the student art that decorated the hallways. Among the landscapes and portraits were many depictions of animals. I couldn't help noting that of the thousands of species to choose from, the most frequently drawn mammal was the zebra. And the most represented

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animal of any kind was the butterfly. We live in Wisconsin and, this being the middle of winter, the kids were not drawing what they saw out the window. So, why all the butterflies and zebras?

I am certain that these pieces of art reflect the children's deep connection to animal forms—their shapes, patterns, and colors. We all feel that connection. That's why we visit zoos to see exotic animals, flock to the new phenomenon of butterfly aviaries, go to aquaria, and spend billions on our animal companions—dogs, cats, birds, and even fish. We most often choose our favorite breeds and species on aesthetic grounds. Yet, we are also mesmerized, and sometimes terrified, by the more extreme animal forms: giant squids, carnivorous dinosaurs, or bird-eating spiders.

The same attraction to and fascination with animal forms has motivated the greatest naturalists for centuries. In cold, gray, damp pre-Victorian England, young Charles Darwin read Alexander von Humboldt's *Personal Narrative,* a 2000-page account of his voyage to and around South America. Darwin was so consumed that he later claimed that all he thought, spoke, or dreamt about were schemes to get to see the sights of the Tropics that Humboldt described. He leaped at the chance when the opportunity to sail on the *Beagle* arose in 1831. Darwin later wrote to Humboldt, "My whole course of life is due to having read and re-read as a youth, this personal narrative." Two other Englishmen, Henry Walter Bates, a twenty-two-year-old office clerk and avid bug collector, and his self-taught naturalist friend, Alfred Rüssel Wallace, also dreamt of travel abroad to collect new species. Upon reading an American's account of a journey to Brazil, Bates and Wallace immediately decided to head there (in 1848). Darwin's voyage lasted five years, Bates remained in the Tropics for eleven years, and Wallace spent fourteen years over the course of two journeys. These dreamers would, based upon the thousands of species that they saw and collected, launch the first revolution in biology.

There must be something about living in northern climates that inspires dreams of the Tropics. I grew up in Toledo, Ohio, surrounded

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by city parks and farm fields, near the shores of the less than bountiful Lake Erie. My dreams of paradise were fed by magazines and the TV show *Animal Kingdom* (broadcast in black and white). Decades later, I have been lucky enough to see the animals of the African savannah, the jungles of Central America, and the barrier reefs of Australia and Belize (as a tourist, not as a courageous explorer—trust me). And they are even more awe-inspiring than I had imagined.

On the open grasslands of Kenya, herds of zebras and elephants graze while solitary giraffes, ostriches, and cheetahs stroll by. Striped horses, gigantic gray mammals with six-foot-long noses, and spotted cats that can outrun a Jeep? If these creatures did not exist, they would be almost too incredible to believe.

In the rain forests, the richness is generally in smaller creatures. In the dappled light created by gaps in the canopy, brightly painted butterflies such as the red and yellow *Heliconius* or the sparkling metallic blue *Morpho* dance. In the litter below, red-and-turquoise-splotched poison arrow frogs call and vivid green leaf-cutter ants go about their vast harvesting projects. The big predators come out at night. I shall never forget the thrill of meeting a six-foot-long, deadly fer-de-lance snake in the pitch darkness and absolute quiet of a jungle in Belize, in a place well populated with jaguars (we saw only fresh tracks, but that was close enough!).

The sea holds even more strange and wonderful forms. Plunge into the shallow waters off an Australian coral island and the variety of fish, corals, and shelly creatures will literally hit you in the face. Neon colors, bodies of all shapes and sizes, fantastic geometrical designs are everywhere, and occasionally there's a glimpse of a giant sea turtle, an octopus, or a darting shark.

The great variety in the size, shape, organization, and color of animal bodies raises deep questions about the origins of animal forms. How are individual forms generated? And how have such diverse forms evolved? These are very old questions in biology, which date back to the time of Darwin, Wallace, and Bates and before, but only very

recently have deep answers been discovered, many of them so surprising and profound that they have revolutionized our views on the making of the animal world and our place in it. The initial inspiration for this story is the attraction we all share to animal form, but my aim is to expand that wonder and fascination to *how* form is created—that is, to our new understanding of the biological processes that generate pattern and diversity in animal design. Underlying the many visible elements of animal form are remarkable processes, beautiful in their own right in the way that they transform a tiny, single cell into a large, complex, highly organized, and patterned creature, and over time, have forged a kingdom of millions of individual designs.

## Embryos and Evolution

The first approach naturalists took to dealing with the great variety of animals was to sort them into groups, such as vertebrates (including fish, amphibians, reptiles, birds, and mammals) and arthropods (insects, crustaceans, arachnids, and more), but between and within these groups there are many differences. What makes a fish different from a salamander? Or an insect from a spider? On a finer scale, clearly a leopard is a cat, but what makes it different from a domestic tabby? And closer to home, what makes us different from our chimpanzee cousins?

The key to answering such questions is to realize that every animal form is the product of two processes—development from an egg and evolution from its ancestors. To understand the origins of the multitude of animal forms, we must understand these two processes and their intimate relationship to each other. Simply put, development is the process that transforms an egg into a growing embryo and eventually an adult form. The evolution of form occurs through changes in development.

Both processes are breathtaking. Consider that the development of

an entire complex creature begins with a single cell—the fertilized egg. In a matter of just a day (a fly maggot), a few weeks (a mouse), or several months (ourselves), an egg grows into millions, billions, or, in the case of humans, perhaps 10 trillion cells formed into organs, tissues, and parts of the body. There are few, if any, phenomena in nature that inspire our wonder and awe as much as the transformation from egg to embryo to the complete animal. One of the great figures in all of biology, Darwin's close ally Thomas H. Huxley, remarked:

The student of Nature wonders the more and is astonished the less, the more conversant he becomes with her operations; but of all the perennial miracles she offers to his inspection, perhaps the most worthy of admiration is the development of a plant or of an animal from its embryo.

*Aphorisms and Reflections* (1907)

The intimate connection between development and evolution has long been appreciated in biology. Both Darwin, in *The Origin of Species* (1859) and *The Descent of Man* (1871), and Huxley in his short masterpiece, *Evidence as to Man's Place in Nature* (1863), leaned heavily on the facts of embryology (as they were in the mid-nineteenth century) to connect man to the animal kingdom and for indisputable evidence of evolution. Darwin asked his reader to consider how slight changes, introduced at different points in the process and in different parts of the body, over the course of many thousands or a million generations, spanning perhaps tens of thousands to a few million years, can produce different forms that are adapted to different circumstances and that possess unique capabilities. That is evolution in a nutshell.

For Huxley, the nub of the argument was simple: we may marvel at the process of an egg becoming an adult, but we accept it as an everyday fact. It is merely then a lack of imagination to fail to grasp how changes in this process that are assimilated over long periods of time, far longer than the span of human experience, shape life's diversity. Evolution is as natural as development.

As a natural process, of the same character as the development of a tree from its seed, or of a fowl from its egg, evolution excludes creation and all other kinds of supernatural intervention.

*Aphorisms and Reflections* (1907)

While Darwin and Huxley were right about development as key to evolution, for more than one hundred years after their chief works, virtually no progress was made in understanding the mysteries of development. The puzzle of how a simple egg gives rise to a complete individual stood as one of the most elusive questions in all of biology. Many thought that development was hopelessly complex and would involve entirely different explanations for different types of animals. So frustrating was the enterprise that the study of embryology, heredity, and evolution, once intertwined at the core of biological thought a century ago, fractured into separate fields as each sought to define its own principles.

Because embryology was stalled for so long, it played no part in the so-called Modern Synthesis of evolutionary thought that emerged in the 1930s and 1940s. In the decades after Darwin, biologists struggled to understand the mechanisms of evolution. At the time of *The Origin of Species,* the mechanism for the inheritance of traits was not known. Gregor Mendel's work was rediscovered decades later and genetics did not prosper until well into the 1900s. Different kinds of biologists were approaching evolution at dramatically different scales. Paleontology focused on the largest time scales, the fossil record, and the evolution of higher taxa. Systematists were concerned with the nature of species and the process of speciation. Geneticists generally studied variation in traits in just a few species. These disciplines were disconnected and sometimes hostile over which offered the most worthwhile insights into evolutionary biology. Harmony was gradually approached through an

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integration of evolutionary viewpoints at different levels. Julian Huxley's book *Evolution: The Modern Synthesis* (1942) signaled this union and the general acceptance of two main ideas. First, that gradual evolution can be explained by small genetic changes that produce variation which is acted upon by natural selection. Second, that evolution at higher taxonomic levels and of greater magnitude can be explained by these same gradual evolutionary processes sustained over longer periods.

The Modern Synthesis established much of the foundation for how evolutionary biology has been discussed and taught for the past sixty years. However, despite the monikers of "Modern" and "Synthesis," it was incomplete. At the time of its formulation and until recently, we could say that forms do change, and that natural selection is a force, but we could say nothing about *how* forms change, about the visible drama of evolution as depicted, for example, in the fossil record. The Synthesis treated embryology as a "black box" that somehow transformed genetic information into three-dimensional, functional animals.

The stalemate continued for several decades. Embryology was preoccupied with phenomena that could be studied by manipulating the eggs and embryos of a few species, and the evolutionary framework faded from embryology's view. Evolutionary biology was studying genetic variation in populations, ignorant of the relationship between genes and form. Perhaps even worse, the perception of evolutionary biology in some circles was that it had become relegated to dusty museums.

Such was the setting in the 1970s when voices for the reunion of embryology and evolutionary biology made themselves heard. Most notable was that of Stephen Jay Gould, whose book *Ontogeny and Phytogeny* revived discussion of the ways in which the modification of development may influence evolution. Gould had also stirred up evolutionary biology when, with Niles Eldredge, he took a fresh look at the patterns of the fossil record and forwarded the idea of *punctuated equilibria*—that evolution was marked by long periods of stasis (equilibria) interrupted by brief intervals of rapid change (punctuation).

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Gould's book and his many subsequent writings reexamined the "big picture" in evolutionary biology and underscored the major questions that remained unsolved. He planted seeds in more than a few impressionable young scientists, myself included.

To me, and others who had been weaned on the emerging successes of molecular biology in explaining how genes work, the situations in embryology and in evolutionary biology were both unsatisfying, but they presented enormous potential opportunities. Our lack of embryological knowledge seemed to turn much of the discussion in evolutionary biology about the evolution of form into futile exercises in speculation. How could we make progress on questions involving the evolution of form without a scientific understanding of how form is generated in the first place? Population genetics had succeeded in establishing the principle that evolution is due to changes in genes, but this was a principle without an example. No gene that affected the form and evolution of any animal had been characterized. New insights in evolution would require breakthroughs in embryology.

### The Evo Devo Revolution

Everyone knew that genes must be at the center of the mysteries of both development and evolution. Zebras look like zebras, butterflies look like butterflies, and we look like we do because of the genes we carry. The problem was that there were very few clues as to which genes mattered for the development of any animal.

The long drought in embryology was eventually broken by a few brilliant geneticists who, while working with the fruit fly, the workhorse of genetics for the past eighty years, devised schemes to find the genes that controlled fly development. The discovery of these genes and their study in the 1980s gave birth to an exciting new vista on development and revealed a logic and order underlying the generation of animal form.

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Almost immediately after the first sets of fruit fly genes were characterized came a bombshell that triggered a new revolution in evolutionary biology. For more than a century, biologists had assumed that different types of animals were genetically constructed in completely different ways. The greater the disparity in animal form, the less (if anything) the development of two animals would have in common at the level of their genes. One of the architects of the Modern Synthesis, Ernst Mayr, had written that "the search for homologous genes is quite futile except in very close relatives." But contrary to the expectations of *any* biologist, most of the genes first identified as governing major aspects of fruit fly body organization were found to have exact counterparts that did the same thing in most animals, including ourselves. This discovery was followed by the revelation that the development of various body parts such as eyes, limbs, and hearts, vastly different in structure among animals and long thought to have evolved in entirely different ways, was also governed by the same genes in different animals. The comparison of developmental genes between species became a new discipline at the interface of embryology and evolutionary biology—evolutionary developmental biology, or "Evo Devo" for short.

The first shots in the Evo Devo revolution revealed that despite their great differences in appearance and physiology, all complex animals— flies and flycatchers, dinosaurs and trilobites, butterflies and zebras and humans—share a common "tool kit" of "master" genes that govern the formation and patterning of their bodies and body parts. I'll describe the discovery of this tool kit and the remarkable properties of these genes in detail in chapter 3. The important point to appreciate from the outset is that its discovery shattered our previous notions of animal relationships and of what made animals different, and opened up a whole new way of looking at evolution.

We now know from sequencing the entire DNA of species (their *genomes)* that not only do flies and humans share a large cohort of developmental genes, but that mice and humans have virtually identi-

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cal sets of about 29,000 genes, and that chimps and humans are nearly 99 percent identical at the DNA level. These facts and figures should be humbling to those who wish to hold humans above the animal world and not an evolved part of it. I wish the view I heard expressed by Lewis Black, the stand-up comedian, was more widely shared. He said he won't even debate evolution's detractors because "we've got the fossils. We win." Well put, Mr. Black, but there is far more to rely on than just fossils.

Indeed, the new facts and insights from embryology and Evo Devo devastate lingering remnants of stale anti-evolution rhetoric about the utility of intermediate forms or the probability of evolving complex structures. We now understand how complexity is constructed from a single cell into a whole animal. And we can see, with an entirely new set of powerful methods, how modifications of development increase complexity and expand diversity. The discovery of the ancient genetic tool kit is irrefutable evidence of the descent and modification of animals, including humans, from a simple common ancestor. Evo Devo can trace the modifications of structures through vast periods of evolutionary time—to *see* how fish fins were modified into limbs in terrestrial vertebrates, how successive rounds of innovation and modification crafted mouthparts, poison claws, swimming and feeding appendages, gills, and wings from a simple tubelike walking leg, and how many kinds of eyes have been constructed beginning with a collection of photosensitive cells. The wealth of new data from Evo Devo paints a vivid picture of how animal forms are made and evolve.

### The Tool Kit Paradox and the Origins of Diversity

The stories of shared body-building genes and of the similarities of our genome to that of other animals have slowly been gaining in public awareness. What is generally neglected, however, is how the dis-

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covery of this common tool kit and of great similarities among different species' genomes presents an apparent paradox. If the sets of genes are so widely shared, how do differences arise? The resolution of this paradox and its implications are central to my story. The paradox of great genetic similarity among diverse species is resolved by two key ideas that I will develop in the course of the book and will return to repeatedly. These concepts are crucial for understanding how the species-specific instructions for building an animal are encoded in its DNA and how form is generated and evolves. The substance of these ideas has received scant, if any, attention in the general press, but these ideas have profound implications for understanding great episodes in life's history, such as the explosion of animal forms during the Cambrian period, the evolution of diversity within groups such as butterflies or beetles or finches, and our evolution from a common ancestor with chimps and gorillas.

The first idea is that diversity is not so much a matter of the complement of genes in an animal's tool kit, but, in the words of Eric Clapton, "it's in the way that you use it." The development of form depends upon the turning on and off of genes at different times and places in the course of development. Differences in form arise from evolutionary changes in where and when genes are used, especially those genes that affect the number, shape, or size of a structure. We will see that there are many ways to change how genes are used and that this has created tremendous variety in body designs and the patterning of individual structures.

The second idea concerns where in the genome the "smoking guns" for the evolution in form are found. It turns out that it is not where we have been spending most of our time for the past forty years. It has long been understood that genes are made up of long stretches of DNA that are decoded by a universal process to produce proteins, which do the actual work in animal cells and bodies. The genetic code for proteins, a twenty-word vocabulary, has been known for forty years, and it is easy for us to decode DNA sequences into protein sequences. What

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is much less appreciated is that only a tiny fraction of our DNA, just about 1.5 percent, codes for the roughly 25,000 proteins in our bodies. So what else is there in the vast amount of our DNA? Around 3 percent of it, made up of about 100 million individual bits, is *regulatory.* This DNA determines when, where, and how much of a gene's product is made. I will describe how regulatory DNA is organized into fantastic little devices that integrate information about position in the embryo and the time of development. The output of these devices is ultimately transformed into pieces of anatomy that make up animal forms. This regulatory DNA contains the instructions for building anatomy, and evolutionary changes within this regulatory DNA lead to the diversity of form.

In order to understand the role and significance of regulatory DNA in evolution, I have some ground to cover. One must first appreciate how animals are constructed and the roles of genes in embryonic development. This will form the first half of the book and it holds many rewards in its own right. I will illustrate some general features of animal architecture and trends in the evolution of body design that are shared among different groups of animals (chapter 1). I will describe some of the spectacular mutant forms that led biologists to the tool kit of master genes that regulate development (chapters 2 and 3). We will see these genes in action and how they reflect the logic of and order to the building of animal bodies and complex patterns (chapter 4). And we will learn about the devices in the genome that contain the instructions for building anatomy (chapter 5).

In the second half of the book, I will tie together what we know about fossils, genes, and embryos in the making of animal diversity. I will highlight some of the most important, interesting, or compelling episodes in animal evolution that illustrate how nature has forged many individual designs from a small number of building blocks. I will examine in depth the genetic and developmental foundations of the Cambrian Explosion that produced many of the basic types of animals and body parts we know today (chapters 6 and 7). I will probe into the

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origins of butterfly wing patterns as splendid examples of how nature invents by teaching very old genes new tricks (chapter 8). I will tell some stories about the evolution of the plumage of island birds and the coat colors on mammals (chapter 9). These are all very satisfying, aesthetically pleasing tales that provide deep insights into the evolutionary process. But they have more direct ramifications, for they are the case studies that reveal the very kinds of processes that shaped human origins. In the final chapters of the book, I will describe the making of our species, most notable for its "beautiful mind" more than any other physical trait (chapter 10). I will trace our beginning from an apelike ancestor 6 million years ago to track the physical and developmental changes that led to *Homo sapiens.* I will discuss the scope and types of genetic changes that have occurred in the course of our evolution and those that are most likely to account for the evolution of traits we most associate with being human.

## The Grandeur in a More Modern Synthesis: Act III

The continuing story of evolution may be thought of as a drama in at least three acts. In Act I, almost 150 years ago, Darwin closed the most important book in the history of biology by urging his readers to see the grandeur in his new vision of nature—in how, "from so simple a beginning, endless forms most beautiful have been, and are being, evolved." In Act II, the architects of the Modern Synthesis unified at least three disciplines to forge a grand synthesis. Here in Act III, there is also a special grandeur in the view embryology and evolutionary developmental biology provide into the making of animal form and diversity. Part of it is visual, in that we can now see how the endless forms of different animals actually take shape.

But beauty, in science, is much more than skin-deep. The best science is an integrated product of our emotional and intellectual sides, a

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synthesis between what is often referred to as our "left" brain (reasoning) and "right" brain (emotional/artistic) hemispheres. The greatest "eurekas" in science combine both sensual aesthetics and conceptual insight. The physicist Victor Weisskopf (also a pianist) noted, "What is beautiful in science is the same thing that is beautiful in Beethoven. There's a fog of events and suddenly you see a connection. It expresses a complex of human concerns that goes deeply to you, that connects things that were always in you that were never put together before."

In short, the best science offers the same kind of experience as the best books or films do. A mystery or drama engages us, and we follow a story toward some revelation that, in the very best examples, makes us see and understand the world more clearly. The scientist's main constraint is the truth. Can the nonfiction world of science inspire and delight us as much as the imagined world of fiction?

One hundred years ago, Rudyard Kipling published his classic *Just So Stories,* a collection of children's tales inspired by his experiences in India. Kipling's enchanting stories ranged from "How the Leopard Got His Spots" and "How the Camel Got His Hump" to "The Butterfly That Stamped," and wove fanciful tales of how some of our favorite and most unusual creatures acquired prominent features. As delightful as the *Just So* explanations are of how spots, stripes, humps, and horns came to be, biology can now tell stories about butterflies, zebras, and leopards that I contend are every bit as enchanting as Kipling's fairy tales. What's more, they offer some simple, elegant truths that deepen our understanding of all animal forms, including ourselves.

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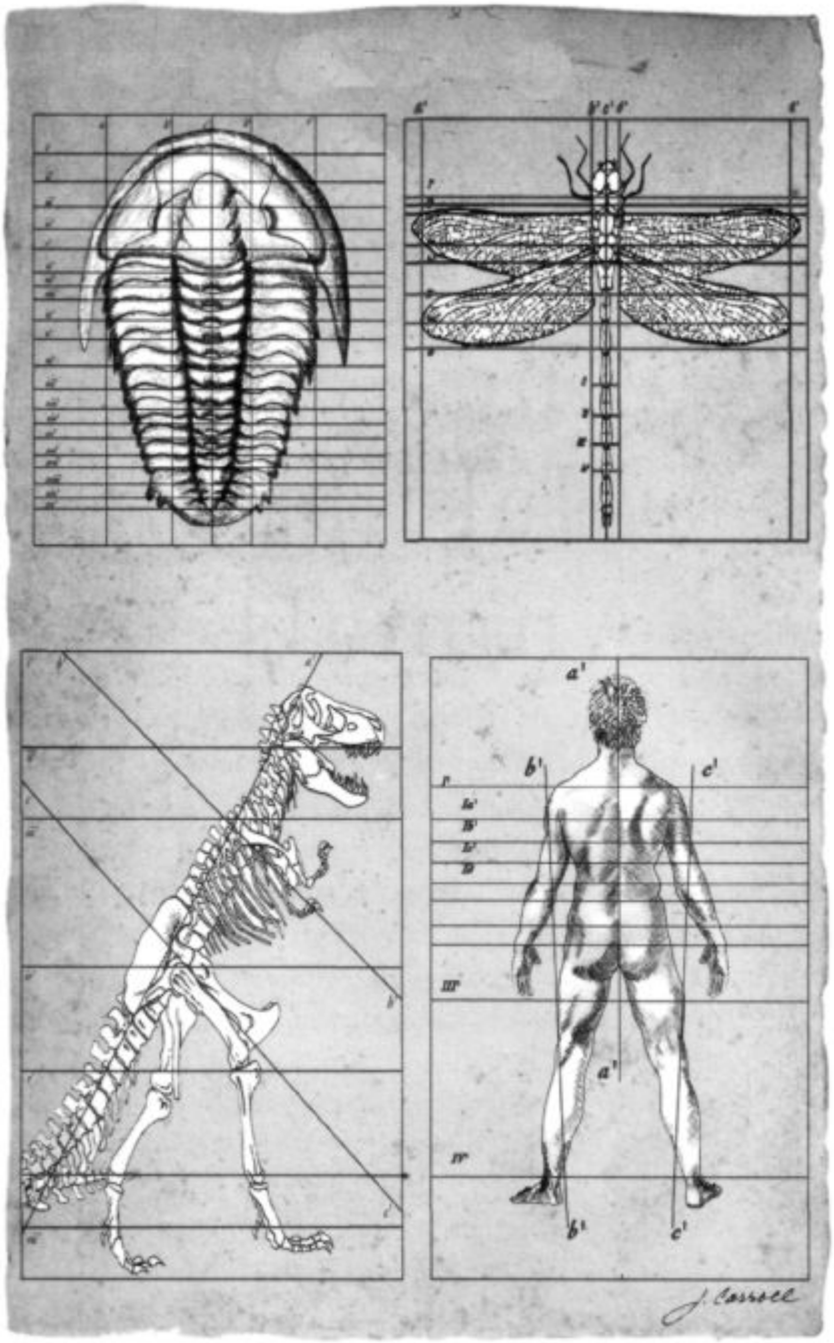
*Part I*

# The Making of Animals



Animal architectures, modern and ancient. jamie carroll

# *1*

# Animal Architecture: Modern Forms,

# Ancient Designs

It is the mystery and beauty of organic form that sets the problem for us.

—Ross Harrison, embryologist (1913)

The amazing variety of animal forms does not end with those on land or in the sea. Belowground, buried in as little as a few inches of sand or up to several thousand feet of rock, is the story of 600 million years of animal history—from the enigmatic forms of early animals in Canadian shale, to the enormous bodies of dinosaurs

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in the buttes and valleys of the American West, and the teeth and skull fragments of our bipedal ancestors in the Rift Valley of east Africa. And some of what lies below the ground can be quite surprising given what breathes just above.

I learned this firsthand only recently in, of all places, Florida, a favorite destination for vacationers and retirees seeking sun, entertainment, and relaxation. It is a land of palm trees, soft sandy beaches, graceful pelicans and ospreys, gentle manatees and dolphins, and *Homo sapiens* in plaid pants . . . but also of six-foot-long armadillos,

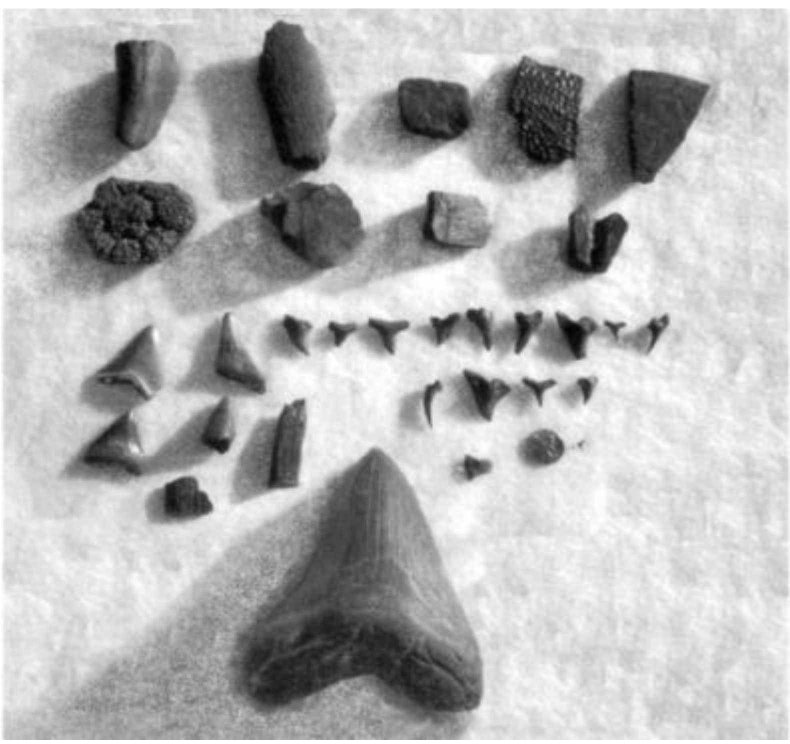

**Fig. 1.1 Fossils from a Florida riverbed.** Mammal bone, turtle shell fragments, and shark teeth abound. Note the variety of shapes and sizes. The largest tooth is from the enormous shark *Charcharadon megalodon.* fossils collected and photographed

BY PATRICK CARROLL

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tusked mastodons, sixty-foot-long sharks, camels, rhinoceroses, jaguars, and saber-toothed cats?

Yes, indeed. Well, it depends on where you look.

Journey inland to a river cutting through the sandy soil and a shovel of gravel from the riverbed might contain teeth from any of ten species of shark, from the intricately serrated and curved snaggletooth, to the absolutely terrifying six-inch flesh rippers of the long extinct behemoth *Charcharadon megalodon* (figure 1.1). In the same gravel there will also be bones of Florida's geologically recent past—of tapirs, sloths, camels, horses, glyptodonts, mastodons, dugongs, and other species now vanished.

The diversity of living and fossil animal forms in just this one locale frames the two central mysteries at hand: How are individual forms made? And, how have so many different forms evolved?

At first, the variety of animal forms may seem overwhelming. But there are some general, long established trends in animal design that we can make sense of. In this chapter, we'll search for some generalities in animal architecture and evolution that will help us reduce this mind-boggling diversity to some basic themes.

## The Construction of Animals from Building Blocks

A basic theme of animal design becomes obvious when one tries to figure out just what bone or tooth one has found in that shovelful of Florida river gravel. The challenge of the game is both to match the fossil to a species, and also to determine where in the animal it belonged. Why is this so hard? This is one demonstration of a basic fact of animal design. Related animals, such as vertebrates, are made up of very similar parts.

Now say, with a bit of expert help, one is able to figure out that a piece of bone is from a dugong (an extinct sea cow). But if it is a rib, which rib?

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Or, if a toe bone is from an extinct horse, which toe is it? From individual bones, it is really difficult to tell. Why this is the case punctuates a second basic fact of animal design—that individual animals are made up of numbers of the same kinds of parts, like building blocks.

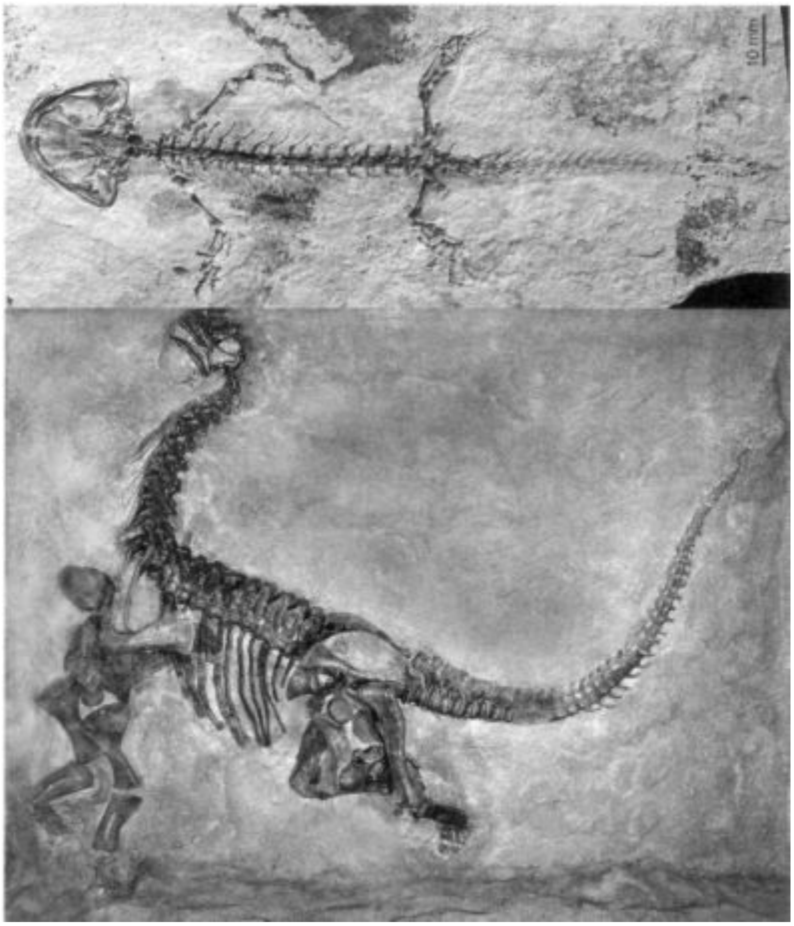


Fig. 1.2 **The modular architecture of vertebrates.** Top, a Jurassic salamander about 10 centimeters in length. Bottom, *Camarasaurus,* a Jurassic sauropod dinosaur, almost 19 feet in

length. SALAMANDER COURTESY OF NEIL SHUBIN, UNIVERSITY OF CHICAGO; *CAMARASAURUS* COURTESY OF CARNEGIE MUSEUM OF NATURAL HISTORY, ALL RIGHTS RESERVED

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Some of these parts can be small, such as an individual toe bone, others gigantic, like the backbones (vertebrae) of some vertebrates. These basic elements are ancient and their proportions maintained over vast differences in body size. Both enormous sauropod dinosaurs and small, delicate salamanders from the Jurassic age (over 150 million years ago) display the same repeating modular architecture of the vertebrate body plan (figure 1.2).

The theme of modular design is by no means limited to vertebrates. The famous fossils of the Burgess Shale, some of the first large, complex animals that populated the Cambrian seas more than 500 million years ago, display all sorts of variations on modular body plans (figure 1.3), as do their living descendants today.

The attraction to these fossils is manifold. Certainly, there is a sense of awe and wonder in seeing and touching extinct beasts that lived in worlds that have long since vanished. But we are also drawn to their *form.* The fossils demonstrate evolution's pervasive use of repeating parts and modular architecture in forging animal designs.

Individual body parts also reflect this theme of modular design. Our limbs, for example, are of similar modular design, each limb built of several pieces (thigh, calf, ankle; upper arm, forearm, wrist) and the hands and feet bear five similar digits (figure 1.4). The modular architecture of the limbs of four-legged vertebrates is also an ancient design, plainly evident in the Jurassic fossils.

Sometimes, the modular design of a structure may not at first be apparent. The complex patterns on a butterfly wing may appear chaotic, but on closer inspection one can see that the overall pattern is also built of repeating motifs. The underside of the blue *Morpho* butterfly has repeating patterns of lines, chevrons, and spots where each of the individual elements are separated by the wing veins (figure 1.5). This shows that each division of the wing enclosed by veins is a unit. The overall pattern is a product of repeating these modular units, each with some variations on the size or shape of the lines, chevrons, or spots within.

The repeating patterns on body structures extend down to very fine

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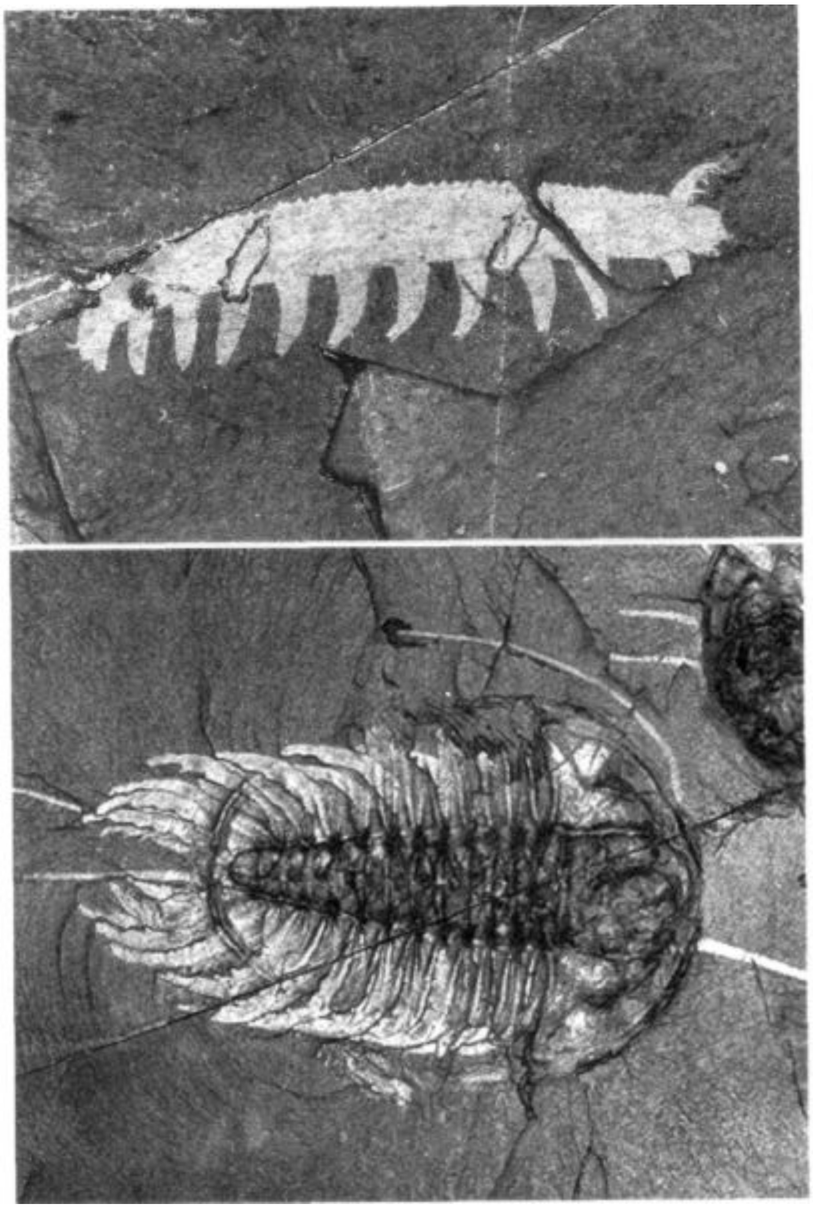

FIG. **1.3 The modular architecture of Cambrian animals.** The

lobopodian *Ayshaeia pedunculata* (above) and trilobite *Olenoides serratus* (below) display repetitively organized, modular body

forms. PHOTOS COURTESY OF CHIP CLARK, SMITHSONIAN INSTITUTION

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**Fig. 1.4 The modular design of a human hand.** The finger bones revealed by an X ray display a serially reiterated architecture. COURTESY OF JAMIE CARROLL

details, some almost out of range of the naked eye. Such beautiful butterfly wing patterns are actually built from tiny scales on the wing. Each scale is a projection of single cells that are assembled in many rows in the wing. Each scale has its own specific color, like the brushstrokes on a pointillist painting that when combined in a field of thousands and millions of scales, create the overall pattern we admire. The body patterns of fish, snakes, and lizards are also composed of scales (different from those of butterflies) arrayed in a regular geometric pattern. The reflective or refractive properties of scales depend on even

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Fig. **1.5 Serially repeating designs within butterfly wings** are

shown in the underside of this *Morpho* butterfly. Each wing is made up of serially reiterated subunits demarcated by two veins and the wing edge. Each subunit contains variations of the same elements—eyespots, bands, and chevrons. butterfly gift of nipam

PATEL, PHOTO BY JAMIE CARROLL

finer cellular microanatomy that determines the wavelengths of light that are absorbed or reflected (figure 1.6).

From just these few descriptions, we can begin to appreciate the immense task of development—to build large, complex animals beginning with only a tiny single cell. There are millions of details, and the details count. A small shift in an early process would have a cascade of later effects. What processes can assemble both a massive dinosaur and paint the delicate details of a spot on a butterfly?

Given such enormous differences in scale, and such great variety in animal forms, it would seem that the details of development would present what molecular biologist Günther Stent described only twenty years ago as "a near infinitude of particulars which have to be sorted out case by case." But biologists have been surprised and delighted to find there are generalities we can make about form and, fortunately,

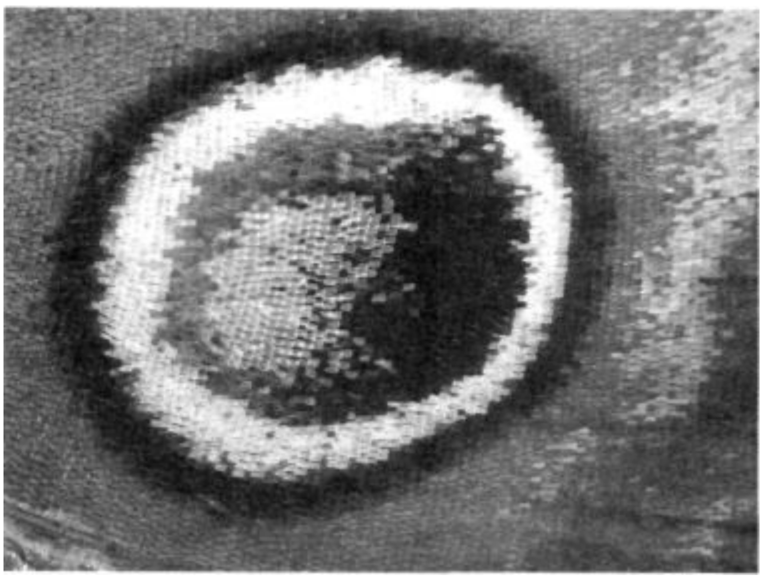

Fig. 1.6 **Repetition on a fine scale.** The scales of a butterfly wing are like the strokes of a pointillist painting, each stroke being a single scale of a particular color; collectively they form geometric pattern elements. photo by steve paddock

these generalities also extend far more deeply than outward appearances, into the genetic machinery of development. I'll start with the outward similarities here and work my way down to the genes that do the job in the next two chapters.

## Evolution as Variations in Number and Kind

The modular and repetitive aspects of animal design reflect an order to animal forms. Anatomists have long appreciated that no matter how diverse their outward appearance, animal bodies and their parts are constructed along some perceivable themes. More than a century ago, some of these themes were formally defined by the English biologist

William Bateson. His perspective turns out to be a very helpful framework for thinking about the logic of animal design and understanding how variations on basic themes evolve.

Bateson recognized that many large animals were constructed of repeated parts, and many body parts themselves were constructed of repeated units. In considering particular groups of animals, it appeared that some of the most obvious difference between members of a group were in the *number* and *kind* of repeated structures. For example, while all vertebrates have a modularly constructed backbone made up of individual vertebrae, different vertebrates possess different numbers and kinds of vertebrae. The number of vertebrae from head to tail differs greatly, from fewer than a dozen in frogs, to thirty-three in humans, and up to a few hundred in a snake (figure 1.7). There are also different kinds of vertebrae such as cervical (neck), thoracic, lumbar, sacral, and caudal (tail) vertebrae. The main differences between these types in any one animal are their size and shape and the presence or absence of structures attached to them, such as ribs. There is great diversity in the number of each type in different vertebrates.

A similar pattern applies to arthropod form and diversity. Arthropod bodies are made up of repeating segments, which in the trunk (behind the head) may vary from about eleven segments in insects to dozens in centipedes and millipedes. Groups of segments are distinguished from one another (e.g., the thoracic and abdominal segments) by their size and shape and especially by the appendages that project from them (e.g., the thoracic segments in insects each bear a pair of legs while the abdominal segments do not).

These two groups of animals have successfully exploited every environment on earth (water, land, and air) and are the most complex animals in terms of anatomy and behavior. Both groups are constructed of repeated assemblages of similar parts. Is there a connection between modularity of design and the success in evolutionary diversification? I certainly think so. The challenge for biologists has been to figure out

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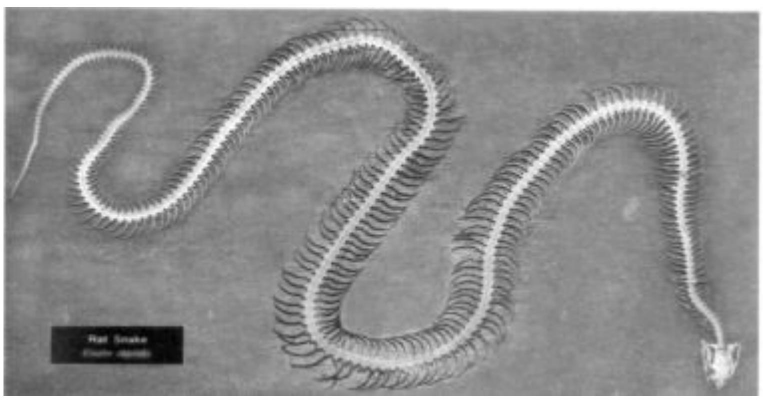

FIG. 1.7 **Snake skeleton.** Hundreds of repeating vertebrae and ribs make up the snake body form. courtesy of dr. kurt

SLADKY, UNIVERSITY OF WISCONSIN

how these animals are built, beginning from just a single cell, and how all sorts of variations on a body design evolve. The modular construction of vertebrates and arthropods, and their variation in the number and kinds of modules, are important clues to the processes involved.

Body parts that are often modular and constructed of similar units often differ between species largely in number and kind. The limbs of four-legged vertebrates (tetrapods) usually bear one to five digits. We recognize five distinct types of digits on our own hands (thumb, forefinger, etc.) and feet. The similarities among digits are obvious, the differences largely a matter of size and shape. The tetrapod limb has been adapted to many functions in a great variety of designs, and the basic five-digit design has persisted for more than 350 million years, although digit number has evolved extensively such that anywhere from one to five digits may be present (for example, camels have two toes, rhinos have three, etc.). The variations on the tetrapod theme are spectacular, as a sample of X rays among vertebrates highlights (figure 1.8). Interestingly, closely related animals can differ widely; some groups have evolved many species that differ from one another in digit number.

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**Fig. 1.8 Diversity of vertebrate limb forms.** All vertebrate

limbs are variations on a common design in which the number, size, and shape of elements (such as digits) differ. courtesy of dr.

KURT SLADKY, UNIVERSITY OF WISCONSIN; SEA TURTLE COURTESY OF DR. CRAIG HARMS, NORTH CAROLINA STATE UNIVERSITY

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## Homology, Serial Homology, and Williston's Law

When comparing body parts between species, it is important to know whether one is comparing the same body part that might have changed in different ways, or one is comparing parts in a series, where the one-to-one relationship may be obscured. For example, the forelimbs of salamanders, sauropods, mice, and our arms are all *homologs.* This means they are the same structure modified in different ways in each species. They are derived from a common ancestral forelimb. Hindlimbs, our legs and the hind legs of four-legged vertebrates, are also homologs. With respect to each other, forelimbs and hindlimbs are *serial homologs,* structures that arose as a repeated series and have become differentiated to varying degrees in different animals. Vertebrae and their associated structures (ribs); tetrapod forelimbs and hindlimbs; digits;

teeth; the mouthparts, antennae, and walking legs of arthropods; and the fore- and hindwings of insects are also serial homologs.

Changes in the number and kind of serial homologs are a principal theme in animal evolution. Let me drill this home with a couple of more examples of familiar structures. If you are a seafood lover, chances are you have dissected a lobster. While dismembering it, perhaps you might have noted the modular design and admired the great variety of body appendages (figure 1.9). There are several aspects to lobster construction that reflect the general themes of modularity and serial homology. First, the body is organized into a head (with the eyes and mouthparts), a thorax (with walking legs), and a long tail (yum!). Second, different sections of the body possess numbers of specific appendages (antennae, claws, walking legs, swimmerets). And third, each jointed appendage is itself segmented, and different kinds of appendages have different numbers of segments overall (compare a claw with a walking leg). If you were feeling adventuresome and dissected an insect or a crab, you'd see some general similarities in body

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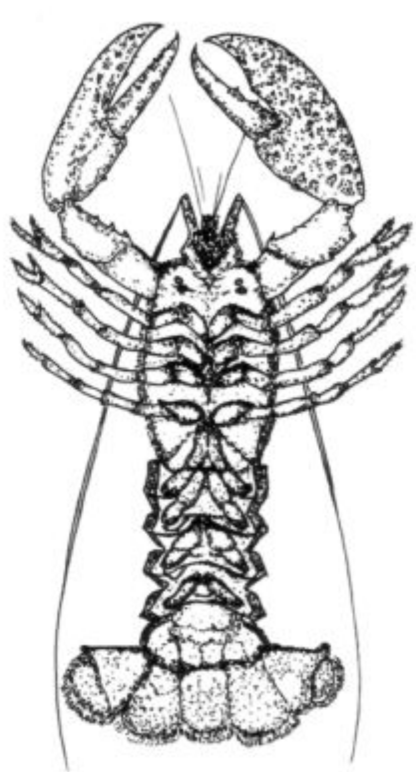

Fig. 1.9 The diversity of the serially repeated appendages of a lobster. The antennae, claws, walking legs, swimmerets, and tail structures are all modifications of a common limb design. drawing

BY JAMIE CARROLL

organization, segmentation, and appendages but, again, differences in the number and kind of serially homologous structures.

A second example of serially homologous parts would be the teeth you used to mince and crush that lobster. Our jaws host a variety of teeth (canines, premolars, incisors, molars, etc.). Again, one of the obvious differences among all sorts of vertebrates are the number and kind of teeth. Primitive reptiles, like great marine forms, had a mouth full of mostly similar teeth, but later species evolved different kinds of teeth, adapted for biting, tearing, and compacting food. The differences in dental hardware reflect differences in diet, with carnivores bearing incisors and

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canines and grazers bearing mostly molars (figure 1.10). We differ from our primate relatives in our dentition (figure

1.11). You may be aware that teeth make hardy fossils and such finds have played a major role in deciphering the identity and lifestyle of our ancestors.

The evolutionary trends in the number and kinds of repeated structures are so pronounced that the paleontologist Samuel Williston

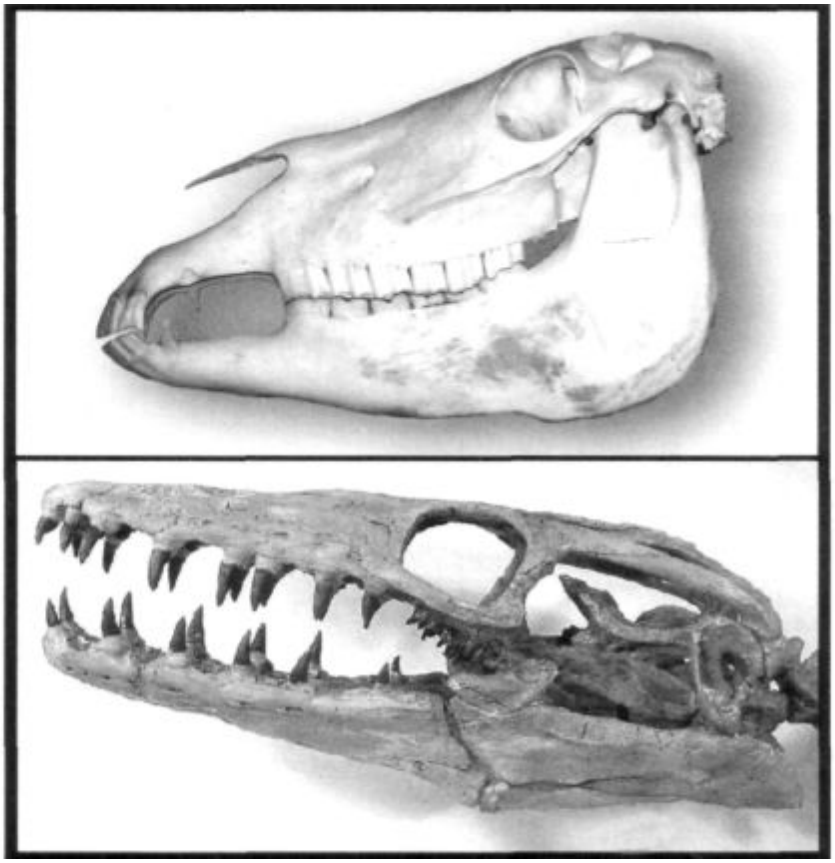

Fig. 1.10 **Teeth in a primitive vertebrate.** In mosasaurs (bottom), all teeth appear mostly similar, whereas later vertebrates (top; here a horse) had teeth of distinct types. reconstruction of

*PLATECARPUS PLAIFRONS* COURTESY OF MIKE EVERHART, OCEANS OF KANSAS PALEONTOLOGY

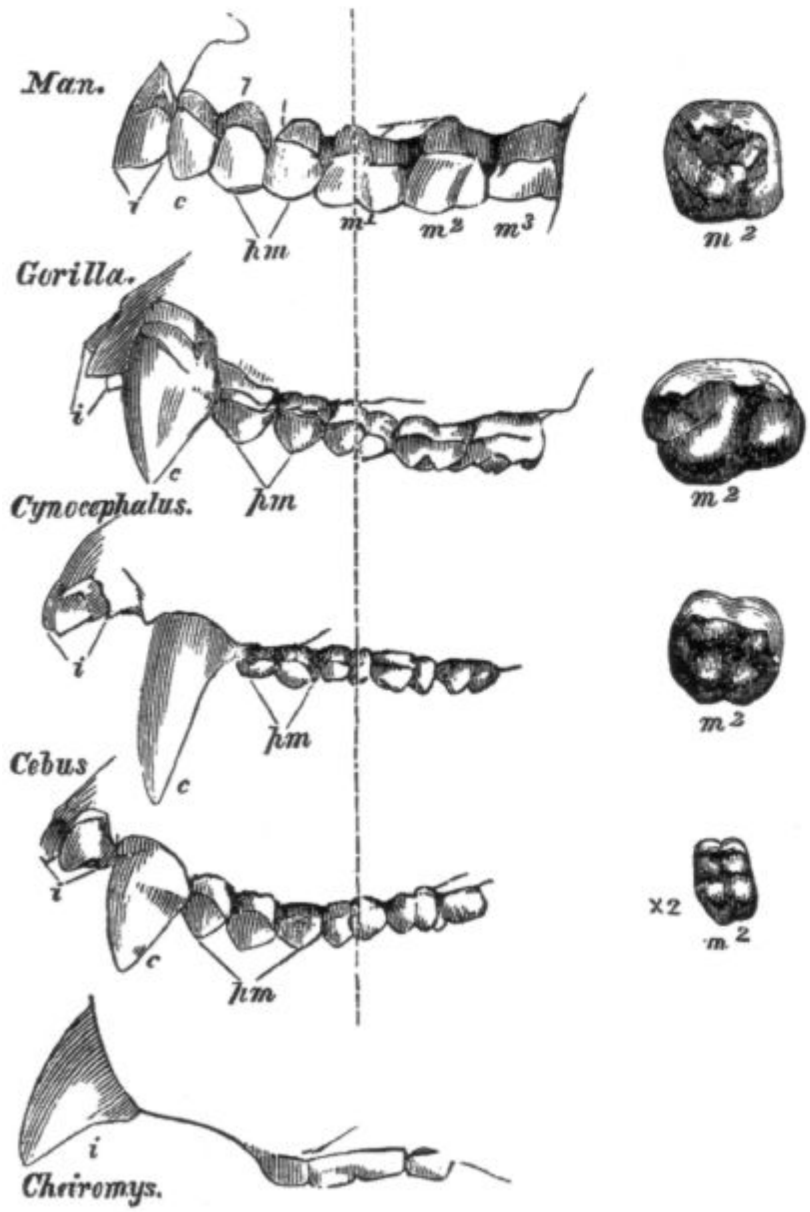


Fig. 1.11 **The diversity of primate dental hardware.** Primates differ in the number and shape of canine, premolar, and molar teeth. from □. □. huxley, *man's place in nature* (1863)

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declared in 1914, "it is [also] a law in evolution that the parts in an organism tend toward reduction in number, with the fewer parts greatly specialized in function." Williston was studying ancient marine reptiles. He noted that in the course of evolution, earlier groups tended to have large numbers of similar serially reiterated parts, but that later groups exhibited reduced numbers and specialized forms of these structures. Furthermore, the specialized pattern rarely reverted to the more general form. One interesting case is that when digits first evolved in tetrapods, there were as many as eight digits per foot. But among these eight, there were no more than five types, which eventually reduced to five digits that were specialized, or further reduced, in later species. Laws in biology are few, and those dared to be articulated are almost certain to be broken by some organisms. Yet Williston's Law is a useful observation that seems to pertain to trends in more than just the ancient marine reptiles he was writing about. The trend appears to be that once expanded in number, serial homologs became specialized in function and reduced in number. The specialization of vertebral, tooth, and digit morphology in vertebrates, and of legs and wings in arthropods, was in fact generally accompanied by a reduction in the number of these repeated structures. Williston and Bateson appear to have captured some simple truths about animal design and evolution, allowing us to boil down the vast history and variety of some of the largest and most diverse groups into some generalities.

## Symmetry and Polarity

In addition to the repetition of modular parts, animal bodies and body parts usually display two additional features —*symmetry* and *polarity*. Most familiar animals are bilaterally symmetrical in that they have matching right and left sides with a central axis of symmetry running down the middle of the long axis of the body. This design also imposes a front/rear orientation to animals and has enabled the evolution of

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many efficient modes of locomotion. Some animals exhibit other symmetries, such as the pentaradial (five-fold) echinoderms, a group including sea urchins, sand dollars, and a spectacular variety of other species (figure 1.12). The axes of symmetry in an animal are clues to how the animal is built.

So, too, is the polarity of an animal and its parts. In most animals there are three axes of polarity: head to tail, top to bottom (back and front in ourselves, since we stand up), and near to far from the body (in reference to structures that project from the main body—such as a limb whose parts are organized perpendicular to the main body). Individual structures also have polarity. Think of the hand, which has three axes oriented by the thumb to pinkie, back to palm, and wrist to fingertip directions.

## How Is Form Encoded in the Genome?

Modularity, symmetry, and polarity are nearly universal features of animal design, certainly of larger, more complex animals such as butterflies and zebras. These features and the evolutionary trends noted by

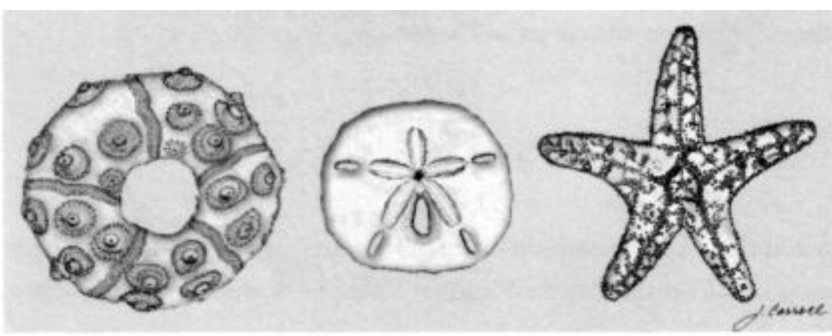

Fig. 1.12 **Other symmetrical animal forms.** Echinoderms such as sea urchins (left), sand dollars (center), and starfish (right) are radially symmetrical. drawing by Jamie Carroll

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Williston and Bateson suggest that there is order and logic to animal architectures. They suggest that underneath the great variety of animal forms, there are some general "rules" to be discovered about how animals are built and evolve.

In the course of this book, I will focus on four main questions:

1. What are some of the major "rules" for generating animal form?

2. How is the species-specific information for building a particular animal encoded?

3. How does diversity evolve?

4. What explains large-scale trends in evolution, such as the change in number and function of repeated parts?

Where do we look for these rules and instructions? In DNA. In the entire complement of DNA of a species (the genome), there exists the information for building that animal. The instructions for making five fingers, or two eyespots, or six legs, or black and white stripes are somehow encoded in the genomes of the species that bear these traits. Does this mean there are genes for fingers, genes for spots, genes for stripes, etc.? I will focus on how anatomy is encoded in the genome in the first part of the book.

I'll tackle evolutionary diversity in the second part of the book. Somehow, different species with three versus four fingers, two versus seven eyespots, six versus eight legs, or that are all black or all white, must have different instructions encoded in their DNA. Evolution of form is ultimately then a question of genetics. But in order to understand how genes sculpt all of this breathtaking animal beauty, we will first look to monsters for some critical clues.

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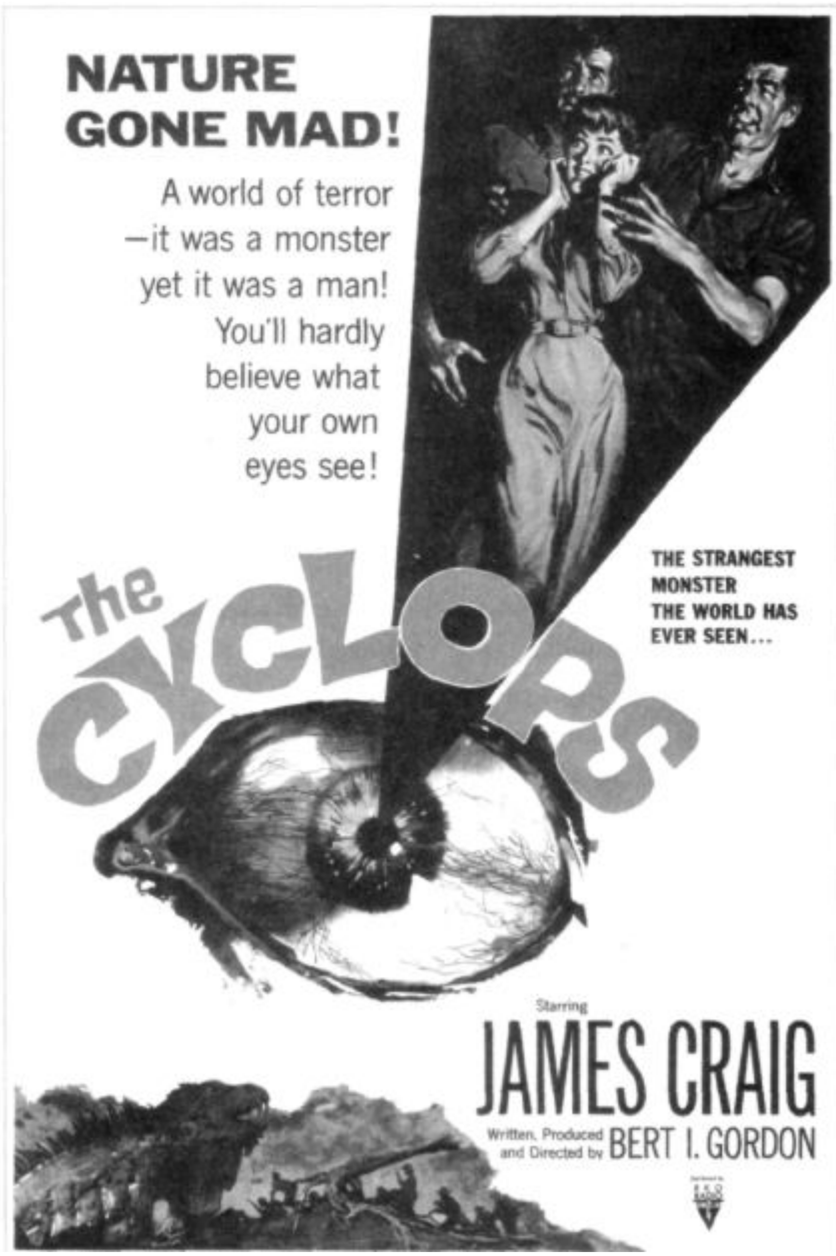


Poster for the movie *The Cyclops* (1956). □ & □ productions, inc.

# 2

# Monsters,

# Mutants,

# and Master Genes

"Do you know, I always thought Unicorns were fabulous monsters, too? I never saw one alive before!"

"Well, now that we *have* seen each other," said the Unicorn, "if you'll believe in me, I'll believe in you. Isn't that a bargain?"

—Lewis Carroll, *Through the Looking Glass* (1872)

*CREATURE FEATURE* was a staple of Saturday afternoon television when I was a kid. My best friend, Dave, was addicted to the show. He'd hole up in his basement with the curtains drawn, lights off, a baseball bat at his side, and all sorts of contraptions rigged to the door and windows in case one of the featured monsters happened to visit him in the middle of the show. He'd watch hours of Godzilla, Dracula, the Mummy, or worse. Dave would later recount the plot lines for us and speculate on the relative strengths and unique powers of all the beasts. Fueled by an active imagination, which was probably also stoked by the five-gallon tin of popcorn and the can of Betty Crocker frosting that were his standard refreshments, these creatures had become almost *real* to him.

Our fascination with and terror of monsters are universal and ancient. From Greek mythology to □ movies, writers have imagined all sorts of giants, hybrids, and ghoulish creatures. I didn't share Dave's appetite for monster movies (or cans of frosting, for that matter), but monsters have played an important role in advances in embryology. One of the most successful approaches to figuring out how animal forms develop correctly has been the study of dramatic monsters with the wrong number of parts, or parts in the wrong places. Some of these forms were man-made creations, some the product of accidents and injuries during gestation, and others the result of rare mutational events in nature. The insights gained from study of these kinds of monsters have recently converged to reveal specific mechanisms underlying the assembly of all animal bodies and body parts.

### The Myth and Reality of Cyclops

I never bought into tales of the dead coming alive, humans transformed into bats or flies, gigantic skyscraper-scaling gorillas, creatures that were half human, half horse/goat/snake/fish/whatever, fire breathers, or invisible bodies. I put them all into the same category of dark fairy tales. I did the same with monsters with one central eye, but here is where I might have been too hasty to dismiss a creature.

While I was vaguely familiar with the mythology of Cyclops, I did not know that animals with one central eye were actually well-known to science. In fact, at one time in Utah, 5 to 7 percent of newborn sheep

**Fig. 2.1 Cyclopic lamb**. Caused by exposure of mother at critical period to cyclopamine, a toxin produced by the plant *Veratrum californicum.* photo courtesy of dr. lynne james, poisonous plant

RESEARCH CENTER, LOGAN, UTAH

were afflicted with cyclopia, a lethal malformation in which they bear a single central eye, lack most nasal and jaw structures, and have incompletely developed brain hemispheres (figure 2.1). The formal term is *holoprosencephaly,* meaning single forebrain, and the key defects are that the forebrain and eyes fail to become separated into two symmetrical structures.

The high frequency of cyclopia in sheep was eventually found to be associated with the presence of a plant, the lily *Veratrum californicum,* in the pastures in which their mothers grazed. Ingestion of this plant during a period of gestation (around the fourteenth day) was the critical factor. It turns out that the plant produces a chemical called

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cyclopamine that has a teratogenic (from the Greek *teras,* meaning monster) effect on the developing embryo.

Cyclopamine is just one of many known teratogens. Many other chemicals have adverse affects on development of embryos. The drug thalidomide, originally developed to treat nausea during pregnancy, is probably the most notorious, having caused thousands of birth defects in humans in the late 1950s and early 1960s. While these molecules have been known for decades, there was no progress in understanding how they acted until the recent convergence of embryology with molecular biology. These advances have stemmed from more specific experiments, especially through the manipulation of embryos and genes.

## Newt Lips and Chicken Wings

Over the past century, biologists have used scalpels, needles, tweezers, and all sorts of tools to chop, strangle, burn, blend, spin, and prick embryos to try to uncover some rules for building an animal. Pioneers in embryology relied entirely on physical methods to move and remove cells and then observe what unfolded in the embryo. From these crude tortures, some dramatic monsters were produced whose striking features revealed a few central principles governing the organization of developing animals.

Foremost among these pioneers was Hans Spemann, the first, and for a span of more than sixty years, the only embryologist to win the Nobel Prize (but as we will see embryologists have lately been catching up). One of the very first illuminating experiments he carried out was to test whether the first two cells of a newt embryo had similar or different properties. Spemann used a fine baby's hair, taken from his own daughter, to tie off and separate individual halves of the embryo. The cells on each side of the knot gave rise to normal newt tadpoles, demonstrating that the two halves of early amphibian embryos could give rise to two entirely identical animals.

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When Spemann divided the egg differently by tying it perpendicular to the furrow between the two cells of the embryo, he obtained a dramatically different result. Only one side made a normal tadpole, while the other made a disorganized mess of belly tissue. This eventually led to the recognition that a region of the embryo, called the dorsal lip of the blastopore, was critical for the organization of the embryo. If this region of the embryo was removed, the embryo formed a blob of tissue lacking structures that normally form on the top (dorsal) side of the animal. More spectacularly, if this dorsal lip region was transplanted to the presumptive belly region of another developing embryo, it organized a second embryonic axis and *two* embryos formed that were joined together (figure 2.2)! Spemann dubbed this region "the organizer" because he deduced that it organized the dorsal part of the embryo into neural structures and could initiate the development of another embryonic axis.

The spectacular effects of the Spemann organizer revealed that one way order is brought about in development is by interactions between one part of an embryo and other parts. Some other organizers with dramatic properties have been discovered that show that this principle works on many scales in development: across the whole embryo, within individual body parts, and right down to intricate details of patterns. Let's look at two more organizers that illustrate these dramatic activities.

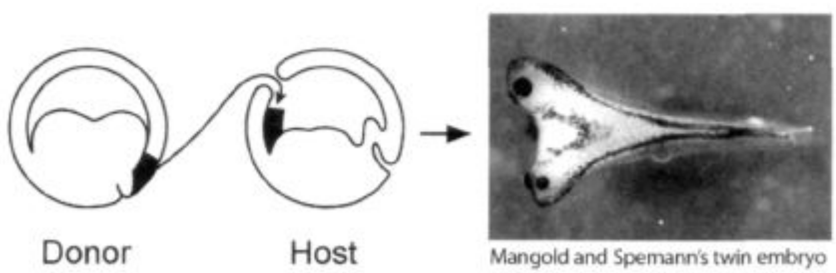


Fig. 2.2 **Induction of a second axis and embryo in a frog tadpole.** Transplantation of "organizer" tissue to a different site induces the formation of a conjoined embryo. photo courtesy of

HIROKI KURODA AND EDDY DE ROBERTIS, UCLA

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The formation of limbs has long held the fascination of embryologists. Beginning from just a small bud on the flank of the embryo early in development, the limb takes shape in many stages. In a three-day-old chicken embryo, the bud is initially only about 1 millimeter long and 1 millimeter wide but this will grow more than a thousand-fold by the time the chick hatches. In the intervening period, this tiny pad of tissue will grow outward, lengthen, and develop bone, cartilage, muscles, tendons, digits, and feathers in a beautiful display of the coordinated processes of development. Perhaps most striking is the orderly formation of cartilage elements (which will later be replaced with bone). The cartilage is formed around condensations of cells and laid down in order from the shoulder to the wrist and then to the digits. The whole process can be seen with special stains (figure 2.3). The order of events in limb development and the polarity of the digits suggests that, like the embryo, there must be some sort of system that cues cells as to what they will become.

Several decades ago, John Saunders, another pioneer embryologist, discovered an organizer of polarity in the chicken embryo wing bud. A chicken wing normally has three digits, which we can identify due to their size and shape as digits 2, 3, and 4 (in order from the front to the back of the wing; digits 1 and 5 do not form in the wing). When Saunders transplanted a chunk of tissue from the posterior part of the growing limb bud (near where digit 4 would originate) to an anterior position (where digit 2 would normally appear), a wing with extra digits formed. The digits were a mirror image duplication of the normal pattern—that is, instead of the 2 3 4 sequence of wing digits, a pattern of 4 3 2 3 4 formed (figure 2.4). The wing's mirror image polarity suggested that cells in the posterior zone of the limb bud organized the polarity of the digit sequence (4, 3, 2), such that when moved elsewhere, the 4, 3, 2, sequence was induced in a new place.

The realms of influence of Spemann's organizer and the zone of polarizing activity (ZPA) in the chick limb are pretty large, affecting the development of the entire embryo or a large body part. But organ-

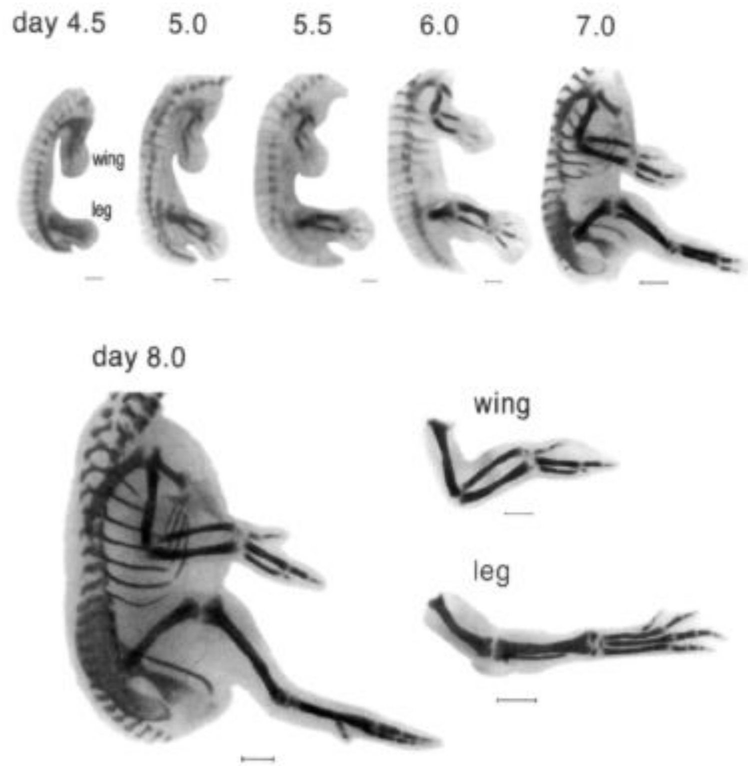


Fig. **2.3 Limb formation in a chicken.** The wing and leg buds grow dramatically over several days of embryonic development. The laying down of cartilage, which precedes bone deposition, is visualized with a special stain and proceeds in order from upper limb parts to the digits. Note that the details of wing and leg anatomy differ in detail. photos courtesy of joseph j. lancman and john

FALLON, DEPARTMENT OF ANATOMY, UNIVERSITY OF WISCONSIN

izers have been found that act in finer scales. In 1980, Fred Nijhout of Duke University showed that the eyespot patterns on butterfly wings were also induced by an organizer. When Nijhout killed a tiny patch of cells that would form the center of the eyespot, no eyespot formed. More interesting, he found that when this small group of cells was isolated from the developing butterfly wing in the first day of the chrysalis stage and transplanted to a site elsewhere on the wing, a new eyespot

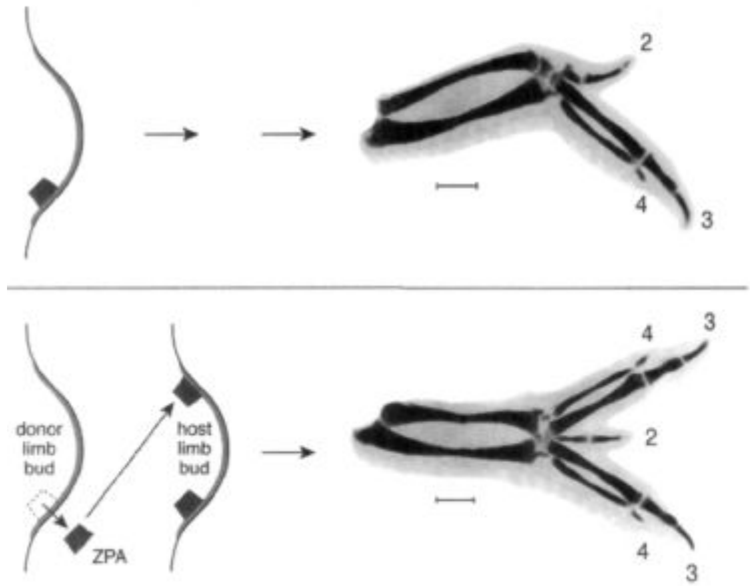


Fig. **2.4 Induction of Polydactyly in a chicken.** Transplantation of the zone of polarizing activity in the developing wing bud from a posterior site to a new anterior position induces extra digits with opposite polarity to the normal digit pattern. photos courtesy of

JOSEPH J. LANCMAN AND JOHN FALLON, DEPARTMENT OF ANATOMY, UNIVERSITY OF WISCONSIN

now appeared (figure 2.5). Only cells at the future center of the eye-spot had this property. Nijhout dubbed the eyespot organizer the "focus."

All organizers share the property of influencing the formation of pattern, or *morphogenesis,* in tissues or cells. The basic interpretation of their special activity is that the cells of organizers produce substances that can influence the development of other cells. Such substances have been dubbed morphogens. The effects of organizers depend upon their distance from target cells: cells nearby are most affected whereas cells farther away in the newt embryo, limb bud, or butterfly wing are not (or less) affected. It has long been thought that

Fig. 2.5 **Induction of eyespots in a butterfly.** Transplantation of cells at the center of a developing eyespot to other locations in the developing wing induces an eyespot in those locations. photo courtesy OF DR. H. FREDERIK NIJHOUT, FROM HIS *THE DEVELOPMENT AND EVOLUTION OF BUTTERFLY WING PATTERNS,* USED BY PERMISSION OF SMITHSONIAN INSTITUTION PRESS

morphogens produced in one site diffuse outward and form *concentration gradients* from their source. The idea then is that cells surrounding the source respond according to the amount of morphogen they experience. For example, in the chicken wing bud, cells close to the ZPA develop the posterior type of digit (digit 4), and those farther away progressively develop more anterior type of digits (digits 3 and 2 respectively). In the butterfly eyespot, the concentric rings of differently colored scales are thought to reflect different responses to different levels of the focal morphogen at different distances from the focal source. The morphogens responsible for the activity of organizers were some of the most sought "Holy Grails" of embryology. The major difficulty that retarded further advances was that the organizer activity was a property of collections of cells. Any cell makes thousands of substances and it was always possible that more than one substance was responsible for organizer activity. While transplantation was a powerful tool, embryologists needed some way to find morphogens in the complex soup of cell biochemistry. They would wait decades.

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## Hopeful Monsters

The animals created by Spemann, Saunders, and Nijhout were man-made monsters with duplicated axes or extra digits or altered wing spots. But these sorts of abnormalities were not unknown in nature. In fact, Bateson, in his 1894 treatise *Material for the Study of Variation,* catalogued and described a whole parade of "monsters" from across the animal kingdom that displayed extra, missing, or altered parts. Bateson culled from museums, collectors, and anatomy departments across Europe a menagerie of oddities including: a sawfly and a bumblebee with legs in place of their left antennae; crayfish with extra oviducts; butterflies with missing or extra eyespots; frogs with extra vertebrae or transformations of vertebral types; and much more (figure 2.6).

Bateson divided these abnormalities into two basic types: those in which the number of repeated parts was altered and those in which one body part was transformed into the likeness of another. He called the latter variants *homeotic* (from the Greek *homeos* meaning same or similar), and this will be a very important term to remember. Bateson's motivation for collecting these oddities was to show that leaps in morphology can occur in nature and thus could be the basis of evolutionary change. I have to say right off the bat that, as intuitive and appealing as Bateson's reasoning may first appear, biologists generally believe with very good reason that the notion of evolution making such large leaps in a single bound is very, very unlikely. The fact that such variations arise does not mean that these are founders of new types or species. Rather, from what we now know these monsters are almost certainly misfits that will be swept away by the power of natural selection with no chance of passing on their traits. This notion of "hopeful monsters" giving rise to new forms in one single bound has been very difficult to dispel, particularly in the popular scientific press (the BBC even produced a program with this title a few years ago, despite my pleas with the producer that it was a discredited idea). It is a seductive notion, but without any merit. In the course of this

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book we shall see that there is no support for, nor any need to invoke, hopeful monsters as agents of evolution.

Perhaps the most obvious limitation presented by Bateson's catalog is that most examples presented defects in only one of a pair of structures. While provocative, these one-of-a-kind museum pieces were rare finds

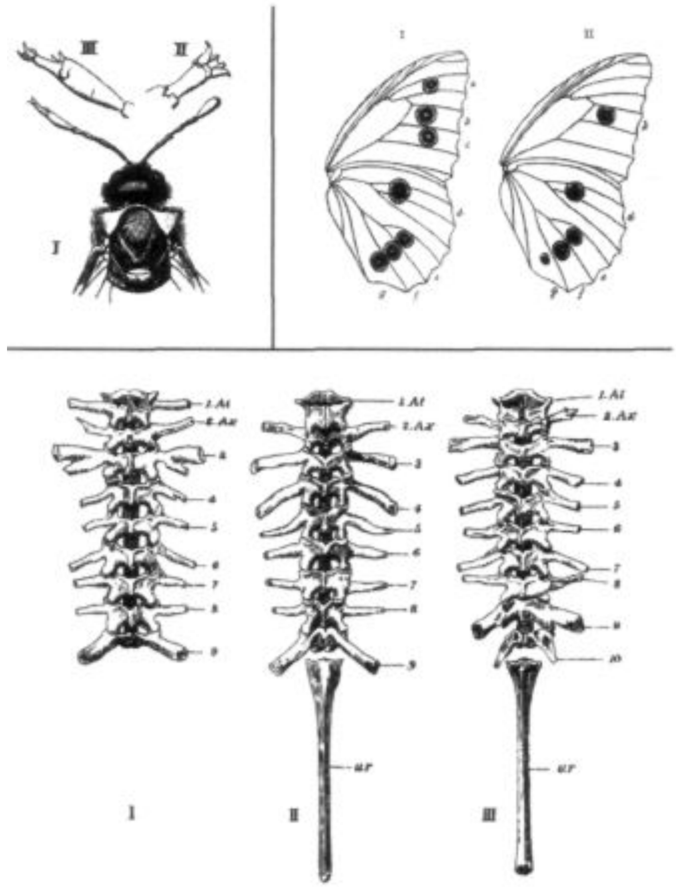

Fig. 2.6 **Some of Bateson's monsters.** Upper left, a homeotic transformation in a sawfly where one antenna is transformed into a leg. Upper right, eyespots missing from a butterfly wing. Lower panels, variation in vertebrae and their projections in a frog. from

W. BATESON, *MATERIALS FOR THE STUDY OF VARIATION* (1894)

and their causes were unknown. It was important to understand, for example, whether such forms were heritable or might be the result of physical damage to the embryo while it was forming (and thus would not be inherited). It did turn out that Bateson's kinds of monsters were informative, not so much for telling us about the true cause of evolution, but for insights into development that bear on evolution. As foretold in one of my favorite essays by the late Stephen Jay Gould, one that in fact influenced a change in direction early in my scientific training, Bateson's monsters were "helpful" scientifically, but hopeless as individuals.

### How Many Fingers? Human Digit Variation from Anne Boleyn to Baseball Pitchers

Bateson's collection of variations also included cases of humans bearing extra ribs, men with one or a pair of extra nipples, a spectacular case of eight fingers arranged in mirror image symmetry on a left hand, and individuals with extra digits on one or both hands (figure 2.7). The latter conditions, termed Polydactyly, are actually not that rare, occurring about 5 to 17 times per 10,000 live births.

There is quite a range of degrees of Polydactyly, from the appearance of just an extra flap or bud of skin on the side of the pinkie or thumb to duplications of the nail, individual bones, or entire digits. Extra digits may be separate or fused to other digits; the latter condition is known as synpolydactyly. In some cases, the condition is fully bilateral on both hands and feet (figure 2.8).

Humans can fare quite well with extra digits. There are famous cases of polydactylism in history, including Anne Boleyn, wife of Henry VIII, who apparently had an extra nail on one hand. It is also reported that King Charles VIII of France and Winston Churchill may have had extra digits. Antonio Alfonseca, a relief pitcher for the 2003 baseball World Series Champion Florida Marlins, has six digits on both hands and feet. The extra finger does not affect his pitching grip,

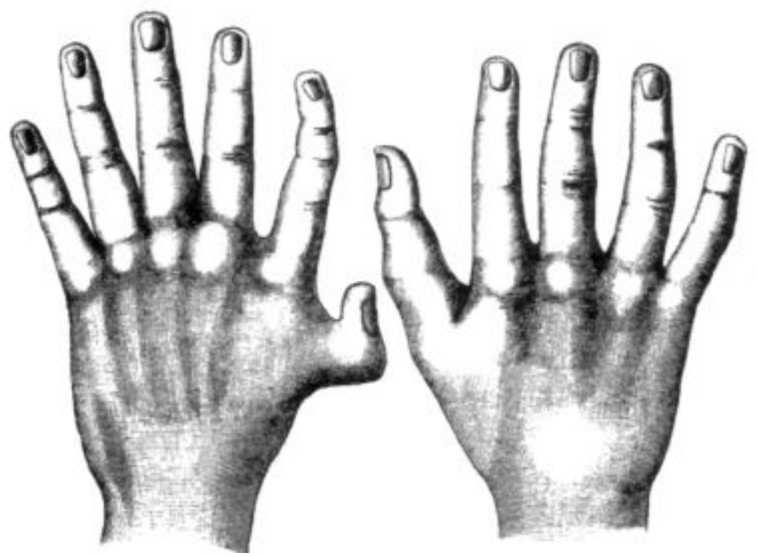

Fig. 2.7 **Polydactyly of a human hand.** from w. bateson, *materials for the study of variation* (1894)

so it does not affect his success on the mound. It does appear, however, to offer some psychological advantage as opponents often refer to batting against Alfonseca as "facing the six-fingered man."

Polydactyly is often heritable and pedigrees of polydactylous families are well-known. Indeed, it is reported that in a region of Turkey near Ephesus called Altiparmak, some families have taken the last name Altiparmak, meaning six-fingered ones.

Polydactyly is known widely throughout vertebrates, especially in cats, mice, and chickens. It is striking that similar digit patterns can occur in different animals, including humans, and they can be induced by experimental manipulations or inherited. This suggested that there could be some mechanisms in common for generating extra human fingers and chicken digits. But no progress was made into the mechanisms underlying digit number and pattern until advances were made in understanding some spectacular mutants in animals that have no fingers or toes—the humble fruit fly.

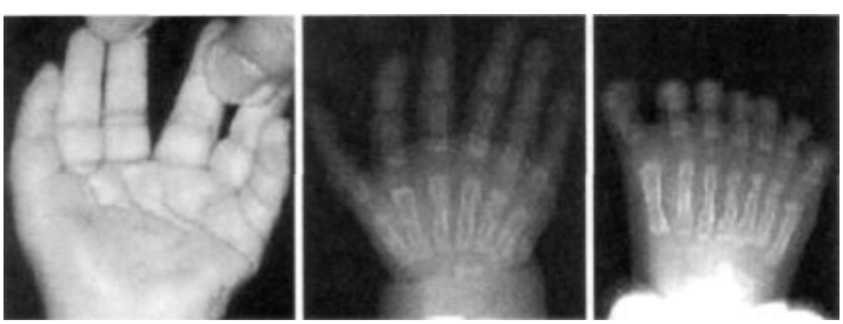

**Fig. 2.8 Polydactyly on both hands and feet.** This patient has six fingers on each hand and seven toes on each foot. photos courtesy OF DR. ROBERT HILL, MRC HUMAN GENETICS UNIT, EDINBURGH,

scotland; from *proceedings of the national academy of science, usa* 99 (2002): 7548

## Frankenflies

In order to make further progress into what monsters could teach us about the rules of development, a continual supply of abnormal types was needed, monsters that would breed true in the laboratory such that their offspring and subsequent generations would exhibit the same characteristics. In 1915, geneticist Calvin Bridges obtained the first true breeding homeotic mutant in the fruit fly *Drosophila melanogaster,* which was then just beginning to become a leading species for genetic investigations. Bridges isolated a spontaneous mutation that caused the tiny hindwings of the fruit fly to resemble the large forewings. He dubbed this mutant *bithorax.* Subsequently, several more homeotic mutants were identified in *Drosopbila.* For example, a rather spectacular mutant *Antennapedia* causes the development of legs in place of the antennae on the head (figure 2.9).

It is remarkable how these homeotic mutants can so completely transform one structure into another. It is not that development is stunted or fails, but that the fate of an entire structure is altered, such that a part is put in the wrong place or the wrong number of parts

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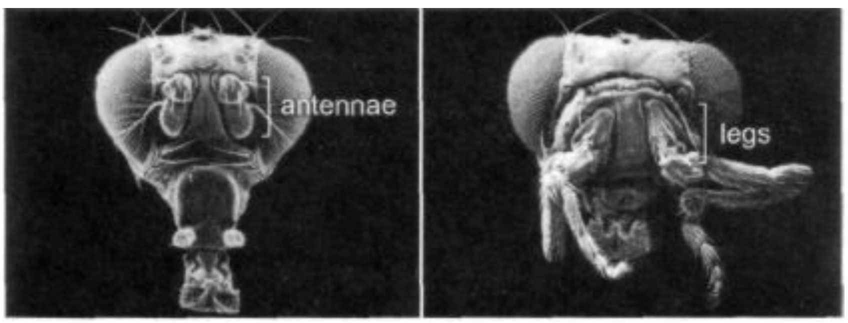


**Fig. 2.9 Homeotic mutant fruit fly.** Left, a normal fly head with antennae; right, an *Antennapedia* mutant fly in which the antennae are transformed into legs. photos courtesy of dr. rudy turner,

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form. Crucially, the transformation is of one serial homolog into the likeness of another (antenna to leg, hindwing to forewing). They are also so intriguing because each transformation is due to a mutation at a *single* gene. In *Drosophila,* only a small number of "homeotic" genes give homeotic forms when they are mutated, indicating that a small number of "master" genes govern the differentiation of serially homologous body parts in the fly.

The spectacular effects of homeotic mutants inspired what would become a revolution in embryology, and then another in evolutionary biology. But in order to appreciate their meaning and the insights they have to offer, we have to dig deeper to understand how these master genes work. How can one gene affect one whole structure and not another? What do the genes encode that have such large effects on animal bodies? Perhaps your first response is: "A fruit fly? Why should I get excited about a fruit fly?" The answers to all of these questions unfold from understanding more about DNA and how genes work, and along the way we'll learn some surprising discoveries about the makeup of different animal genomes.

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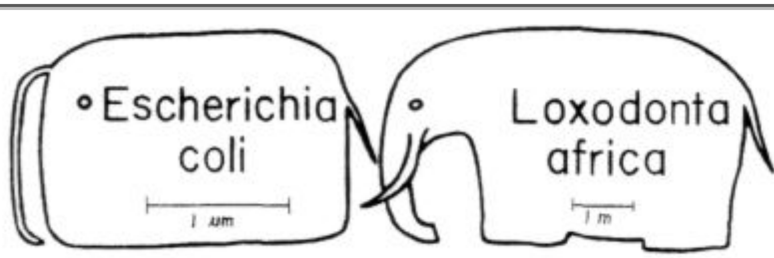


Whimsical representation of Monod's famous quip. courtesy of