CHAPTER ELEVEN

THE MEANING OF IT ALL

THE ZOO IN YOU

My professional introduction to academia happened in the early 1980s, during my college years, when I volunteered at the American Museum of Natural History in New York City. Aside from the excitement of working behind the scenes in the collections of the museum, one of the most memorable experiences was attending their raucous weekly seminars. Each week a speaker would come to present some esoteric study on natural history. Following the presentation, often a fairly low-key affair, the listeners would pick the talk apart point by point. It was merciless. On occasion, the whole thing felt like a human barbecue, with the invited speaker as the spit-roasted main course. Frequently, these debates would devolve into shouting sessions with all the high dudgeon and operatic pantomime of an old silent movie, complete with shaken fists and stomped feet.

Here I was, in the hallowed halls of academe, listening to seminars on taxonomy. You know, taxonomy—the science

of naming species and organizing them into the classification scheme that we all memorized in introductory biology. I could not imagine a topic less relevant to everyday life, let alone one less likely to lead eminent senior scientists into apoplexy and the loss of much of their human dignity. The injunction "Get a life" could not have seemed more apt.

The irony is that I now see why they got so worked up. I didn't appreciate it at the time, but they were debating one of the most important concepts in all of biology. It may not seem earth-shattering, but this concept lies at the root of how we compare different creatures—a human with a fish, or a fish with a worm, or anything with anything else. It has led us to develop techniques that allow us to trace our family lineages, identify criminals by means of DNA evidence, understand how the AIDS virus became dangerous, and even track the spread of flu viruses throughout the world. The concept I'm about to discuss supplies the underpinning for much of the logic of this book. Once we grasp it, we see the meaning of the fish, worms, and bacteria that lie inside of us.

The articulation of truly great ideas, of the laws of nature, begins with simple premises that all of us see every day. From simple beginnings, ideas like these extend to explain the really big stuff, like the movement of the stars or the workings of time. In that spirit, I can share with you one true law that all of us can agree upon. This law is so profound that most of us take it completely for granted. Yet

it is the starting point for almost everything we do in paleontology, developmental biology, and genetics.

This biological "law of everything" is that every living thing on the planet had parents.

Every person you've ever known has biological parents, as does every bird, salamander, or shark you have ever seen. Technology may change this, thanks to cloning or some yet-to-be-invented method, but so far the law holds. To put it in a more precise form: every living thing sprang from some parental genetic information. This formulation defines parenthood in a way that gets to the actual biological mechanism of heredity and allows us to apply it to creatures like bacteria that do not reproduce the way we do.

The extension of this law is where its power comes in. Here it is, in all its beauty: all of us are modified descendants of our parents or parental genetic information. I'm descended from my mother and father, but I'm not identical to them. My parents are modified descendants of their parents. And so on. This pattern of descent with modification defines our family lineage. It does this so well that we can reconstruct your family lineage just by taking blood samples of individuals.

Imagine that you are standing in a room full of people whom you have never seen before. You are given a simple task: find out how closely related each person in the room is to you. How do you tell who are your distant cousins, your super-distant cousins, your great-granduncles seventy-five

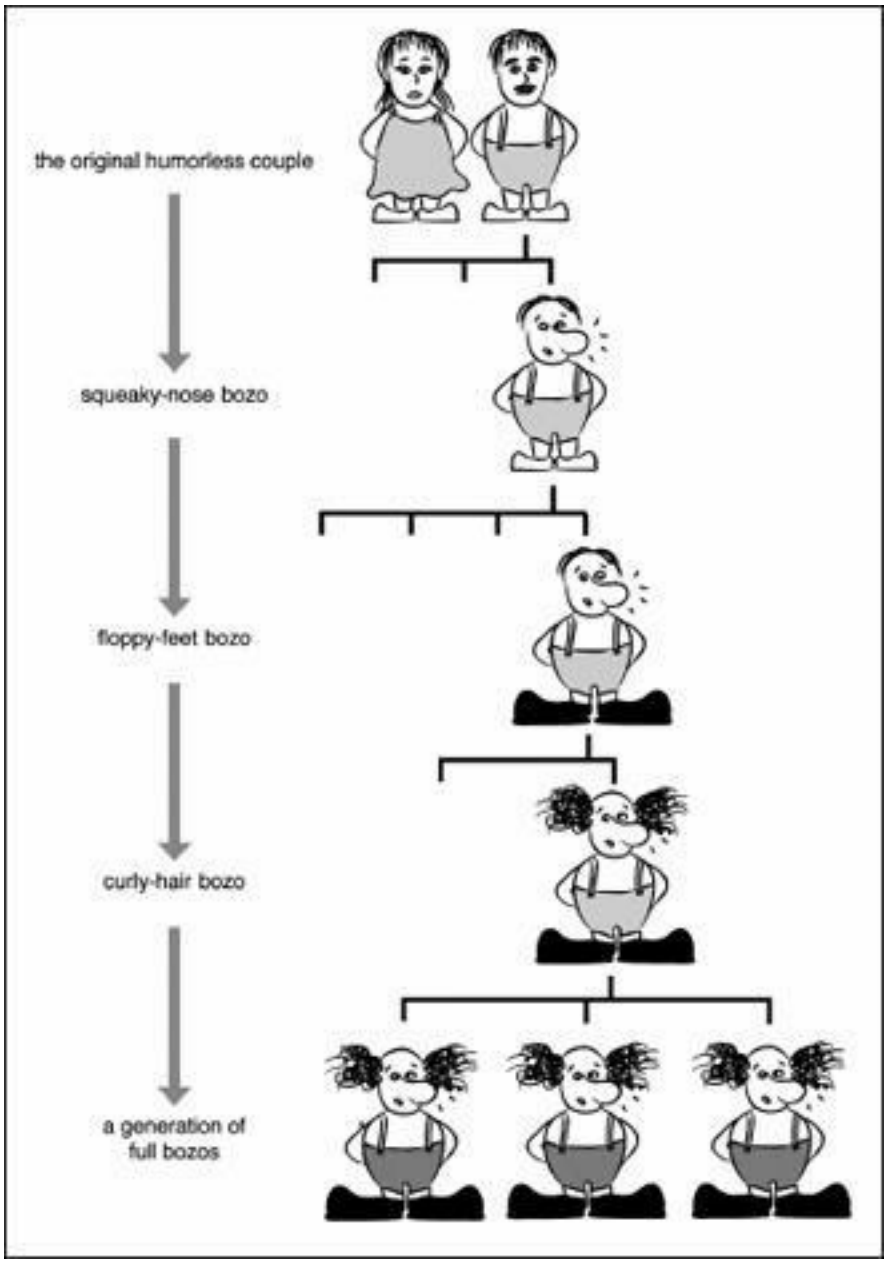
times removed?

To answer this question, we need a biological mechanism to guide our thinking and give us a way to test the accuracy of our hypothesized family tree. This mechanism comes from thinking about our law of biology. Knowing how descent with modification works is key to unlocking biological history, because descent with modification can leave a signature, which we can detect.

Let's take a hypothetical humorless, quite unclown-like couple who have children. One of their sons was born with a genetic mutation that gave him a red rubber nose that squeaks. This son grows up and marries a lucky woman. He passes his mutated nose gene to his children, and they all have his red rubber nose that squeaks. Now, suppose one of his offspring gets a mutation that causes him to have huge floppy feet. When this mutation passes to the next generation, all of his children are like him: they have a red rubber nose that squeaks and huge floppy feet. Go one generation further. Imagine that one of these kids, the original couple's great-grandchild, has another mutation: orange curly hair. When this mutation passes to the *next* generation, all of his children will have orange curly hair, a rubber nose that squeaks, and giant floppy feet. When you ask "Who is this bozo?" you'll be inquiring about each of our poor couple's great-great-grandchildren.

This example illustrates a very serious point. Descent with modification can build a family tree, or lineage, that we can identify by characters. It has a signature that we

immediately recognize. Like a nested set of Russian dolls, our hypothetical lineage formed groups within groups, which we recognize by their unique features. The group of "full bozo" great-great-grandchildren is descended from an individual who had only the squeaky nose and the huge floppy feet. This individual was in a group of "proto-bozos," who are descended from an individual who had only the rubber nose that squeaks. This "pre-proto-bozo" was descended from the original couple, who didn't look overtly clown-like.



The bozo family tree.

This pattern of descent with modification means that you could easily have hypothesized the bozo family tree without me telling you anything about it. If you had a room full of the various generations of bozos, you would have seen that all clown kin are in a group that possesses a squeaky nose. A subset of these have orange hair and floppy

feet. Nested within this subset is another group, the full bozos. The key is that the features—orange hair, squeaky nose, big floppy feet—enable you to recognize the groups. These features are your evidence for the different groups, or in this case generations, of clowns.

Replace this family circus with real features—genetic mutations and the body changes that they encode—and you have a lineage that can be identified by biological features. If descent with modification works this way, then our family trees have a signature in their basic structure. So powerful is this truth that it can help us reconstruct family trees from genetic data alone, as we see from the number of genealogical projects currently under way. Obviously, the real world is more complex than our simple hypothetical example. Reconstructing family trees can be difficult if traits arise many different times in a family, if the relationship between a trait and the genes that cause it is not direct, or if traits do not have a genetic basis and arise as the result of changes in diet or other environmental conditions. The good news is that the pattern of descent with modification can often be identified in the face of these complications, almost like filtering out noise from a radio signal.

But where do our lineages stop? Did the bozos stop at the humorless couple? Does my lineage stop at the first Shubins? That seems awfully arbitrary. Does it stop at Ukranian Jews, or northern Italians? How about at the first humans? Or does it continue to 3.8-billion-year-old pond

scum, and beyond? Everybody agrees that their own lineage goes back to some point in time, but just how far back is the issue.

If our lineage goes all the way back to pond scum, and does so while following our law of biology, then we should be able to marshal evidence and make specific predictions. Rather than being a random assortment of creatures, all life on earth should show the same signature of descent with modification that we saw among the bozos. In fact, the structure of the entire geological record shouldn't be random, either. Recent additions should appear in relatively young rock layers. Just as I am a more recent arrival than my grandfather in my family tree, so the structure of the family tree of life should also have its parallels in time.

To see how biologists actually reconstruct our relatedness to other creatures, we need to leave the circus and return to the zoo we visited in the first chapter of the book.

A (LONGER) WALK THROUGH THE ZOO

As we've seen, our bodies are not put together at random. Here, I use the word "random" in a very specific sense; I mean that the structure of our bodies is definitely not random with respect to the other animals that walk, fly, swim, or crawl across this earth. Some animals share part

of our structure; others do not. There is order to what we share with the rest of the world. We have two ears, two eyes, one head, a pair of arms, and a pair of legs. We do not have seven legs or two heads. Nor do we have wheels.

A walk in the zoo immediately shows our connections to the rest of life. In fact, it will show that we can group much of life in the same way we did with the bozos. Let's go to just three exhibits at first. Start with the polar bears. You can make a long list of the features that you share with polar bears: hair, mammary glands, four limbs, a neck, and two eyes, among lots of other things. Next, consider the turtle across the way. There are definitely similarities, but the list is a bit shorter. You share four limbs, a neck, and two eyes (among other things) with the turtle. But unlike polar bears and you, turtles don't have hair or mammary glands. As for the turtle's shell, that seems unique to the turtle, just as the white fur was unique to the polar bear. Now visit the African fish exhibit. Its inhabitants are still similar to you, but the list of commonalities is even shorter than the list for turtles. Like you, fish have two eyes. Like you, they have four appendages, but those appendages look like fins, not arms and legs. Fish lack, among many other features, the hair and mammary glands that you share with polar bears.

This is beginning to sound like the Russian doll set of groups, subgroups, and sub-subgroups that appeared in the bozo example. Fish, turtles, polar bears, and humans all share some features—heads, two eyes, two ears, and so on. Turtles, polar bears, and humans have all these features,

and they also have necks and limbs, features not seen in fish. Polar bears and humans form an even more elite group, whose members have all of these features and also hair and mammary glands.

The bozo example gives us the means to make sense of our walk through the zoo. In the bozos, the pattern of groups reflected descent with modification. The implication is that the full-bozo kids shared a more recent relative than they do with the kids who have only a squeaky nose. That makes sense: the parent of the squeaky-nosed kids is the great-great grandparent of the full bozos. Applying this same approach to the groups we encountered during our zoo walk means that humans and polar bears should share a more recent ancestor than they do with turtles. This prediction is true: the earliest mammal is much more recent than the earliest reptile.

The central issue here is deciphering the family tree of species. Or, in more precise biological terms, their pattern of relatedness. This pattern even gives us the means to interpret a fossil such as *Tiktaalik* in light of our walk through the zoo. *Tiktaalik* is a wonderful intermediate between fish and their land-living descendants, but the odds of it being our exact ancestor are very remote. It is more like a cousin of our ancestor. No sane paleontologist would ever claim that he or she had discovered "The Ancestor." Think about it this way: What is the chance that while walking through any random cemetery on our planet I would discover an actual ancestor of mine? Diminishingly

small. What I would discover is that all of the people buried in these cemeteries—no matter whether that cemetery is in China, Botswana, or Italy—are related to me to different degrees. I can find this out by looking at their DNA with many of the forensic techniques in use in crime labs today. I'd see that some of the denizens of the cemeteries are distantly related to me, others are related more closely. This tree would be a very powerful window into my past and my family history. It would also have a practical application because I could use this tree to understand my predilection to get certain diseases and other facts of my biology. The same is true when we infer relationships among species.

The real power of this family tree lies in the predictions it allows us to make. Chief among these is that as we identify more shared characteristics, they should be consistent with the framework. That is, as I identify features from cells, DNA, and all the other structures, tissues, and molecules in the bodies of these animals, they should support the groupings that we identified during our walk. Conversely, we can falsify our groupings by finding features inconsistent with them. That is, if there exist many traits shared by fish and people that aren't seen in polar bears, our framework is flawed and needs to be revised or jettisoned. In cases where the evidence is ambiguous, we apply a number of statistical tools to assess the quality of the characteristics supporting the arrangements in the family tree. In instances where there is ambiguity, the

genealogical arrangement is treated as a working hypothesis until we can find something conclusive to allow us to either accept or reject it.

Some groupings are so strong that, for all intents and purposes, we consider them fact. The fish–turtle–polar bear–human grouping, for example, is supported by characteristics from hundreds of genes and virtually all features of the anatomy, physiology, and cellular biology of these animals. Our fish-to-human framework is so strongly supported that we no longer try to marshal evidence for it —doing so would be like dropping a ball fifty times to test the theory of gravity. The same holds for our biological example. You would have the same chance of seeing your ball go up the fifty-first time you dropped it as you would of finding strong evidence against these relationships.

We can now return to the opening challenge of the book. How can we confidently reconstruct the relationships among long-dead animals and the bodies and genes of recent ones? We look for the signature of descent with modification, we add characteristics, we evaluate the quality of the evidence, and we assess the degree to which our groups are represented in the fossil record. The amazing thing is that we now have tools to probe this hierarchy, using computers and large DNA sequencing labs to perform the same analyses you performed during your walk through the zoo. We now have access to new fossil sites around the world. We can see our bodies' place in the natural world better than we ever could.

From Chapter 1 through Chapter 10, we have shown that deep similarities exist between creatures living today and those long deceased—ancient worms, living sponges, and various kinds of fish. Now, armed with knowledge of the pattern of descent with modification, we can begin to make sense of it all. Enough fun at the circus and zoo. It's time to get down to business.

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We have seen that inside our bodies are connections to a menagerie of other creatures. Some parts resemble parts of jellyfish, others parts of worms, still others parts of fish. These aren't haphazard similarities. Some parts of us are seen in every other animal; others are very unique to us. It is deeply beautiful to see that there is an order in all these features. Hundreds of characters from DNA, innumerable anatomical and developmental features—all follow the same logic as the bozos we saw earlier.

Let's consider some of the features we've already talked about in the book and show you how they are ordered.

With every other animal on the planet, we share a body composed of *many cells.* Call this group multicellular life. We share the trait of multicellularity with everything from sponges to placozoans to jellyfish to chimpanzees.

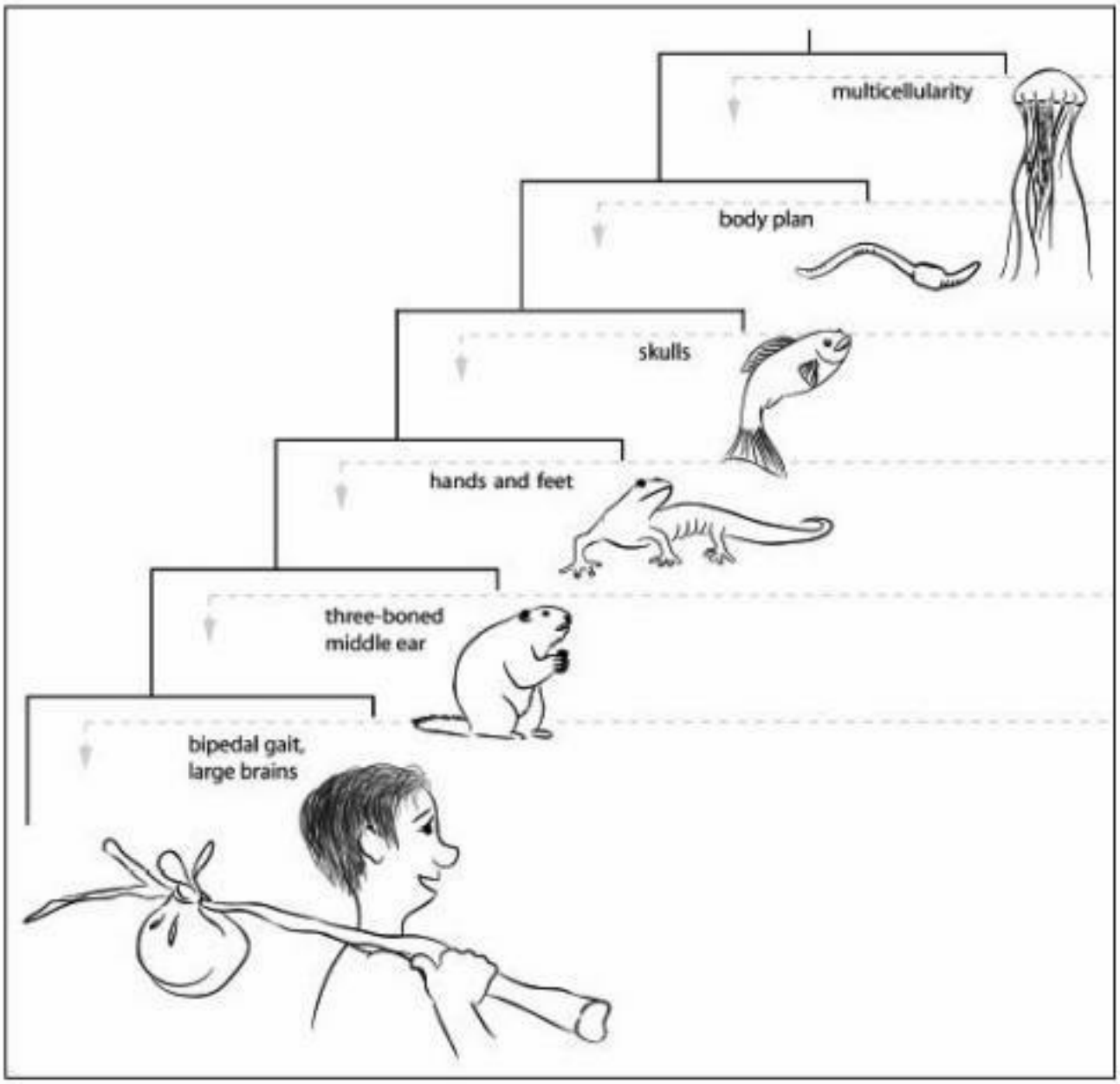
A subset of these multicellular animals have *a body plan like ours,* with a front and a back, a top and a bottom, and a left and a right. Taxonomists call this group Bilateria (meaning "bilaterally symmetrical animals"). It includes every animal from insects to humans.

A subset of multicellular animals that have a body plan like ours, with a front and a back, a top and a bottom, and a left and a right, also have *skulls and backbones.* Call these creatures vertebrates.

A subset of the multicellular animals that have a body plan like ours, with a front and a back, a top and a bottom, and a left and a right, and that have skulls, also have *hands and feet.* Call these vertebrates tetrapods (animals with four limbs).

A subset of the multicellular animals that have a body plan like ours, with a front and a back, a top and a bottom, and a left and a right, that have skulls, and that have hands and feet, also have a *three-boned middle ear.* Call these tetrapods mammals.

A subset of the multicellular animals that have a body plan like ours with a front and a back, a top and a bottom, and a left and a right, that have skulls and backbones, that have hands and feet, and that have a three-boned middle ear, also have *a bipedal gait and enormous brains.* Call these mammals people.



A human family tree, all the way back to jellyfish. It has the same structure as the one for the bozos.

The power of these groupings is seen in the evidence on which they are based. Hundreds of genetic, embryological, and anatomical features support them. This arrangement allows us to look inside ourselves in an important way.

This exercise is almost like peeling an onion, exposing

layer after layer of history. First we see features we share with all other mammals. Then, as we look deeper, we find the features we share with fish. Deeper still are those we share with worms. And so on. Recalling the logic of the bozos, this means that we see a pattern of descent with modification deeply etched inside our own bodies. That pattern is reflected in the geological record. The oldest many-celled fossil is over 600 million years old. The earliest fossil with a three-boned middle ear is less than 200 million years old. The oldest fossil with a bipedal gait is around 4 million years old. Are all these facts just coincidence, or do they reflect a law of biology we can see at work around us every day?

Carl Sagan once famously said that looking at the stars is like looking back in time. The stars' light began the journey to our eyes eons ago, long before our world was formed. I like to think that looking at humans is much like peering at the stars. If you know how to look, our body becomes a time capsule that, when opened, tells of critical moments in the history of our planet and of a distant past in ancient oceans, streams, and forests. Changes in the ancient atmosphere are reflected in the molecules that allow our cells to cooperate to make bodies. The environment of ancient streams shaped the basic anatomy of our limbs. Our color vision and sense of smell has been molded by life in ancient forests and plains. And the list goes on. This history is our inheritance, one that affects our lives today and will do so in the future.

My knee was swollen to the size a grapefruit, and one of my colleagues from the surgery department was twisting and bending it to determine whether I had strained or ripped one of the ligaments or cartilage pads inside. This, and the MRI scan that followed, revealed a torn meniscus, the probable result of twenty-five years spent carrying a backpack over rocks, boulders, and scree in the field. Hurt your knee and you will almost certainly injure one or more of three structures: the medial meniscus, the medial collateral ligament, or the anterior cruciate ligament. So regular are injuries to these three parts of your knee that these three structures are known among doctors as the "Unhappy Triad." They are clear evidence of the pitfalls of having an inner fish. Fish do not walk on two legs.

Our humanity comes at a cost. For the exceptional combination of things we do—talk, think, grasp, and walk on two legs—we pay a price. This is an inevitable result of the tree of life inside us.

Imagine trying to jerry-rig a Volkswagen Beetle to travel at speeds of 150 miles per hour. In 1933, Adolf Hitler commissioned Dr. Ferdinand Porsche to develop a cheap car that could get 40 miles per gallon of gas and provide a reliable form of transportation for the average German family. The result was the VW Beetle. This history, Hitler's plan, places constraints on the ways we can modify the Beetle today; the engineering can be tweaked only so far

before major problems arise and the car reaches its limit.

In many ways, we humans are the fish equivalent of a hot-rod Beetle. Take the body plan of a fish, dress it up to be a mammal, then tweak and twist that mammal until it walks on two legs, talks, thinks, and has superfine control of its fingers—and you have a recipe for problems. We can dress up a fish only so much without paying a price. In a perfectly designed world—one with no history—we would not have to suffer everything from hemorrhoids to cancer.

Nowhere is this history more visible than in the detours, twists, and turns of our arteries, nerves, and veins. Follow some nerves and you'll find that they make strange loops around other organs, apparently going in one direction only to twist and end up in an unexpected place. The detours are fascinating products of our past that, as we'll see, often create problems for us—hiccups and hernias, for example. And this is only one way our past comes back to plague us.

Our deep history was spent, at different times, in ancient oceans, small streams, and savannahs, not office buildings, ski slopes, and tennis courts. We were not designed to live past the age of eighty, sit on our keisters for ten hours a day, and eat Hostess Twinkies, nor were we designed to play football. This disconnect between our past and our human present means that our bodies fall apart in certain predictable ways.

Virtually every illness we suffer has some historical component. The examples that follow reflect how different branches of the tree of life inside us—from ancient humans,

to amphibians and fish, and finally to microbes—come back to pester us today. Each of these examples show that we were not designed rationally, but are products of a convoluted history.

OUR HUNTER-GATHERER PAST: OBESITY, HEART DISEASE, AND HEMORRHOIDS

During our history as fish we were active predators in ancient oceans and streams. During our more recent past as amphibians, reptiles, and mammals, we were active creatures preying on everything from reptiles to insects. Even more recently, as primates, we were active tree-living animals, feeding on fruits and leaves. Early humans were active hunter-gatherers and, ultimately, agriculturalists. Did you notice a theme here? That common thread is the word "active."

The bad news is that most of us spend a large portion of our day being anything but active. I am sitting on my behind at this very minute typing this book, and a number of you are doing the same reading it (except for the virtuous among us who are reading it in the gym). Our history from fish to early human in no way prepared us for this new regimen. This collision between present and past has its signature in many of the ailments of modern life.

What are the leading causes of death in humans? Four of the top ten causes—heart disease, diabetes, obesity, and stroke—have some sort of genetic basis and, likely, a

historical one. Much of the difficulty is almost certainly due to our having a body built for an active animal but the lifestyle of a spud.

In 1962, the anthropologist James Neel addressed this notion from the perspective of our diet. Formulating what became known as the "thrifty genotype" hypothesis, Neel suggested that our human ancestors were adapted for a boom-bust existence. As hunter-gatherers, early humans would have experienced periods of bounty, when prey was common and hunting successful. These periods of plenty would be punctuated by times of scarcity, when our ancestors had considerably less to eat.

Neel hypothesized that this cycle of feast and famine had a signature in our genes and in our illnesses. Essentially, he proposed that our ancestors' bodies allowed them to save resources during times of plenty so as to use them during periods of famine. In this context, fat storage becomes very useful. The energy in the food we eat is apportioned so that some supports our activities going on now, and some is stored, for example in fat, to be used later. This apportionment works well in a boom-bust world, but it fails miserably in an environment where rich foods are available 24/7. Obesity and its associated maladies—age-related diabetes, high blood pressure, and heart disease—become the natural state of affairs. The thrifty genotype hypothesis also might explain why we love fatty foods. They are high-value in terms of how much energy they contain, something that would have conferred a distinct advantage in our

distant past.

Our sedentary lifestyle affects us in other ways, because our circulatory system originally appeared in more active animals.

Our heart pumps blood, which is carried to our organs via arteries and returned to the heart by way of veins. Because arteries are closer to the pump, the blood pressure in them is much higher than in veins. This can be a particular problem for the blood that needs to return to our heart from our feet. Blood from the feet needs to go uphill, so to speak, up the veins of our legs to our chest. If the blood is under low pressure, it may not climb all the way. Consequently, we have two features that help the blood move up. The first are little valves that permit the blood to move up but stop it from going down. The other feature is our leg muscles. When we walk we contract them, and this contraction serves to pump the blood up our leg veins. The one-way valves and the leg-muscle pumps enable our blood to climb from feet to chest.

This system works superbly in an active animal, which uses its legs to walk, run, and jump. It does not work well in a more sedentary creature. If the legs are not used much, the muscles will not pump the blood up the veins. Problems can develop if blood pools in the veins, because that pooling can cause the valves to fail. This is exactly what happens with varicose veins. As the valves fail, blood pools in the veins. The veins get bigger and bigger, swelling and taking tortuous paths in our legs.

Needless to say, the arrangement of veins can also be a real pain in the behind. Truck drivers and others who sit for long stretches of time are particularly prone to hemorrhoids, another cost of our sedentary lives. During their long hours of sitting, blood pools in the veins and spaces around the rectum. As the blood pools, hemorrhoids form—an unpleasant reminder that we were not built to sit for too long, particularly not on soft surfaces.

PRIMATE PAST: TALK IS NOT CHEAP

Talking comes at a steep price: choking and sleep apnea are high on the list of problems we have to live with in order to be able to talk.

We produce speech sounds by controlling motions of the tongue, the larynx, and the back of the throat. All of these are relatively simple modifications to the basic design of a mammal or a reptile. As we saw in Chapter 5, the human larynx is made up mostly of gill arch cartilages, corresponding to the gill bars of a shark or fish. The back of the throat, extending from the last molar tooth to just above the voice box, has flexible walls that can open and close. We make speech sounds by moving our tongue, by changing the shape of our mouth, and by contracting a number of muscles that control the rigidity of this wall.

Sleep apnea is a potentially dangerous trade-off for the ability to talk. During sleep, the muscles of our throat relax.

In most people, this does not present a problem, but in some the passage can collapse so that relatively long stretches pass without a breath. This, of course, can be very dangerous, particularly in people who have heart conditions. The flexibility of our throat, so useful in our ability to talk, makes us susceptible to a form of sleep apnea that results from obstruction of the airway.

Another trade-off of this design is choking. Our mouth leads both to the trachea, through which we breathe, and to our esophagus, so we use the same passage to swallow, breathe, and talk. These three functions can be at odds, for example when a piece of food gets lodged in the trachea.

FISH AND TADPOLE PAST: HICCUPS

This annoyance has its roots in the history we share with fish and tadpoles.

If there is any consolation for getting hiccups, it is that our misery is shared with many other mammals. Cats can be stimulated to hiccup by sending an electrical impulse to a small patch of tissue in their brain stem. This area of the brain stem is thought to be the center that controls the complicated reflex that we call a hiccup.

The hiccup reflex is a stereotyped twitch involving a number of muscles in our body wall, diaphragm, neck, and throat. A spasm in one or two of the major nerves that control breathing causes these muscles to contract. This

results in a very sharp inspiration of air. Then, about 35 milliseconds later, a flap of tissue in the back of our throat (the glottis) closes the top of our airway. The fast inhalation followed by a brief closure of the tube produces the "hic."

The problem is that we rarely experience only a single hic. Stop the hiccups in the first five to ten hics, and you have a decent chance of ending the bout altogether. Miss that window, and the bout of hiccups can persist for an average of about sixty hics. Inhaling carbon dioxide (by breathing into the classic paper bag) and stretching the body wall (taking a big inhalation and holding it) can end hiccups early in some of us. But not all. Some cases of pathological hiccups can be extremely prolonged. The longest uninterrupted hiccups in a person lasted from 1922 to 1990.

Our tendency to develop hiccups is another influence of our past. There are two issues to think about. The first is what causes the spasm of nerves that initiates the hiccup. The second is what controls that distinctive hic, the abrupt inhalation–glottis closure. The nerve spasm is a product of our fish history, while the hic is an outcome of the history we share with animals such as tadpoles.

First, fish. Our brain can control our breathing without any conscious effort on our part. Most of the work takes place in the brain stem, at the boundary between the brain and the spinal cord. The brain stem sends nerve impulses to our main breathing muscles. Breathing happens in a pattern. Muscles of the chest, diaphragm, and throat

contract in a well-defined order. Consequently, this part of the brain stem is known as a "central pattern generator." This region can produce rhythmic patterns of nerve and, consequently, muscle activation. A number of such generators in our brain and spinal cord control other rhythmic behaviors, such as swallowing and walking.

The problem is that the brain stem originally controlled breathing in fish; it has been jerry-rigged to work in mammals. Sharks and bony fish all have a portion of the brain stem that controls the rhythmic firing of muscles in the throat and around the gills. The nerves that control these areas all originate in a well-defined portion of the brain stem. We can even see this nerve arrangement in some of the most primitive fish in the fossil record. Ancient ostracoderms, from rocks over 400 million years old, preserve casts of the brain and cranial nerves. Just as in living fish, the nerves that control breathing extend from the brain stem.

This works well in fish, but it is a lousy arrangement for mammals. In fish, the nerves that control breathing do not have to travel very far from the brain stem. The gills and throat generally surround this area of the brain. We mammals have a different problem. Our breathing is controlled by muscles in the wall of our chest and by the diaphragm, the sheet of muscle that separates our chest from our abdomen. Contraction of the diaphragm controls inspiration. The nerves that control the diaphragm exit our brain just as they do in fish, and they leave from the brain

stem, near our neck. These nerves, the vagus and the phrenic nerve, extend from the base of the skull and travel through the chest cavity to reach the diaphragm and the portions of the chest that control breathing. This convoluted path creates problems; a rational design would have the nerves traveling not from the neck but from nearer the diaphragm. Unfortunately, anything that interferes with one of these nerves can block their function or cause a spasm.

If the odd course of our nerves is a product of our fishy past, the hiccup itself is likely the product of our history as amphibians. Hiccups are unique among our breathing behaviors in that an abrupt intake of air is followed by a closure of the glottis. Hiccups seem to be controlled by a central pattern generator in the brain stem: stimulate this region with an electrical impulse, and we stimulate hiccups. It makes sense that hiccups are controlled by a central pattern generator, since, as in other rhythmic behaviors, a set sequence of events happens during a hic.

It turns out that the pattern generator responsible for hiccups is virtually identical to one in amphibians. And not in just any amphibians—in tadpoles, which use both lungs and gills to breathe. Tadpoles use this pattern generator when they breathe with gills. In that circumstance, they want to pump water into their mouth and throat and across the gills, but they do not want the water to enter their lungs. To prevent it from doing so, they close the glottis, the flap that closes off the breathing tube. And to close the glottis,

tadpoles have a central pattern generator in their brain stem so that an inspiration is followed immediately by a closing glottis. They can breathe with their gills thanks to an extended form of hiccup.

The parallels between our hiccups and gill breathing in tadpoles are so extensive that many have proposed that the two phenomena are one and the same. Gill breathing in tadpoles can be blocked by carbon dioxide, just like our hiccups. We can also block gill breathing by stretching the wall of the chest, just as we can stop hiccups by inhaling deeply and holding our breath. Perhaps we could even block gill breathing in tadpoles by having them drink a glass of water upside down.

SHARK PAST: HERNIAS

Our propensity for hernias, at least for those hernias near the groin, results from taking a fish body and morphing it into a mammal.

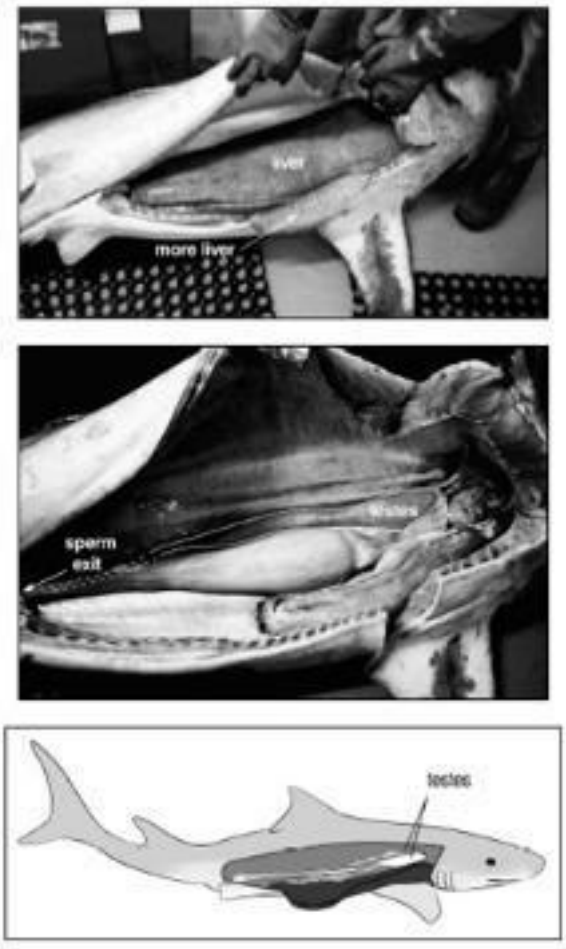
Fish have gonads that extend toward their chest, approaching their heart. Mammals don't, and therein lies the problem. It is a very good thing that our gonads are not deep in our chest and near our heart (although it might make reciting the Pledge of Allegiance a different experience). If our gonads were in our chest, we wouldn't be able to reproduce.

Slit the belly of a shark from mouth to tail. The first thing

you'll see is liver, a lot of it. The liver of a shark is gigantic. Some zoologists believe that a large liver contributes to the buoyancy of the shark. Move the liver away and you'll find the gonads extending up near the heart, in the "chest" area. This arrangement is typical of most fish: the gonads lie toward the front of the body.

In us, as in most mammals, this arrangement would be a disaster. Males continuously produce sperm throughout our lives. Sperm are finicky little cells that need exactly the right range of temperatures to develop correctly for the three months they live. Too hot, and sperm are malformed; too cold, and they die. Male mammals have a neat little device for controlling the temperature of the sperm-making apparatus: the scrotum. As we all know, the male gonads sit in a sac. Inside the skin of the sac are muscles that can expand and contract as the temperature changes. Muscles also lie in our sperm cords. Hence, the cold shower effect: the scrotum will tuck close to the body when it is cold. The whole package rises and falls with temperature. This is all a way to optimize the production of healthy sperm.

The dangling scrotum also serves as a sexual signal in many mammals. Between the physiological advantages of having gonads outside the body wall, and the occasional benefits this provides in securing mates, there are ample advantages for our distant mammalian ancestors in having a scrotum.



Open a shark and you find a huge liver (top). Push the liver aside and you see gonads, which extend relatively close to the heart, as they do in other primitive creatures. Photos courtesy of Dr. Steven Campana, Canadian Shark Research Laboratory.

The problem with this arrangement is that the plumbing that carries sperm to the penis is circuitous. Sperm travel from the testes in the scrotum through the sperm cord. The cord leaves the scrotum, travels up toward the waist, loops over the pelvis, then goes through the pelvis to travel through the penis and out. Along this complex path, the sperm gain seminal fluids from a number of glands that

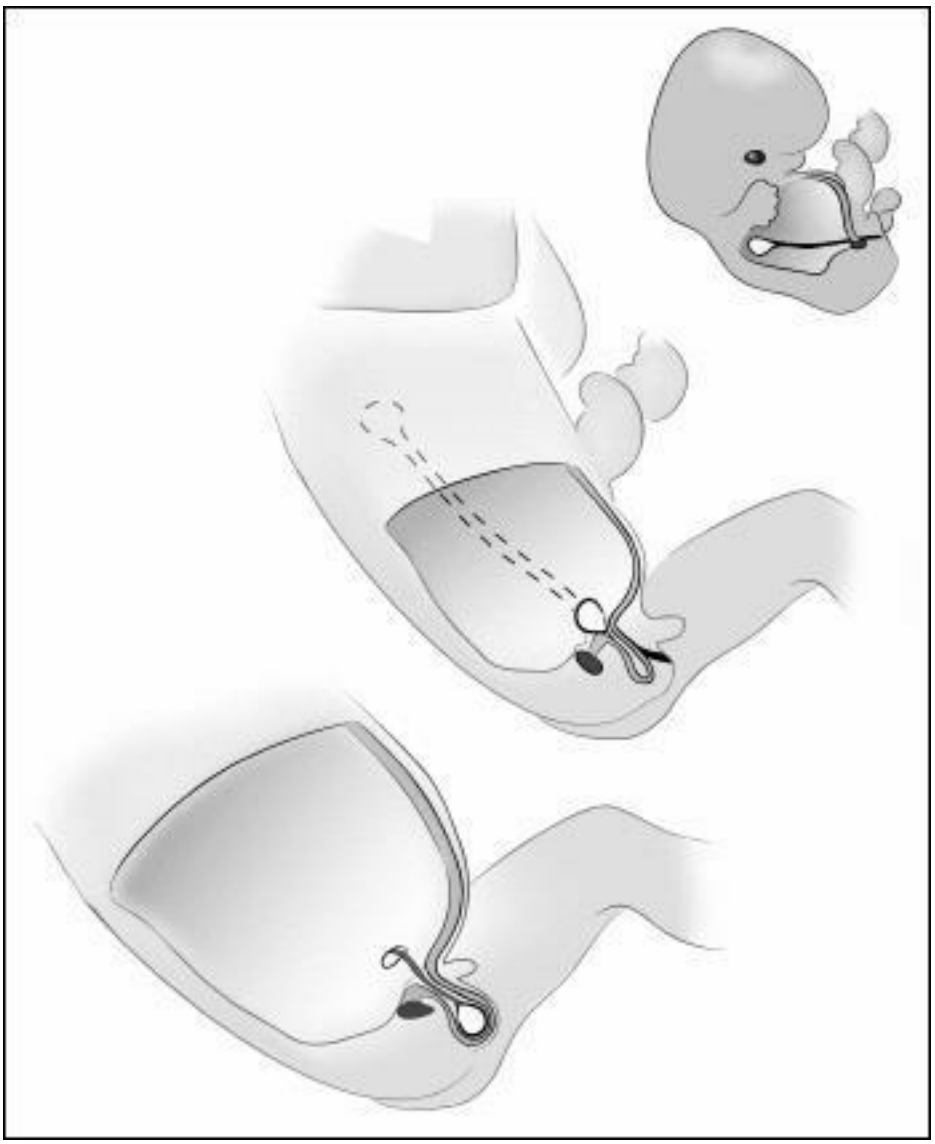
connect to the tube.

The reason for this absurd route lies in our developmental and evolutionary history. Our gonads begin their development in much the same place as a shark's: up near our livers. As they grow and develop, our gonads descend. In females, the ovaries descend from the midsection to lie near the uterus and fallopian tubes. This ensures that the egg does not have far to travel to be fertilized. In males, the descent goes farther.

The descent of the gonads, particularly in males, creates a weak spot in the body wall. To envision what happens when the testes and spermatic cord descend to form a scrotum, imagine pushing your fist against a rubber sheet. In this example, your fist becomes equivalent to the testes and your arm to the spermatic cord. The problem is that you have created a weak space where your arm sits. Where once the rubber sheet was a simple wall, you've now made another space, between your arm and the rubber sheet, where things can slip. This is essentially what happens in many types of inguinal hernias in men. Some of these inguinal hernias are congenital—when a piece of the gut travels with the testes as it descends. Another kind of inguinal hernia is acquired. When we contract our abdominal muscles, our guts push against the body wall. A weakness in the body wall means that guts can escape the body cavity and be squeezed to lie next to the spermatic cord.

Females are far tougher than males, particularly in this

part of the body. Because females do not have a giant tube running through it, their abdominal wall is much stronger than a man's. This is a good thing when you think of the enormous stresses that female body walls go through during pregnancy and childbirth. A tube through the body wall just wouldn't do. Men's tendency to develop hernias is a trade-off between our fish ancestry and our mammal present.



The descent of the testes. During growth, the testes

descend from the gonads' primitive position high up in the body. They end up lying in the scrotum, which is an outpocket of the body wall. All of this leaves the body wall of human males weak in the groin area.

MICROBIAL PAST: MITOCHONDRIAL DISEASES

Mitochondria exist inside every cell of our bodies, doing a remarkable number of things. Their most obvious job is to turn oxygen and sugars into a kind of energy we can use inside our cells. Other functions include metabolizing toxins in our livers and regulating different parts of the function of our cells. We notice our mitochondria only when things go wrong. Unfortunately, the list of diseases caused by malfunctioning mitochondria is extraordinarily long and complex. If there is a problem in the chemical reactions in which oxygen is consumed, energy production can be impaired. The malfunction may be confined to individual tissues, say the eyes, or may affect every system in the body. Depending on the location and severity of the malfunction, it can lead to anything from weakness to death.

Many of the processes we use to live reflect our mitochondria's history. The chain reaction of chemical events that turns sugars and oxygen into usable energy and carbon dioxide arose billions of years ago, and versions of it

are still seen in diverse microbes. Mitochondria carry this bacterial past inside of them: with an entire genetic structure and cellular microstructure similar to bacteria, it is generally accepted that they originally arose from free-living microbes over a billion years ago. In fact, the entire energy-generating machinery of our mitochondria arose in one of these kinds of ancient bacteria.

The bacterial past can be used to our advantage in studying the diseases of mitochondria—in fact, some of the best experimental models for these diseases *are* bacteria. This is powerful because we can do all kinds of experiments with bacteria that are not possible with human cells. One of the most provocative studies was done by a team of scientists from Italy and Germany. The disease that they studied invariably kills the infants who are born with it. Called cardioencephalomyopathy, it results from a genetic change that interrupts the normal metabolic function of mitochondria. In studying a patient who had the disease, the European team identified a place in the DNA that had a suspicious change. Knowing something about the history of life, they then turned to the microbe known as *Paracoccus denitrificans,* which is often called a free-living mitochondrion because its genes and chemical pathways are so similar to those of mitochondria. Just how similar was revealed by the European team. They produced the same change in the bacteria's genes that they saw in their human patient. What they found makes total sense, once we know our history. They were able to simulate parts of a

human mitochondrial disease in a bacterium, with virtually the same change in metabolism. This is putting a many-billion-year part of our history to work for us.

The example from microbes is not unique. Judging by the Nobel Prizes awarded in medicine and physiology in the past thirteen years, I should have called this book *Your Inner Fly, Your Inner Worm,* or *Your Inner Yeast.* Pioneering research on flies won the 1995 Nobel Prize in medicine for uncovering a set of genes that builds bodies in humans and other animals. Nobels in medicine in 2002 and 2006 went to people who made significant advances in human genetics and health by studying an insignificant-looking little worm (*C. elegans*). Similarly, in 2001, elegant analyses of yeast (including baker's yeast) and sea urchins won the Nobel in medicine for increasing our understanding of some of the basic biology of all cells. These are not esoteric discoveries made on obscure and unimportant creatures. These discoveries on yeast, flies, worms, and, yes, fish tell us about how our own bodies work, the causes of many of the diseases we suffer, and ways we can develop tools to make our lives longer and healthier.