Freaks *of* Nature

What Anomalies Tell Us about Development and Evolution

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TWO

Arresting Features

Development is All about Time

. . . the analysis of normal developmental processes and the experimental study of monstrous development [are] one and the same problem."

Charles Stockard (1921)[1]

. . . the speeds at which the internal factors work are of great importance in development, and variations in the relative speeds of the various factors may play an important part in the relation of ontogeny to phylogeny."

Gavin de Beer (1940)[2]

For one moment, many years ago, I was a great drummer—at least I felt like one. In any event, it was just a moment. I had been working for days on the most complicated beat I had ever attempted. It required each of my limbs to dance rapidly in a temporally precise pattern that, as the beat was notated, seemed too intricate for one body with just four limbs. But on this day I nailed it, my hands and feet punching out the rhythm as my mind, lagging slightly behind, observed and enjoyed the

goings-on as much as a second listener might have. From this respectful distance, my mind started to intrude, now trying to control—not just observe—the individual movements of each of my limbs. Suddenly everything fell apart, sticks and limbs colliding like a pile-up on the interstate.

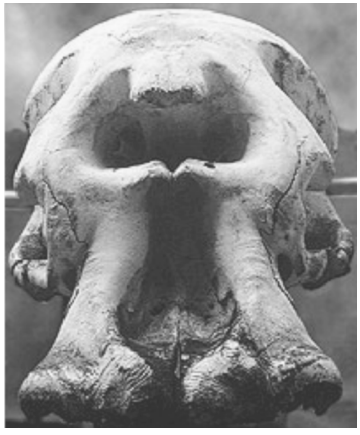
Successful drumming requires well-timed effort among diverse parts: finely tuned commands from the nervous system controlling muscles that are connected to stiff bones by elastic tendons. This mechanical system is extended to sticks gripped firmly yet flexibly in each hand, and to the "skin" of each drum. Every strike of the stick against the drumhead produces a reaction that influences the timing of the next strike. Hit off center or too hard and the stick bounces off in a direction or with a speed that's unexpected, altering and occasionally disrupting the timing of subsequent movements. In my case, merely focusing on my limb movements was enough to upset the delicate timing relationships that I had achieved through hours of practice.

Development also entails a balance among diverse parts interacting through time. As we will now see, even subtle disruptions to this balance can dramatically alter the development of the face and head, resulting in the emergence of unexpected and even monstrously novel structures. But it will also become clear that these "unexpected" novelties are not randomly produced. On the contrary, as Pere Alberch observed, there is a logic to monsters. To fully appreciate that logic, we must never neglect the central importance of time.

FACE TIME

"Ever wonder where our worst nightmares come from?" So began a 2003 news report announcing the discovery of the fossilized remains of a giant and now long-extinct "one-eyed" creature on the Greek island of Crete.[3] Considered in the context of Homer's terrifying description of a man-eating Cyclops in *The Odyssey*, written over 2500 years ago, the discovery suggests a possible source for Homer's inspiration.[4] But although this fossil belonged to an elephantine relative, not to a Cyclops, the news report's allusion to a single "eye socket" implies a connection between myth and reality that is not far fetched. Consider a modern elephant's skull, such as the one shown on the following page, with a large hole in the forehead. Of course the hole is not an eye socket. Rather it marks the location of the nasal cavity to which the trunk connects. The true eye sockets sit inconspicuously off to the sides. Thus, looking at this skull head-on, we see a large central hole that an ancient Greek, unfamiliar with living elephants, could easily have mistaken for the former home of a single, centrally located eye.

Although compelling, the notion that mythological creatures emerged from human encounters with the fossils of long-extinct creatures may not be the whole story. As mentioned in Chapter 1, the iconic images of the Roman gods Janus and Atlas eerily reflect embryological, not paleontological, forms. The same may be true of Homer's Cyclops. After all, why imagine



An elephant skull. Note the large central nasal cavity. The eye sockets are barely visible off to the sides.

adding flesh to bone to envision a Cyclops when some infants of humans and other animals appear in the exact form—if not size—of Homer's creation? Perhaps—and this is mere speculation—the mythical Cyclops arose by combining a mistaken interpretation of a giant fossil skull with the unmistakable horror of a tiny cyclopic infant.

Leaving aside the origins of the mythical Cyclops, we need not speculate about the origins of cyclopia because we already know a lot about it. For example, we know that cyclopia is the extreme form of a series of abnormalities that affect the entire face. These facial abnormalities mask equally extreme problems with the brain. In fact, cyclopia and its associated defects are known collectively as *holoprosencephaly,* a name that highlights the failure of the forebrain to divide into two separate halves. The incidence of holoprosencephaly may be as high as 1 in 250 fetuses, but because most of them do not survive to term, only

about 1 in 16,000 infants are actually born with this condition.[5] In the most severe cases, including cyclopia, nearly all will die within one week.[6]

In the early twentieth century, the zoologist Harris Hawthorne Wilder sought to develop a conceptual framework to better understand cyclopia and related abnormalities. In particular, it impressed Wilder that "the cases usually classed as 'monstrosities' can be as natural and symmetrical in their development as are normal individuals…."[7] But it is not so easy to adopt Wilder's noble perspective while gazing upon a cyclopic infant. Wilder's perspective can come only with repeated exposure and desensitization.

For example, consider the sketches on the following page from one of Wilder's papers.[8] If this is your first experience with cyclopia, you may wonder whether such creatures are any more real than the most fanciful beasts of human imagination. At first, you may find that the single eye grips your attention. But over time, you may begin to notice the empty space between eye and mouth and even perhaps that odd structure above the eye (at first, I thought this structure was only a smudge on the page). Would you, like Wilder, choose to describe these images as "natural"?

Because my introduction to cyclopia came through a cartoon, I remained unconvinced that such infants actually exist until I saw photographic proof. But although the photographs convinced me of the reality of cyclopia, each image—of chemically preserved infants staring with that single unblinking eye—only pushed me further away from the lofty perspective that

Two sketches from Wilder's "Cosmobia" series depicting two forms of cyclopia. Note the absence of a nose in the middle of the face and the proboscis above the eye.

Wilder espoused. The cartoons, on the other hand, provided much-needed distance such that, over time, I gradually came to appreciate cyclopia as a biological form worthy of careful attention.

As I became accustomed to the presence of a single, centrally located eye and as I studied Wilder's other sketches, one question became increasingly salient and puzzling to me. What, I wondered, might account for the fact that some of the infants Wilder examined had noses and some did not?

Today, scientists inundate us with "discoveries" of genes for every identifiable trait, such as depression, thrill seeking, and jealousy. Well, within the realm of identifiable human traits, the nose is certainly more distinct than depression or thrill seeking. So, does its absence in a cyclopic infant imply that the "gene for the nose" has wandered off with the "gene for two eyes"? Are these two genes somehow linked, like conjoined twins? Or perhaps these two genes comprise a single fragment of DNA that serves two facial functions.

To entertain these simplistic genetic fantasies is to take our eyes off the developmental processes that truly matter. Wilder

revealed these processes by creating and ordering a series of images (not unlike a geologist conveying the erosive power of water using time-lapse photography). Thus, the next face in Wilder's series, presented below, now shows two eyes—close-set but nonetheless distinct—and, for the first time, a nose.

The nose's appearance in its proper location seems almost refreshing, as if the world has been made right again. But where did it come from? Glance back and forth between the various sketches and the answer presents itself: That "thing" above the cyclopic eye is a nascent nose (a *proboscis* in technical jargon), its path to the middle of the face blocked by eyes that have not gotten out of the way. In Wilder's words, written a century ago, "the nose, which is prevented from coming down in the usual manner through a downward growth of the fronto-nasal process, remains above the double eye and presents a shape something like a proboscis, decidedly abnormal, but characteristic of all monsters in whom there is no space between the eye components."[9]

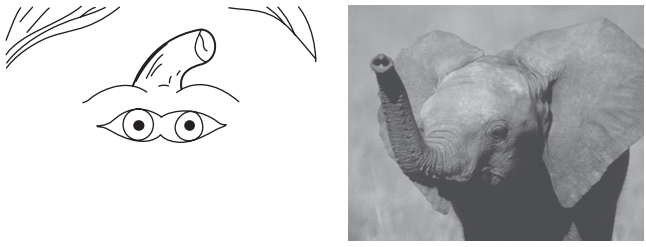
Two more sketches from Wilder's "Cosmobia" series depicting a properly located but rudimentary nose (left) and a fully formed nose (right).

But even the nose depicted here, having squeezed through the narrow space afforded by the barely separated eyes, is only "a small and narrow nose rudiment, usually with a single median nostril." When the eyes provide more space, as shown in the final sketch in this series, a normal nose results.

We now know much more than Wilder did about how the developing eyes influence the developing nose. In particular, the eyes do not begin as a single centrally located eye-field that then divides and moves laterally to produce two eyes.[10] Rather, the eye-fields begin as a continuous line of cells awaiting a chemical trigger that suppresses activity in the eye field's central region. When this suppression occurs, the line of cells is divided into two separate eye-fields that can then develop further into two properly placed eyes.

Like cars arriving at a crowded intersection, the group of cells that will produce a nose cannot move along until the eye fields have given way. The nose cannot go around, and so it must wait for an opening and that opening must arrive on time. Otherwise, the face will be stuck with that oddly shaped and positioned proboscis that signifies the cyclopic infant.

The fact that the same cells that build a nose can so easily produce a tubular proboscis reflects a fundamental developmental process—called *induction*—whereby interactions between neighboring tissues stimulate changes in gene activity and produce new tissue. In other words, body parts arise when cells of one type interact with neighboring cells of another type, with the *interaction* producing gene activity that *induces* the development

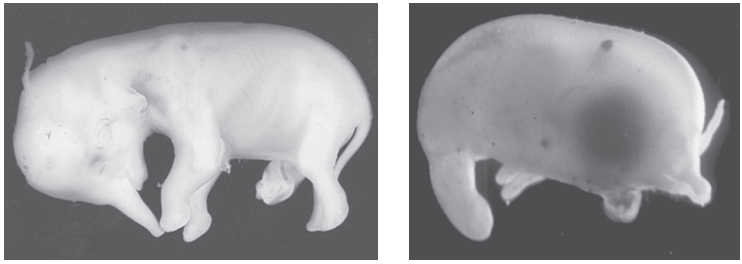


Enlargement of Wilder's sketch of a cyclopic infant to show the proboscis located above the eye (left). A young elephant (right).

of the body part in question. Aquiline nose here—ungainly proboscis over there.

Does the shape of the proboscis of the cyclopic infant remind you of the trunk of an elephant? If so, perhaps—and here I am really speculating—elephants evolved trunks by manipulating the developmental interactions among the cells that produce eyes and proboscis. This speculation seems a bit less fanciful when we compare the fetus of a normal elephant[11] with that of a cyclopic mouse, as shown on the following page.[12] Now the striking resemblance between their enlarged proboscises is even more apparent. Thus, not only does the nasal cavity of an elephant resemble the bony socket for a cyclopic eye, but the fleshy trunk that connects to the nasal cavity also resembles the nose of a cyclopic fetus. Whereas the former resemblance may be superficial, the latter may reflect a deep embryological link.

Although this embryological link between the proboscises of elephants and cyclopic infants is speculative, the lesson illustrated by Wilder's sketches is not: The same tissue can grow to be a nose or a proboscis depending upon the nature of the local cellular interactions. In the case of the nose, avoiding the



An African elephant fetus fifty-eight days after conception (left). An embryonic mouse engineered without the sonic hedgehog gene (right); note the enlarged proboscis.

development of an unsightly proboscis depends upon the *timely* movement of cells from one locale to another.

Around the same time as Homer, 7,000 miles west of Crete in Tlatilco, a small village on the outskirts of present-day Mexico City, sculptors were representing a different category of facial disfigurement. Their striking creations would mesmerize the archaeologists who unearthed them 3,000 years later. These small ceramic figurines depict gracefully rendered female forms. Most are naked, with bulging thighs, slim waists, blunted arms, and heads adorned with fancy hair-dos. Each face is fully realized, often giving the impression of a mask concealing the true face underneath.

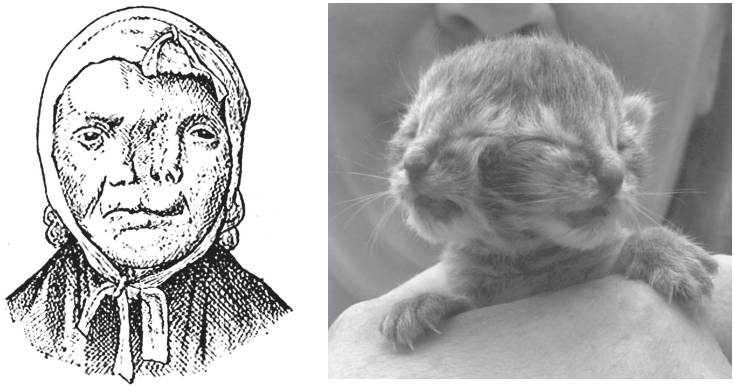
A few dozen of the figurines offer much more than mere stylized representations of the female form. These figurines are typical in every respect but one: the presence of two faces occupying the single head. Scholars have usually interpreted such sculptures as representations of mythological or spiritual beings. Indeed, why would we think anything different about these two-faced Neolithic figurines?

Tlatilco figurine depicting diprosopia, in this case characterized by two mouths, two noses, and three eyes.

To answer this question, we must compare additional figurines. When Gordon Bendersky, a physician and medical historian, made such a comparison, he noted that the figurines ranged from two overlapping faces sharing a single central eye socket through near-total facial separation with the emergence of four distinct eyes.[13] Such a series might easily be mistaken for artistic variations, but it appears that these ancient sculptors had more than art in mind. As Bendersky notes, the clinical precision of the Tlatilco figurines may distinguish their makers as among the first medical illustrators known to history.

The condition modeled by these sculptors is *diprosopia* (pronounced di-PRO-so-pia), a rare congenital malformation that entails duplication of facial features. As the subsequent

illustration of a woman from a medical textbook attests,[14] diprosopia does not necessarily lead to early death, although individuals with more extreme conditions, like the kitten in the figure, typically do not live long.



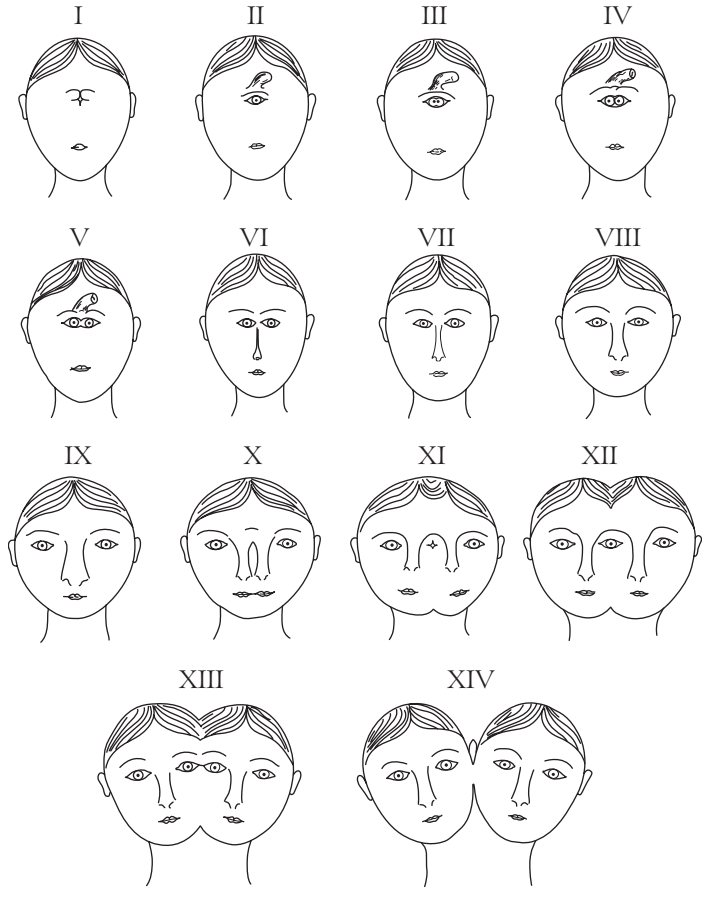
A woman (left) and kitten (right) with diprosopia. The kitten exhibits a more extreme form of this condition.

In an odd parallel of history that transcends 3,000 years of fascination with congenital malformation, the Tlatilco figurines bring us back to Wilder, who discussed diprosopia in the same paper in which he discussed cyclopia. Remarkably, despite a formidable temporal gap, a link between Tlatilco and Wilder binds this narrative together: The gradual transitions in the Tlatilco figurines convinced Bendersky of their real-world origins, just as the gradual transitions in biological forms helped Wilder to appreciate the embryological forces that, like a subterranean river, unite the surface features.

Now let's look at Wilder's complete series, presented on the following page. It is anchored on one end by cyclopic monsters with missing features—*monstra in defectu*—and, on the other, by diprosopic monsters with an excess of features—*monstra in excessu*. Struck by the neat arrangement of this series, he coined a term, *Cosmobia*, from the Greek, meaning *orderly living beings,* to capture his perspective on the developmental origins of monsters.

According to this perspective, cyclopia and diprosopia are not distinct conditions, but rather aspects of a single condition that occupy opposite ends of a continuous spectrum. Somewhere in the middle, around plates VII and VIII, the range of "normalcy" is contained, almost lost in a sea of diversity. Within this broad context, normalcy can seem mundane, its form no more or less miraculous, or special, or more perfect than the others. Wilder was adamant on this last point, taking issue with the notion that cyclopia and diprosopia are deformations. "Abnormal they certainly are in the sense of not being the usual form in which a given species manifests itself," Wilder wrote, "but they are not deformed."[15]

As Wilder acknowledged, he was not the first to recognize the "imperceptible gradations" that comprise a series of monsters.[16] Rather, his unique contribution was to note the "symmetrical anomalies on either side of a normal being"[17] that connect the previously disconnected *monstra in defectu* with *monstra in excessu*. In his *Theory of Cosmobia*, he inferred "a cause existing in the germ, or applied during the very early stages of development"[18] through which the full range of monsters could be created artificially.



Wilder's complete "Cosmobia" series, from cyclopia (I) through normalcy (VII) through diprosopia (X–XI). Beyond diprosopia lies a condition known as dicephalus. Contrary to what this series suggests, dicephalus is not a further extension of diprosopia, but rather a variant of conjoined twinning.

By *germ,* Wilder meant the genetic material contained within sperm and egg. It was his belief that "the ultimate cause of the development of the organism and its architectural details lies in the germ."[19] So it followed that "true excessive or defective Cosmobia can be produced experimentally only through a cause

which is applied early enough to lead to the formation of a germ that differs as much from the normal type of germ as the resulting organism differs from the normal adult."[20]

In 1908, as the 40-year-old Wilder wrote these words, he was corresponding with Charles Stockard, a scientist ten years his junior who had different ideas about the developmental origins of monsters. At the end of Wilder's paper, in a section devoted to recent work in the field, he admitted that Stockard's experiments with minnow and trout embryos "quite forbid me from taking a strong view concerning a germinal variation as always the necessary cause which I might otherwise have done."[21] Thus, Wilder was struggling to understand organisms as products of complex developmental cascades rather than as revelations of genetic predestination. This struggle would define in even more dramatic fashion the career of Charles Stockard and, indeed, the chaotic century that, in 1908, was just beginning.

CHARLES STOCKARD'S CENTURY

When I think back on my graduate school research at the University of Chicago, the image that comes most readily to mind is my sitting alone in a room late into the night and watching two rats, bathed in red light,[22] having sex. I know how strange that sounds, but there are more people watching rats have sex than you might imagine. In fact, the scientific study

of rat sexual behavior has provided invaluable insights into the hormonal and neural mechanisms that underlie complex behavior. The great successes in this area of research include the discovery of how hormones control the estrus cycle, prepare the reproductive system for fertilization, and act on the nervous system to promote those behaviors that make reproduction possible. For my graduate work, I needed to identify female rats in heat, a state that occurs every four or five days. To identify such females, I routinely inspected vaginal cells, extracted using a swab, under a microscope.

That a vaginal swab could reveal an animal's reproductive state was discovered by George Papanicolaou, a 34-year-old assistant to Charles Stockard at Cornell University Medical College in New York City. Working with guinea pigs, Stockard needed to know when his females were in heat. Papanicolaou had the idea that monitoring vaginal cells might provide useful information quickly and efficiently.

As is so often the case in science, the value of Papanicolaou's idea projected far beyond Stockard's relatively narrow concerns. Years later, he was to make the serendipitous observation that the vaginal cells of some women are abnormal. He surmised that the presence of such abnormal cells predicts cervical cancer, still one of the leading causes of death among women. Working against an incredulous medical community, he was finally able to publish his findings in a major professional journal in 1941. Papanicolaou's method, originally devised to help Stockard identify guinea pigs in heat, is now known as the Pap smear.

But back in 1910, Stockard's research had nothing to do with cervical cancer or sexual behavior. Rather, he was interested in the effects of alcohol intoxication on the offspring of pregnant guinea pigs. These were heady times for alcohol research: The temperance movement would soon achieve its greatest victory in the United States with the 1919 ratification of the Constitution's Eighteenth Amendment, prohibiting the manufacture, sale, or transportation of alcoholic beverages. Aligned with this effort were eugenics proponents, who sought to uplift the human race through selective breeding of "superior" individuals and, when necessary, the sterilization of "degenerates." Eugenicists believed that alcoholics were corrupting the human race by passing on their inferior traits to future generations.

So when Stockard showed that prolonged and repeated alcohol intoxication in guinea pigs produced gross malformations in offspring—including complete absence of eyes—that could be passed down to the next generation, eugenicists immediately embraced his findings.[23] Stockard so welcomed their embrace that he framed his work on intoxicated guinea pigs and their "weak" offspring as the study of "racial degeneration."[24]

An immediate challenge to Stockard's conclusions came from a young geneticist, Raymond Pearl. Like Stockard, Pearl focused on the effects of alcohol intoxication, but using chickens instead of guinea pigs. He exposed male and female chickens to alcohol for one hour each day from birth to adulthood, at which time they were mated. Although alcohol treatment lowered fertility rates, Pearl found that those offspring that were

produced were heartier and less likely to be deformed in comparison to the offspring of untreated parents. He attributed his findings to the detrimental effects of alcohol *only* on those eggs and sperm that were already weak—strong eggs and sperm were unaffected. Pearl further argued that although some of the weak and alcohol-exposed eggs and sperm produced deformed offspring, the predominant effect on them was lowered fertility. Thus, Pearl argued, alcohol exposure weeded out the inferior embryos, leaving behind the hardiest survivors. For Pearl, this Darwinian explanation resolved the "apparent contradiction" between his results and those of Stockard.[25]

Beyond the particulars of laboratory science, Pearl was convinced that the perceived social and political consequences of Stockard's findings flew in the face of common sense. After all, Pearl noted, the affluent and the intellectual are no strangers to the pleasures of alcohol. So if Stockard's findings were relevant to the human condition, as so many contended, Pearl—as a "hearty drinker" and a member of the educated New England elite[26]—could "see no escape from the further conclusion that a great majority of the individuals belonging to the higher intellectual and social classes in the countries of Western Europe today ought to be blind, dwarfed, and degenerate wretches…."[27] In contrast, Stockard's embryological perspective convinced him of alcohol's detrimental effects on the embryo. But with the conflict between Stockard and Pearl resting so heavily on the issue of racial degeneracy and social

policy, it was easy to lose sight of the basic scientific issues that had not yet been resolved.

Of course, today we are acutely aware that alcohol is a powerful teratogen that, when consumed during pregnancy, causes (among other things) the death of rapidly dividing cells in the developing embryo. Depending on the quantity and timing of alcohol consumption, a variety of malformations and neurological problems, now collectively referred to as *fetal alcohol syndrome,* can result. Unfortunately, confirmation of alcohol's teratogenic effects would be delayed many decades, in part because Prohibition, by removing alcohol from the public sphere, ameliorated concerns about the negative consequences of alcohol consumption.[28]

Incredibly, in a turnabout, Stockard reassessed his own research and embraced Pearl's Darwinian explanation. He then promoted alcohol as a tool for achieving eugenic goals. Although once an advocate of efforts to improve prenatal care, he now suggested—before a stunned audience of temperance advocates in 1920—that alcohol, "if used in a eugenic way," could "eliminate bad individuals" by preventing them from being born.[29] Pearl was appalled and, in 1927, would distill his disdain for the eugenics movement in a remarkable article published in *The American Mercury*. In one particularly powerful passage, he described eugenics as "a mingled mess of ill-grounded and uncritical sociology, economics, anthropology, and politics, full of emotional appeals to class and race prejudices, solemnly put forth as science, and unfortunately accepted as such by the general public."[30]

As we now know, despite the efforts of Pearl and many others, the eugenics movement would not be extinguished with words. Over the next decade, Germany would carry the banner of eugenics with pride, creating sterilization programs designed to bar the mentally and physically handicapped from a future that the Nazis had reserved only for superior beings.

Germany was not alone. In 1937, at a conference organized jointly by the American Eugenics Society and the New York Academy of Medicine, the physicians in attendance discussed, with some urgency, the need for sterilization, contraception, and selective breeding as countermeasures lest society, as one attendee commented, "deteriorate due to the improper distribution of births…."[31]

In attendance at that conference was Charles Stockard, now a distinguished senior scientist and newly appointed President of the Board of Scientific Directors of the pro-eugenics Rockefeller Institute for Medical Research (later renamed The Rockefeller University). Stockard reportedly communicated his concerns in this way:

> If we are going to continue to live in this world and not face ultimate extermination, we must give thought to the effect of the artificial conditions of civilization, as they affect human breeding. Ultimately, propagation should be absolutely prevented among low grade and defective stocks who are unable to pull their own weight in the social organization. Not only is there statistical certainty that they will produce offspring

> who, on the average, will have similar hereditary limitations, but, in addition, they provide a home environment which makes proper development impossible. We have never been willing to face these questions in a large enough way….[32]

In two years, Stockard would be dead. Soon thereafter in Berlin, his words, and those of his eugenicist colleagues, would be put into action in the form of a newly authorized program to exert ultimate control over hundreds of thousands of troubled people deemed unworthy of life. For this program—housed in a villa at 4 Tiergartenstrasse—sterilization did not go far enough. The T-4 *euthanasia* program was born.

Was Charles Stockard evil? In light of his active support for eugenics and the tragic legacy of that movement, one might reasonably conclude that he was. But it may be more useful to view Stockard's mission as emblematic of a troubled period in our political, scientific, and social history. In this one man, we can glimpse a century of conflict and confusion regarding such core concepts as genes, inheritance, and environment. In him, we see a scientist who began his career studying the effects of the environment on individual development, and ended it as a rabid proponent of eugenics, devoting his time to an ambitious examination of the inheritance of form and behavior in pure-bred and hybrid dogs (which he housed at his specially built farm near Peekskill, New York).[33]

Ironically, the young Stockard's challenge to Wilder prevented that elder scientist from taking "a strong view" on the

role of genes in the production of cyclopia and other malformations. This is the Stockard to whom we will soon return. But before we do, let's briefly examine the efforts of those early scientists who, like the young Stockard, sought to alter embryonic development within the confines of the laboratory.

DEVIATING DEVELOPMENT

The efforts of Etienne Geoffrey Saint-Hilaire to classify the world of monsters, described in Chapter 1, were followed in 1820 by his experiments aimed at understanding the developmental processes that produce the normal and the monstrous.[34] Skeptical of the *preformationist* notion that development unfolds according to a preordained plan that is unaffected by developmental conditions, Etienne sought to "deviate development" by altering the incubation environment of chicken eggs.[35] These experiments never yielded definitive results. Similar efforts by his son, Isidore, were even less successful.

In 1860, forty years after Etienne began his experiments, the Academy of Sciences in Paris announced the Prix Alhumbert. This prize was to be awarded to the best paper demonstrating environmental modification of a developing embryo. With Isidore sitting as a member of the commission that created this competition, two awardees were announced in 1862. One of them, Camille Dareste, is now regarded as the founder of experimental teratology (though Dareste himself bestowed that distinction on Etienne).

Dareste, like Etienne, manipulated the incubation environment of chick embryos. He heated, cooled, shook, and chemically treated his eggs. Although his methods were neither perfect nor novel, he was more systematic and successful than the Saint-Hilaires and the scientist with whom he shared the Prix Alhumbert. Dareste found that his manipulations produced the severest abnormalities when he applied them early in embryonic development. He inferred that his treatments succeeded in producing malformations because they somehow slowed or arrested the process of development.

Dareste's observations and inferences make clear that from its inception, experimental teratology was intimately linked with the most basic issues of normal embryology. Nonetheless, teratology and embryology would develop as separate fields, a separation that is unnatural. Writing more than a century after Dareste claimed his prize, one embryologist described the situation like this:

> If an experiment is performed on an embryo, and the embryo nonetheless develops normally, the investigator believes he is an embryologist studying regulation. If the embryo fails to regulate and develops abnormally, if something overt goes wrong, he is studying abnormal development and he is a teratologist. An embryologist uses abnormal development as a key to the normal; an experimental teratologist tries to see where normal development went wrong and why, especially if he has clinical inclinations. But since whatever an experimental investigator does to an embryo (and in many cases

> the experimentalist may be Nature) some things go right and some go wrong, all distinctions between embryology and experimental teratology become blurred; the disciplines are symbiotic.[36]

This symbiosis is evident in the seamless transition from the work of Dareste to that of Charles Stockard.

PRECIOUS MOMENTS

In 1907, Stockard reported the first in a series of methodical studies using the eggs of minnows and trout that would lead him to the same inference as Dareste's: that his experimental treatments somehow slowed or arrested the process of normal embryonic development. Moreover, Stockard's work would allow him to pinpoint those developmental moments when embryos gain the capacity to become monsters.

As with Wilder's Cosmobia series, Stockard's monsters comprise a range of deformities from the single to the double—from cyclopia to two-headedness. That such similar series exist for both human and minnow attests to the power of experimental embryology to probe the most fundamental biological processes. This power derives from a simple yet profound fact of embryology: Widely divergent forms of life share the earliest phases of development. Thus, as we face the striking developmental parallels between two evolutionarily distant animals, our attention is

diverted toward those earliest embryonic moments after the egg has been fertilized, when the embryo is still overtly indistinguishable as a human or a minnow. At this time, the eyes, head, and tail are little more than fields of cells, knocking into one another, dividing, folding, gradually becoming recognizable parts.

The once-popular preformationist view of development, which had motivated Etienne Geoffrey Saint-Hilaire's foray into experimental work, imagined that the fertilized egg was, like nested Russian dolls, simply a diminutive version of the final organism into which it would grow. In stark contrast, the alternative, epigenetic view appreciates that

> the egg's organization suffices only for its development to the next immediate developmental stage, which must then make additional instructive materials to develop into a further stage, which must in turn repeat the process.... In this view, development is a series of generative processes, each building on the organization of the previous stage.[37]

Monsters help us to appreciate the critical differences between these two perspectives. How? If an embryo unfolds into a monster, then a preformationist has little choice but to imagine that the monster existed in nascent embryonic form from the outset or, at the very least, resulted from an extreme deformation of the early embryo. But if we view development epigenetically as a step-by-step, cascading series of generative processes, then a monster can be neatly understood as the destination produced

when an embryo takes an alternate path at some time *during* development. There is no need for prestructure, preform, or predesign; such static notions leave no space for *time*.

But time matters. As Stockard demonstrated in a variety of ways, the production of cyclopic and two-headed minnows is limited to a narrow window of opportunity—he called them "moments of supremacy"; today, we generally refer to them as *sensitive* or *critical periods.* For example, when Stockard exposed embryonic minnows to cool temperatures, he produced monsters of all kinds—but only if the exposure occurred within the first twenty-four hours after fertilization. In contrast, if Stockard waited more than twenty-four hours, he encountered what he called a "moment of indifference." Nothing remarkable happened.

What might be going on within the embryo that would distinguish a moment of indifference from a moment of supremacy? Building on Dareste's linkage between developmental arrest and the production of monsters, Stockard suggested that this linkage is particularly strong during a moment of supremacy because it is a time "when certain important developmental steps are in rapid progress or are just ready to enter upon rapid changes, a moment when a particular part is developing at a rate much in excess of the rate of other parts in general."[38] Accordingly, the nature of the insult—cooling, oxygen deprivation, and so on—is less important than the effect of that insult on the developmental rate. If development is slowed at the right moment, there will be monsters.

Stockard's idea that development is most modifiable when parts are changing rapidly is similar to the notion that bones are most easily deformable when growth is rapid. As with bones, which grow rapidly in brief spurts, Stockard pointed out that "eggs develop with rhythmical changes in rate,"[39] with periods of relative quiet interspersed with brief moments of turbulent transformation.

Stockard placed great emphasis upon the rhythm and rate of development. Imagine a car race, with each car representing a different embryonic cell or group of cells, and the speed of the cars representing the rate of development. If all of the cars are traveling at the same slow speed, then instructing all of them to slow down or even stop will have a negligible effect on their order in the race. Moreover, when the cars are allowed to speed up again, the previous relationships among the cars can be easily recovered.

But now imagine that the cars are traveling at different speeds. If they are suddenly commanded to stop, it will be nearly impossible to tell which car was where at the moment that the command was issued; and because each car will slow down at a different rate, cars will be passing each other even as they slow down, producing even more confusion about the relationship among the cars before the stop order was given. In a similar vein, cooling an embryo as it is undergoing a period of rapid transformation is more likely to disrupt normal development than if the same disruption is performed during a period of relative calm.

After fertilization, the first such transformative period is *gastrulation,* a process in which the newly fertilized egg begins to form discernible layers that will eventually develop into skin, gut, and brain. In addition, the primary axes of the body are established at this time, including the distinction between front and back, and top and bottom. In short, gastrulation is a moment of supremacy—of profound reorganization—of rapid and complex change. It is during gastrulation that embryonic development is most easily disrupted by the kinds of manipulations that Stockard used. Although the result of these manipulations to the embryos is often death, many of those embryos that survive develop abnormally, exhibiting a variety of malformations that includes cyclopia and twinning.

So we see that numerous environmental manipulations, applied early enough in development, are capable of producing a diversity of monstrous forms. This diversity was still another point of emphasis for Stockard. He noted his creation of "double monsters of varying degrees, from separate twins, fused but with complete bodies and tails, to double bodies and single tails, and finally different degrees of double headedness on single bodies. There are specimens exhibiting . . . cyclopia, and all types of malformed eyes . . . ."[40] But this observation did not imply to Stockard the random emergence of defects. On the contrary, he found that he could disrupt the development of any particular organ by precisely timing the environmental insult:

> The localized anomaly may involve only the eye, only the bilaterality of the brain, only the ear, only the mouth structures,

> only the kidneys…, only the genitalia, etc. It is evident that such anomalies could not occur unless there was a certain moment of specific and peculiar susceptibility *on the part of each organ* during which any unfavorable condition would act on it in a selective way.[41]

Moreover, because proliferation of particular organs continues beyond embryonic development, specific moments of susceptibility continue into postnatal life as well.

All of this makes clear once again how our understanding of monstrous development is intimately connected with the intricacies of normal development. It is because of this intimate connection that manufacturing monsters is surprisingly easy.

Just as Wilder commented on Stockard in his paper about monsters, so too did Stockard comment on Wilder. The elder scientist, Stockard wrote, was "misled" about the cause of monsters, thinking it was "more probable that orderly deviations from the normal would arise in the germ-plasm than that they should occur as a result of some modification during individual development."[42]

Wilder was wrong to think that monsters could arise only via a genetic mechanism, encoded in egg or sperm; as Stockard demonstrated, environmental factors can reliably alter the course of development to produce monsters. Still, Wilder was not completely wrong: for example, as is now known, genetic mutations underlie some cases of cyclopia, especially those that

run in families.[43] Moreover, we should not forget that even environmental factors can produce their effects by modifying the activity of genes or the action of their products.

In other words, both Wilder and Stockard were right and wrong, their disagreement reflecting an either–or, dichotomous mentality concerning the developmental roles of genes and environment. This mentality continues to confuse many people to this day.

But this confusion evaporates by reorienting our thinking. The key is to appreciate that development arises through a network of genetic and nongenetic interactions cascading through time. Within that network, developmental events that rely on a particular gene in one instance can occur through environmental influences in another. As we will examine further in Chapter 5, sex chromosomes are absent in some animals—for example, turtles and crocodiles—but this does not prevent them from developing into males or females.

In such species, incubation temperature replaces the need for sex chromosomes: We say that the effect of temperature on the developmental network is *interchangeable*[44] with the genetic mechanism that triggers the same process in, for example, humans and dogs. Similarly, cyclopia and its related conditions—again, known collectively as holoprosencephaly—can arise through either a genetic mutation or an environmental disturbance (for example, if the mother has diabetes or consumes alcohol), but in either case, the same developmental network is being modified. Clearly, we would be wrong to label *all* infants with holoprosencephaly as *mutants.*

Since Stockard's time, we have learned a lot about holoprosencephaly and the network of mechanisms that produces it. Recall that the name itself refers not to a malformed face, but to the failure of the forebrain to divide into two symmetrical halves. In fact, there is considerable variability in the degree to which the forebrain fails to divide, resulting in related variability in brain function and survivability in these infants.[45] Similarly, the faces of infants with holoprosencephaly can display cyclopia as well as a variety of other malformations of the eyes, nose, and mouth (including cleft palate). Thus, one of the characteristics of holoprosencephaly—even in those instances where it runs in families with known genetic mutations—is its variability.

The search for the mechanisms that produce holoprosencephaly in all its forms took its biggest step forward in the 1960s as a result of a cyclopia epidemic among sheep in Utah. The culprit was soon identified: Pregnant ewes were eating a highly toxic range plant known as the false hellebore, *Veratrum californicum*.[46] Subsequent research indicated that ingestion of the plant on the fourteenth day of gestation—that is, around the time of gastrulation, as Stockard would have predicted—was necessary to induce cyclopia. The critical ingredient of the plant was also soon identified and given the name, cyclopamine.

Cyclopamine produces its horrible effects in sheep, as well as goats, rabbits, hamsters, and chickens, so long as it reaches the embryonic environment around the time of gastrulation.[47] To affect so many species in such a predictable way suggested that cyclopamine was interfering with a fundamental developmental

mechanism. This is now known to be the case. As was recently discovered,[48] cyclopamine interferes with the function of a protein called sonic hedgehog (Shh)—the protein that results when the sonic hedgehog gene (*Shh*) is expressed.[49]

Among developmental biologists, *Shh* is a superstar, designated by Evo Devo enthusiasts as one of the "master genes."[50] Although much of the attention that *Shh* has received is deserved, it is easy to get too caught up in all the hoopla. Yes, identifying a relatively small set of genetic components involved in numerous developmental processes has provided important insights into both development and evolution, and *Shh* is undoubtedly a central player in these revelations. But *Shh* is only one component in a complex and dynamic machine. Thus, although mutations of *Shh* can produce holoprosencephaly, there are many other separate mutations that can produce the same condition. Moreover, although the detrimental effects of cyclopamine are mediated through the Shh system, there are other environmental factors that can have similar effects by acting on other components of the developmental network.

One simple, stubborn fact remains: No single genetic or environmental factor is able to account for the diverse malformations exhibited by infants with holoprosencephaly. Even infants with identical Shh mutations can exhibit the full range of malformations associated with the condition. How can this be? As one group of investigators recently noted, this is "one of the most perplexing questions in clinical genetics…."[51] After

all, should we not expect greater control from a gene that has attained the elevated status of "master"?

Our path out of this perplexity brings us back to the central importance of time. *Shh* is not special because of its linkage to particular traits, but rather because of its participation in a variety of similar processes. These processes occur at various locations within the embryo and at various times throughout development. For example, in the head, *Shh* is activated sequentially (and thus its associated protein, Shh, is produced sequentially), beginning in embryonic tissue in the brain and continuing in tissue that will form the face. One group of scientists,[52] working with chicken embryos, identified six distinct times when *Shh* is expressed and when important developmental events are occurring. Then, by exposing the embryo to cyclopamine at these times, the scientists blocked the Shh signaling system at each moment and location, and observed the outcome.

In effect, what these scientists found provides direct and more detailed support for what Stockard argued nearly a century earlier based on his work with minnows: Timing is key.[53] Exposure of chicken embryos to cyclopamine at different times produces specific malformations that reflect the particular region of the brain or face expressing *Shh* at the moment of exposure.

Accordingly, because *Shh* is expressed around the time of gastrulation when the nervous system is only beginning to develop, cyclopamine produces its most dramatic results when given around this time. If the embryo survives, it exhibits a

fused mass of brain tissue. Also, because development of the brain acts as a scaffold upon which the face is constructed, any massive malformation of the brain results secondarily in cyclopia. Wait a bit longer before giving cyclopamine—around the time that *Shh* is again being expressed, but this time specifically in the forebrain—and the result again is a mass of fused brain tissue and a range of severe facial defects (including extremely close-set eyes), but not full-blown cyclopia.

Now, wait a few hours longer—long enough that *Shh* has been expressed in the forebrain but not yet in the face—and now only the face is adversely affected. These facial defects are due to cyclopamine's effects within the face itself, rather than to secondary structural disturbances resulting from a malformed brain. Finally, give cyclopamine after *Shh* has been expressed in the face and the embryo now develops normally, even after very high doses.

Just as the downstream effects of a river dam are more severe the closer it is placed to the river's source, the effects of blocking *Shh* activity with cyclopamine become increasingly severe at earlier times in development. As the developmental process flows downstream, the effects of cyclopamine become increasingly focused to the point when it is possible to produce gross malformations of the face while completely sparing the brain. Thus, according to the authors of this study, "not only was embryonic age an important determinant of the teratogenic effect of cyclopamine but…the timing of *Shh* induction and

expression appeared to be equally relevant to the severity" of the facial defects that cyclopamine produced.[54]

We can now begin to understand how a single mutation of *Shh* can produce such a wide diversity of effects on brain and face: *Shh* is involved in a variety of similar processes that, because they recur at distinct anatomical locations and times, produce distinct results. Moreover, at each moment in developmental time, events at one location can set the stage for those at another; for example, defects in brain development can deprive the face of critical structural support that it will need to develop normally. This complex epigenetic cascade of gene expression and regulation—locked in an intimate embrace with time—makes the challenge of understanding development more than a mere cataloguing of genes.

The failure of the brain to divide into two lobes—and of the eye fields to produce two separate eyes—reflects a failure of development on the embryo's midline. So it is not surprising that cells that are concentrated on the midline express *Shh*. This explains why blocking Shh signaling with cyclopamine can play havoc with the development of structures that normally divide on the midline. Now, returning to the first half of Wilder's Cosmobia series, we can see how blocking *Shh* expression can produce deficits of midline division, as with cyclopia. But what about those conditions, such as diprosopia, that are characterized by an overabundance of division and that account for the other half of Wilder's series?

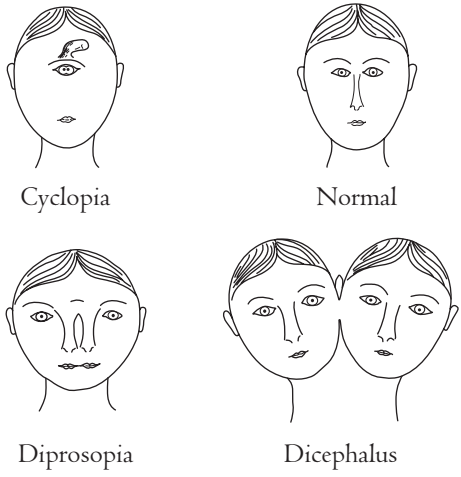
Here, too, we can tap into the epigenetic cascade that includes *Shh* to provide an answer. But now, rather than block Shh signaling with cyclopamine, we increase exposure to the Shh protein and observe the effects. True to expectation, increasing the amount of Shh available to the developing embryo increases activity on the midline, thereby widening the face and brain.

Adding Shh to the developmental stew has not yet produced the additional eyes and noses that characterize diprosopia. But it is clear that the width of the face is a regulated developmental characteristic and that *Shh* is one of many genes, and Shh one of many proteins, involved in this process. As we await final determination of the mechanisms involved, we can marvel at how the basic features of brain and face are constructed from materials both found and purchased within the chemical concoction that is the developing embryo.

PAS DE DEUX

Looks can be deceiving. Recall how Wilder's Cosmobia series depicts a range of conditions: from the collapsed midline of cyclopia, through normalcy, then the widening midline of diprosopia, to dicelphalus. Given Shh's role in the widening of the face, we might imagine that Shh activity (and that of other related molecules) can become so excessive that it actually unzips the embryo to produce two distinct heads. If so, perhaps the unzipping can continue to produce twins that

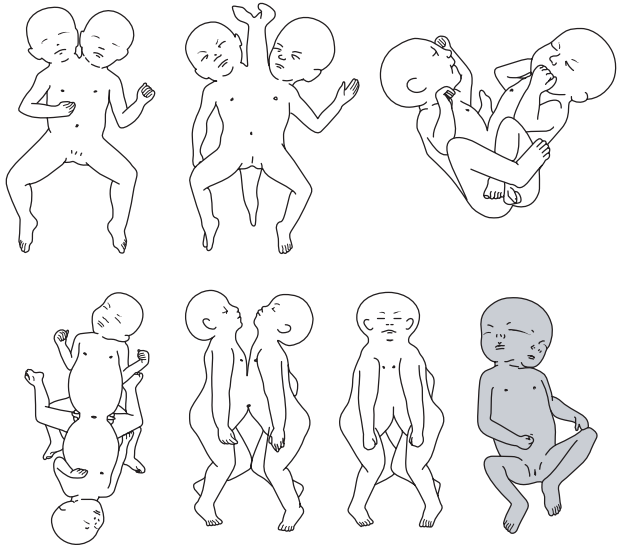
share fewer and fewer parts until two complete but identical twins emerge.



But what I have just described is a fantasy arising from taking Wilder's Cosmobia series and its implied continuity a bit too seriously. In fact, Wilder's complete series does not depict a single process, either in time or space. As discussed, even *Shh* is expressed during development at multiple moments and in multiple locations to produce the graded facial continuum from cyclopia to diprosopia. But to explain dicephalus, the next step in Wilder's series, we must jump back in time—all the way back to the earliest moments of embryonic development. For, rather than representing the next developmental step beyond

diprosopia, dicephalus is a wholly separate process deserving a wholly separate discussion of the mechanisms that produce twins—identical, fraternal, and conjoined.

The following figure displays yet another set of human infants, this one not so much a continuum as a nonexhaustive collection. The shaded figure, illustrating diprosopia, is included here only for contrast. It does not belong with the others. In fact, its inclusion here is as misleading as the inclusion of dicephalus in Wilder's Cosmobia series.



Some examples of human conjoined twinning. The shaded figure (at lower-right) depicts diprosopus, which has a distinct developmental origin and thus should not be included within the category of conjoined twins.

How do we know that diprosopia does not belong within the class of conjoined twins? The answer to this question, which is so elusive that even experts have disagreed, relies on information from a variety of sources. For example, although diprosopic fetuses are more likely to be female, dicephalic fetuses are equally likely to be male or female, thus suggesting the involvement of different developmental processes.[55] Perhaps even more compelling is the fact that the face of a human fetus develops between the fourth and eighth weeks of gestation, whereas gastrulation—after which twinning can no longer occur—is completed by the end of the second week. In other words, by the time that diprosopia develops in a human fetus, the time for conjoined twinning is long past.

Conjoined twins are only the most exotic of twins.[56] The least exotic are fraternal or dizygotic twins, which are produced when two individual eggs are fertilized by two sperm. Each twin develops separately and securely within its own dedicated uterine environment, enveloped within its own amnion and chorion, or the inner- and outermost membranes, respectively, that surround the fetus. Typically, each twin also has a separate, dedicated connection to the mother's circulation through its own placenta.

In contrast with dizygotic twins, identical or monozygotic twins are produced when a fertilized egg divides to produce two independent fetuses. The type of monozygotic twin produced depends on the *timing* of the twinning event. In about one third of all cases of monozygotic twins in humans, this division

occurs within three days of fertilization when the embryo comprises just two cells. Then, when the two embryos implant in the uterine wall, they do so in a fashion similar to that of dizygotic twins. That is, each fetus possesses its own amnion and chorion, as if they were two siblings living in the same house but sleeping in separate bedrooms.

But for the vast majority of monozygotic twins, the twinning event happens within four to eight days after fertilization. At this time, the embryo is in the process of implanting in the uterine wall. Under these circumstances, the resulting twin fetuses come to share a common chorion and, therefore, a common placental circulation. But each is encased within its own amnion, as if the two siblings were sharing the same bedroom but sleeping in different beds.

Very rarely, the monozygotic siblings come to share the same bed as well. In such cases, the twinning event occurs two weeks after fertilization, by which time the embryo has implanted in the uterine wall and gastrulation has occurred. This type of twinning is often associated with malformations and complications, including conjoined twinning, which results from the incomplete division of the embryo. (Although conjoined twinning is now thought by most experts to arise from the division, or fission, of a single embryo,[57] some still maintain that these twins arise from the partial rejoining, or fusion, of two previously separate twins.[58]) These twins are the rarest of the rare, roughly occurring only once in every 100,000 births. Survival is even more rare: Most die within one day of birth.

The most common types of conjoined twins are joined at the chest and abdomen. Some are joined side-to-side (as in dicephalus), others head-to-head or rump-to-rump. Occasionally, one of the twins is malformed, producing an asymmetrical relationship between the two. For example, if one twin lacks a functioning heart, the malformed twin will feed parasitically off the circulation of the other. In some extraordinary cases, as with Laloo and his parasitic twin, described in Chapter 1, one of the twins can grow partially inside the other.

Even more bizarre is *fetus in fetu,* in which one twin grows completely inside the other. In a recent and particularly shocking case,[59] an Indian man who had endured life with a rather large belly found, at the age of thirty-six, that he was having trouble breathing. Believing he had a rapidly growing tumor that was interfering with the movement of his diaphragm, the man's doctors decided to operate. As the surgeon opened up the man's belly and searched for the tumor, he found himself shaking a well-developed hand with long fingernails. Then came more limbs, bones, hair, genitalia—a jumble of body parts that, under different circumstances, would have cohered to form this man's twin brother.

This man lived with a twin he never knew, an odd situation to be sure but one that pales in comparison to the enduring challenges faced by conjoined twins as they struggle to make a life together. Nowhere are these challenges more apparent than with the dicephalic twins Abigail and Brittany Hensel, introduced earlier in this book. Born in Minnesota in 1990, they are among only a handful of such twins in recorded history

to survive with two heads, two spinal cords, two hearts, but only one pair of legs. Each twin primarily controls her own arm. (A third arm, which emerged awkwardly from their shared middle shoulder, was removed soon after birth.) Nonetheless, the twins have learned to coordinate their activities, working jointly to play the piano and shuffle a deck of cards. Such skills have arisen through lifelong learning experiences, just as jazz musicians learn to anticipate and respond to each other's improvisational ideas.

Other aspects of the Hensel twins' behavior must involve even more intimate coordination. After all, the lower half of their body is completely shared. Thus, their two nervous systems likely share control of both legs. It is not difficult to imagine how crosstalk and confusion might result from two nervous systems vying for control over each leg like two dogs fighting over a bone.

But the twins are not rendered immobile by their predicament. Far from it. As with the bipedal goat, these remarkable girls have successfully adapted their behavior to a unique biological condition. It may be that evolution has never favored dicephalus, but evolution also has never precluded living—even thriving—with this condition.

Perhaps more than any two sisters in the world, we would expect the Hensel twins occasionally to disagree. Indeed, in a truly self-defeating act, Brittany reportedly once hit Abigail on the head with a rock.[60] It has also been reported that when the two sisters cannot agree on a destination, paralysis can set in.

Similarly, two-headed snakes have been known to fight over food even though both heads benefit from each meal consumed; and when the two heads pull in opposite directions, one must win the battle if the entire snake—including both heads—is to move forward (and typically one "dominant" head wins most of these battles).

Perhaps these glitches are what doom dicephalic creatures in the wild and prevent the evolution of a dicephalic species. Evolution is a battle waged at the margins—where even the occasional food fight or moment of indecision is enough to compromise survival. Sometimes the costs are quite severe; for example, dicephalic turtles cannot retract both heads into a protective shell that has room for just one. In addition to these obvious costs, a dicephalic species is unlikely to evolve without a clear benefit to possessing two heads.

But if an animal were ever to find itself in an environment that, for whatever reason, did favor the possession of two heads, a dicephalic species could arise very rapidly for one simple reason: *The embryo's potential to produce two heads is no less ancient, and no less fundamental, than its potential to produce just one.* So there it sits, like so many other embryonic potentials, waiting in the wings should evolution ever see fit to call it forward for active duty.

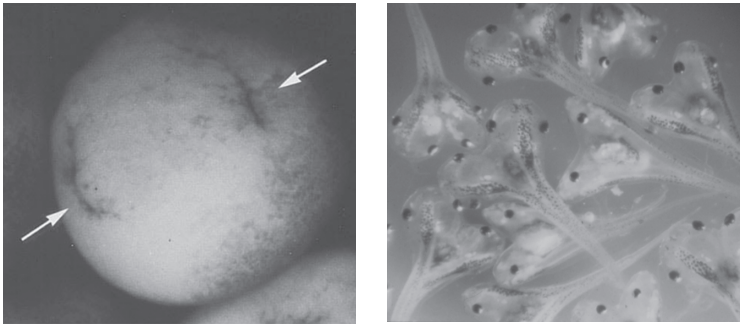
Not only has evolution failed to call dicephalus forward, it has actually shaped the developmental process to make it less likely. This simple observation highlights with particular clarity this singular fact: Like Brittany and Abigail Hensel, evolution and development are inseparable.

THE CONJOINED NATURE OF DEVELOPMENT AND EVOLUTION

To understand the forces that regulate the development of dicephalus and other forms of twinning, let's examine the unfertilized egg—an amorphous sphere resembling a globe with contents distributed into northern and southern hemispheres. A surface "crust" encloses the chemical constituents within, like the peel of an orange enclosing the edible core. When a sperm successfully penetrates the crust—an event that occurs unpredictably at a random location in the egg's northern hemisphere—it leaves its mark like a flag planted in a new world. But even more important, fertilization sets in motion a series of chemical rearrangements and surface rotations that, in short order, establish the precursors to the nervous system and vertebral column. At first only visible as a darkened streak running from pole to pole on the embryo's surface, the incipient vertebral column presents the first visible evidence that a single individual is on its way. In frogs, this individual is a tadpole, hatched a mere 48 hours after fertilization.

Sometimes two streaks arise. When this happens, we know that a twinning event has occurred. In frogs, these twins are typically conjoined, presenting two heads that share a single body, not unlike the Hensels. Such twins in frogs have proved of great value to experimental embryologists seeking to identify the critical events around the time of gastrulation that trigger

the nervous system's formation. By demonstrating how to produce two, we learn how to produce just one.



The fertilized egg of a frog embryo can be artificially stimulated to produce two streaks (left, indicated by arrows), eventually resulting in conjoined twin tadpoles with two heads (right).

What, then, determines twinning? In frogs, scientists have taken note of the rotation of the embryonic crust soon after fertilization, as if the orange's peel were rotating independently of the core. The key to resolving the mystery of twinning was to understand how the rotation of the crust carries along a chemical determinant from one location to another, thereby bringing this determinant into contact with other chemical factors within the core. In this way, chemicals that were once far from each other are now brought into direct contact, instigating *inductive* interactions that trigger the specification of the embryo's *primary axis*, that is, the formation of the nervous system and vertebral column.

Manipulations that alter the rotation of the embryonic crust around the core can trigger the formation of a *secondary*

axis, that is, a twin. Indeed, in the mid-1980s, scientists refined a technique for creating tadpole twins that involved spinning newly fertilized eggs in a centrifuge.[61] However, not any kind of spinning would do. Like bakers refining the recipe for a cake, these scientists found that twins could be reliably produced when embryos experienced a specific centrifugal force (thirty times the force of gravity), for a specific duration (four minutes), and at a specific orientation in relation to the centrifugal force (ninety degrees).

The scientists also found that timing was a critical factor: Eggs that had passed a little less than half the temporal distance between insemination and first cleavage (that is, the time when the single-cell zygote divides into two cells) were much more likely to twin. Subsequent and painstaking research has aimed to identify the critical chemical interactions in the core and crust that trigger the formation of a dual embryo.

We have seen how Charles Stockard, through careful manipulation of the developmental environment, was able to produce minnows and trout with varying degrees of conjoined twinning. In his laboratory, he found that changes in temperature and oxygen supply were effective for producing twins. But outside the laboratory, the true relevance of all this research reveals itself. After all, the natural world is much like a laboratory—though without the control.

For example, dicephalus is relatively common among reptiles because developing eggs are exposed to fluctuating environmental conditions without the protection and care of the mother that laid them. Consider the British grass snake,

of which hundreds of dicephalic creatures have been reported. What makes this species so interesting is that its eggs are typically laid inside compost heaps, within which decomposing organic matter produces heat. This heat is particularly valuable to a pregnant snake seeking to incubate its eggs in an intemperate British climate.

Dicephalus in a British grass snake. High incubation temperatures cause this condition. Therefore, this snake may be a freak, but it is not a mutant.

But a compost heap is the developmental equivalent of a crapshoot. No one—certainly not a snake—can predict or control the amount of heat produced. So when temperatures rise above forty degrees Celsius, most of the eggs will simply fail to hatch. A small percentage of those eggs that do hatch will emerge with two heads. This is one of the risks of incubating eggs outside the mother's body.

Twinning is rare in birds, especially compared to reptiles. But among birds, ducks produce a relatively high percentage of double monsters (about two percent).[62] Why ducks? The answer appears

related not to temperature, but to the rotations experienced by the embryo during early development. Recall how conjoined tadpole twins can be produced experimentally by spinning an egg during a sensitive period of development. Ducks have a large, elastic uterus, in which the egg is free to roll around. It is thought that when these rolling movements happen in just the right way and at just the right time, interactions among the egg's chemical constituents are critically altered. So as with the thermal fluctuations of the compost heap, the duck's uterus appears to provide a natural environment conducive to the production of conjoined twins.

Although reptiles must surrender their eggs to the relative unpredictability of the external environment, birds improve their odds through active participation in the process of incubation. From laying to hatching, mother and father provide warmth and protection. But such continuous parental care masks a momentous discontinuity: In its journey from uterus to nest, the egg must endure a sudden and dramatic change in temperature. Based on everything we have discussed so far, such an event could easily provoke the kinds of embryonic rearrangements that Stockard and others produced experimentally in the laboratory. So why don't we inhabit a world of two-headed birds?

The answer is simple yet profound: To prevent the regular development of double monsters, birds have evolved so that the thermal shock that accompanies the laying of an egg occurs only after the embryo has passed through the most sensitive period of embryonic development—that is, the period that ends with gastrulation. As Stockard noted, the "important matter of a few

hours' difference in egg-laying time lies between the successful class of birds and a hopelessly unfit monstrous condition."[63]

From the preceding discussion, we can begin to sense the folly of maintaining a wall of separation between development and evolution. Such a wall cannot be sustained because *development itself—including the developmental environment—evolves.* Once we appreciate the implications of this obvious yet underappreciated notion, false dichotomies fade away. In their place, a more coherent picture of both development and evolution comes into view. We see that one outcome of the evolutionary process is the avoidance of developmental conditions that produce anomalous and unfit outcomes.

Still, the eccentricities of the natural world will occasionally exceed the regulatory efforts of animals and the reach of evolutionary modification. "No developmental environment in nature is constantly perfect," Stockard observed, "and this fact is the underlying cause of the frequently occurring malformation and monstrous production."[64]

In recent years, biologists have turned increasing attention to the fact that animals construct their environments—their niches—to suit their needs.[65] Termites build elaborate mounds of mud that satisfy the needs of a complex colony; beavers build dams that permit the construction of protective shelters along creek beds; spiders weave webs to ensnare prey; naked mole-rats dig elaborate underground tunnel systems. By extension, the eggshell and the uterus are developmental environments that enable parents to produce viable offspring.

But there can be no distinct line of demarcation between the construction of a nest, dam, web, or tunnel, and the casting of a calcite shell or the physical joining of mother and fetus via the umbilical cord. Nor can we easily demarcate these forms of niche construction from the epic efforts of green turtles to navigate across hundreds of miles of open water back to the sandy beaches on which they were hatched.

As we learn more about the mechanistic details of development, we will come to see that evolution is not omnipotent: It simply cannot produce creatures that development does not allow. On the flip side, as this chapter has illustrated, the oddity of a creature provides little insight into the ease of producing it. Indeed, some of the oddest creatures are remarkably easy to produce.

Traditionally, the driving force behind such oddities—and variability in general—has been the mutation. Even scientists like Marc Kirschner and John Gerhart, who are notable for emphasizing the role that developmental mechanisms play in the evolution of novelty, still look to the mutation to get the evolutionary ball rolling:

> First, genetic variation is required for evolutionary change. Genetic variation initially arises by mutation. Much of the genetic change that is important in evolution comes from the reassortment of mutations of previous generations by sexual reproduction. . . . Novelty in the organism's physiology, anatomy, or behaviors arises mostly by the use of conserved processes in new combinations, at different times, and in different places and amounts, rather than by the invention of new processes.[66]

Mary Jane West-Eberhard shares Kirschner and Gerhart's belief that development is a central player in the production of evolutionary novelties, but she does not share their commitment to the mutation as the sole initiating force:

> Contrary to the notion that mutational novelties have superior evolutionary potential, there are strong arguments for the greater evolutionary potential of environmentally induced novelties. An environmental factor can affect numerous individuals at once, whereas a mutation initially can affect only one.[67]

Elsewhere, she expands on this view:

> First, environmental induction is a major initiator of adaptive evolutionary change. The origin and evolution of adaptive novelty do not await mutation; on the contrary, *genes are followers, not leaders, in evolution*. Second, evolutionary novelties result from the reorganization of preexisting phenotypes and the incorporation of environmental elements. Novel traits are not de novo constructions that depend on a series of genetic mutations. Third, phenotypic plasticity can facilitate evolution by the immediate accommodation and exaggeration of change. It should no longer be regarded as a source of noise in a system governed by genes, or as a 'merely environmental' phenomenon without evolutionary importance.[68]

Gilbert Gottlieb describes a similar path to evolutionary modification, one that begins with "a novel behavioral shift"

that "encourages new environmental relationships."[69] The shift is initiated when animals

> live differently from their forebears. Living differently, especially living in a different place, will subject the animals to new stresses, strains, and adaptations that will eventually alter their anatomy and physiology (without necessarily altering the genetic constitution of the changing population). The new situation will call forth previously untapped resources for anatomical and physiological change that are part of each species' already existing developmental adaptability.[70]

For more than a century, mutants have lorded over the evolutionary domain. Clearly, they will not surrender their preeminent position without a fight. In the meantime, we should be wary of our reflexive tendency to appeal to the mutant when we encounter novel forms. Once again, consider the extreme case of dicephalus. A mutation is not required to produce this condition. Rather, as we have seen, dicephalus—*even* dicephalus—can arise with surprising ease through the alteration of an epigenetic process that, in the course of evolving the capacity to produce one head, incidentally evolved the capacity to produce two. We might even go so far as to say that dicephalus comes *naturally*.