

CHAPTER FIVE

GETTING AHEAD

It was two nights before my anatomy final and I was in the lab at around two in the morning, memorizing the cranial nerves. There are twelve cranial nerves, each branching to take bizarre twists and turns through the inside of the skull. To study them, we bisected the skull from forehead to chin and sawed open some of the bones of the cheek. So there I was, holding half of the head in each hand, tracing the twisted paths that the nerves take from our brains to the different muscles and sense organs inside.

I was enraptured by two of the cranial nerves, the trigeminal and the facial. Their complicated pattern boiled down to something so simple, so outrageously easy that I saw the human head in a new way. That insight came from understanding the far simpler state of affairs in sharks. The elegance of my realization—though not its novelty; comparative anatomists had had it a century or more ago—and the pressure of the upcoming exam led me to forget where I was. At some point, I looked around. It was the middle of the night and I was alone in the lab. I also

happened to be surrounded by the bodies of twenty-five human beings under sheets. For the first and last time, I got the willies. I worked myself into such a lather that the hairs on the back of my neck rose, my feet did their job, and within a nanosecond I found myself at the bus stop, out of breath. It goes without saying that I felt ridiculous. I remember telling myself: Shubin, you've become hard-core. That thought did not last long; I soon discovered I had locked my house keys in the lab.

What made me so hard-core is that head anatomy is deeply mesmerizing, in fact, beautiful. One of the joys of science is that, on occasion, we see a pattern that reveals the order in what initially seems chaotic. A jumble becomes part of a simple plan, and you feel you are seeing right through something to find its essence. This chapter is about seeing that essence inside our own heads. And, of course, the heads of fish.

THE INNER CHAOS OF THE HEAD

Head anatomy is not only complicated but hard to see, since, unlike other parts of the body, the tissues of the head are encapsulated in a bony box. We literally have to saw through the cheek, forehead, and cranium to see the vessels and organs. Having thus opened a human head, we find a clump of what looks like tangled fishing lines. Vessels and nerves make curious loops and turns as they travel through

the skull. Thousands of nerve branches, muscles, and bones sit within this small box. At first glance, the whole array is a bewildering mess.

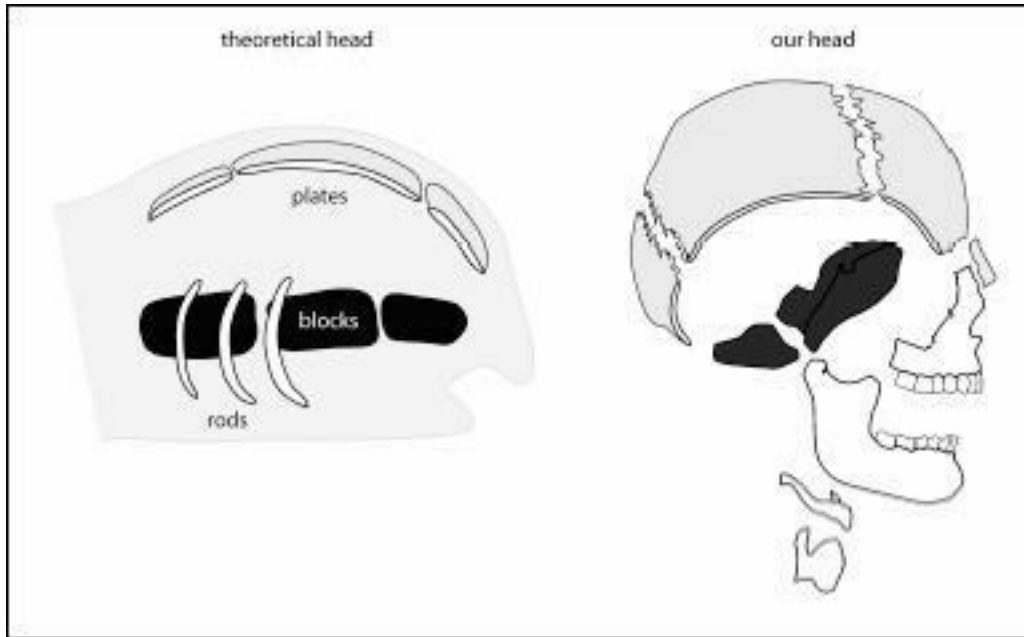
Our skulls are made up of three fundamental parts: think plates, blocks, and rods. The plates cover our brain. Pat the top of your head, and you are feeling them. These large plates fit together like jigsaw-puzzle pieces and form much of our cranium. When we were born, the plates were separate; the open spaces between them, the fontanelles, are visible in infants, occasionally throbbing with the brain tissue underneath. As we grow, the bones enlarge, and by the time we reach the age of two they have fused.

Another part of our skull lies underneath the brain, forming a platform that holds it up. Unlike the plate-like bones at the top, these bones look like complicated blocks and have many arteries and nerves running through them. The third kind of bone makes up our jaws, some bones in our ears, and other bones in our throats; these bones start development looking like rods, which ultimately break up and change shape to help us chew, swallow, and hear.

Inside the skull are a number of compartments and spaces that house different organs. Obviously, the brain occupies the largest of these. Other spaces contain our eyes, parts of our ears, and our nasal structures. Much of the challenge in understanding head anatomy comes from seeing these different spaces and organs in three dimensions.

Attached to the bones and organs in the head are the

muscles we use to bite, to talk, and to move our eyes and whole head. Twelve nerves supply these muscles, each exiting the brain to travel to a different region inside our head. These are the dreaded cranial nerves.



Plates, blocks, and rods: the theme for skulls. Every bone in our head can be traced to one of these things.

The key to unlocking the basics of the head is to see the cranial nerves as more than a jumble. Indeed, most of them really are simple. The simplest cranial nerves have only one function, and they attach to one muscle or organ. The cranial nerve that goes to our nasal structures, the olfactory, has one job: to take information from our nasal tissues to our brain. Some of the nerves that go to our eyes and ears are also simple in this way: the optic nerve is involved with vision; the acoustic nerve works in hearing. About four other cranial nerves only serve muscles—

working to move the eyes inside the orbits, for example, or to move the head around on the neck.

But four of the cranial nerves have given medical students fits for decades. For good reason: the four have very complex functions and take tortuous paths through the head to do their jobs. The trigeminal nerve and the facial nerve deserve special mention. Both exit the brain and break up into a bewildering network of branches. Much like a cable that can carry television, Internet, and voice information, a single branch of the trigeminal or facial nerve can carry information about both sensation and action. Individual fibers for sensation and action emanate from different parts of the brain, are consolidated in cables (what we end up calling the trigeminal and facial nerves), then break up again, sending branches all over the head.

The trigeminal's branches do two major things: they control muscles, and they carry sensory information from much of our face back to our brain. The muscles controlled by the trigeminal nerve include those we use to chew as well as tiny muscles deep inside the ear. The trigeminal is also the major nerve for sensation in the face. The reason a slap to the face hurts so much, beyond the emotional pain, is because the trigeminal carries sensory information from the skin of our face back to our brain. Your dentist also knows the branches of your trigeminal nerve well. Different branches go to the roots of our teeth; a single jab of anesthetic along one of these branches can deaden the sensation of different parts of our tooth row.

The facial nerve also controls muscles and relays sensory information. As its name implies, it is the main nerve that controls the muscles of facial expression. We use these tiny muscles to smile, to frown, to raise and lower our eyebrows, to flare our nostrils, and so on. They have wonderfully evocative names. One of the major muscles that we use in frowning—it moves the corners of our mouth down—is called the depressor anguli oris. Another great name belongs to the muscle we use to furrow our brow in concern: the corrugator supercilli. Flare your nostrils and you are using your nasalis. Each of these muscles, like every other muscle of facial expression, is controlled by branches of the facial nerve. Things like an uneven smile or asymmetrically drooping eyelids are a sign that something might be wrong with the facial nerve on one side of a person's face.

You are probably beginning to see why I was staying up so late to study these nerves. Nothing about them seems to make any sense. For example, both the trigeminal and the facial nerves send tiny branches to muscles inside our ears. Why do two different nerves, which innervate entirely different parts of the face and jaw, send branches to ear muscles that lie adjacent to one another? Even more confusing, the trigeminal and facial almost crisscross as they send branches to our face and jaw. Why? With such oddly redundant functions and tortuous paths, there seems to be no rhyme or reason to their structure, much less to how these nerves match up with the plates, blocks, and rods

that make up our skull.

In thinking about these nerves, I am reminded of my first days here in Chicago in 2001. I had been given space for a research laboratory in a hundred-year-old building and the lab needed new utility cables, plumbing, and air handling. I remember the day when the contractors first opened the walls to get access to the innards of the building. Their reaction to the plumbing and wiring inside my wall was almost exactly like mine when I opened the human head and saw the trigeminal and facial nerves for the first time. The wires, cables, and pipes inside the walls were a jumble. Nobody in his right mind would have designed a building from scratch this way, with cables and pipes taking bizarre loops and turns throughout the building.

And that's exactly the point. My building was constructed in 1896, and the utilities reflect an old design that has been jerry-rigged further with each renovation. If you want to understand the wiring and plumbing in my building, you have to understand its history, how it was renovated for each new generation of scientists. My head has a long history also, and that history explains complicated nerves like the trigeminal and the facial.

For us, that history begins with a fertilized egg.

THE ESSENCE IN EMBRYOS

Nobody starts life with a head: sperm and egg come

together to make a single cell. Between the moment of conception and the third week thereafter, we go from that single cell to a ball of cells, then to a Frisbee-shaped collection of cells, then to something that looks vaguely like a tube and includes different kinds of tissues. Between the twenty-third and twenty-eighth days after conception, the front end of the tube thickens and folds over the body, so the embryo looks as if it's already curled up in the fetal position. The head at this stage looks like a big glob. The base of this glob holds the key to much of the basic organization of our heads.

Four little swellings develop around the area that will become the throat. At about three weeks we see the first two; the other two emerge about four days later. Each swelling looks quite humble on the outside: a simple blob, separated from the next by a little crease. When you follow what happens to the blobs and creases, you begin to see the order and beauty of the head, including the trigeminal and facial nerves.

Of the cells inside each blob, known as arches, some will form bone tissue and others muscle and blood vessels. There is a complex mix of cells inside each arch; some cells divided right there while others migrated a long way to enter the arch itself. When we identify the cells in each arch according to where they end up in the adult, things start to make a lot of sense.

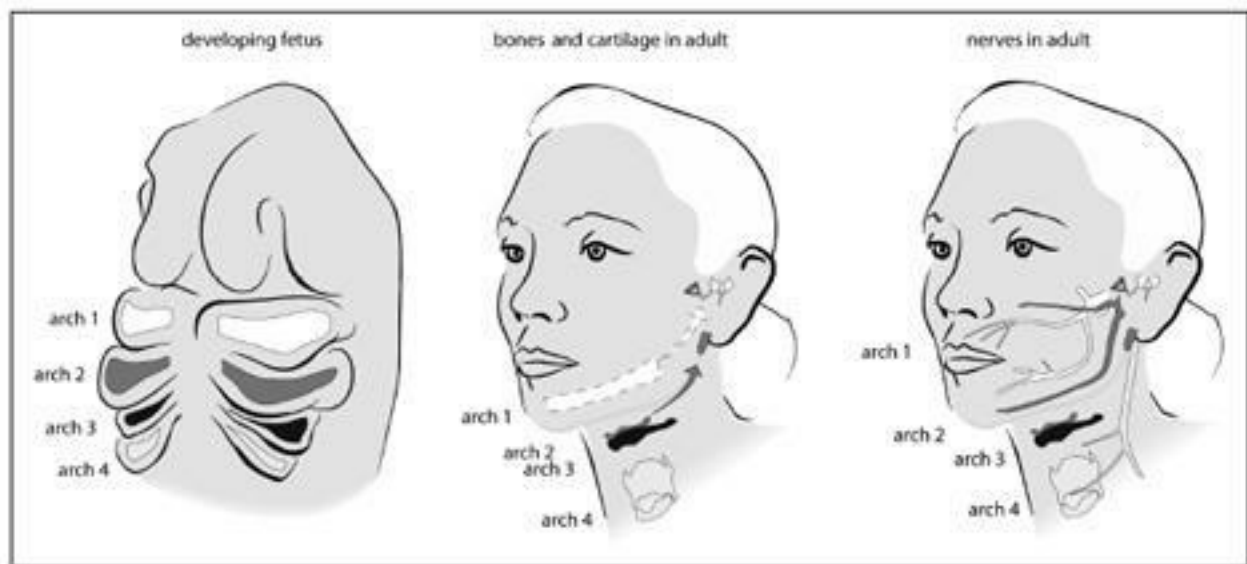
Ultimately, the first arch tissues form the upper and lower jaws, two tiny ear bones (the malleus and incus), and

all the vessels and muscles that supply them. The second arch forms the third small ear bone (the stapes), a tiny throat bone, and most of the muscles that control facial expression. The third arch forms bones, muscles, and nerves deeper in the throat; we use these to swallow. Finally, the fourth arch forms the deepest parts of our throat, including parts of our larynx and the muscles and vessels that surround it and help it function.

If you were to shrink yourself to the size of a pinhead and travel inside the mouth of the developing embryo, you would see indentations that correspond to each swelling. There are four of these indentations. And, like the arches on the outside, cells on the indentations form important structures. The first elongates to form our Eustachian tube and some structures in the ear. The second forms the cavity that holds our tonsils. The third and fourth form important glands, including the parathyroid, thymus, and thyroid.

What I've just given you is one of the big tricks for understanding the most complicated cranial nerves and large portions of the head. When you think trigeminal nerve, think first arch. Facial nerve, second arch. The reason the trigeminal nerve goes to both the jaws and the ear is that all the structures it supplies originally developed in the first arch. The same thing is true for the facial nerve and the second arch. What do the muscles of facial expression have in common with the muscles in the ear that the facial nerve supplies? They are all second arch derivatives. As for the nerves of the third and fourth arches, their complex paths

all relate to the fact that they innervate structures that arose from their respective arches. Those third and fourth arch nerves, among them the glossopharyngeal and vagus, follow the same pattern as the ones in front, each going to structures that developed from the arch they are associated with.



If we follow the gill arches from an embryo to an adult, we can trace the origins of jaws, ears, larynx, and throat. Bones, muscles, nerves, and arteries all develop inside these gill arches.

This fundamental blueprint of heads helps us make sense of one of the apocryphal tales in anatomy. In 1820, so the story goes, Johannes Goethe was walking through the Jewish cemetery in Vienna when he spotted the decomposing skeleton of a ram. The vertebrae were exposed and above them lay a damaged skull. Goethe, in a moment of epiphany, saw that the breaks in the skull made

it look like a gnarled mess of vertebrae. To Goethe, this revealed the essential pattern within: the head is made up of vertebrae that fused and grew a vault to hold our brains and sense organs. This was a revolutionary idea because it linked heads and bodies as two versions of the same fundamental plan. The notion must have been in the drinking water in the early 1800s because other people, among them Lorenz Oken, allegedly came up with virtually the same idea in a similar setting.

Goethe and Oken were both picking up something very profound, although they could not have known it at the time. Our body is segmented, and this pattern is most clearly seen in our vertebrae. Each vertebra is a block that represents a segment of our body. The organization of our nerves is also segmental, correlating closely with the pattern of the vertebrae. Nerves exit the spinal cord to supply the body. The segmental configuration is obvious when you look at the levels of the spinal cord that are associated with each part of our body. For example, the muscles in our legs are supplied by nerves that exit from lower parts of the spinal cord than those that supply our arms. Heads may not look it, but they also contain a very deep segmental pattern. Our arches define segments of bones, muscles, arteries, and nerves. Look in the adult, and you won't see this pattern. We see it only in the embryo.

Our skulls lose all overt evidence of their segmental origins as we go from embryo to adult. The plate-like bones of our skulls form over our gill arches, and the muscles,

nerves, and arteries, which all had a very simple segmental pattern early on, are rewired to make our adult heads.

Knowing something about development can help us predict where to look for what is missing in children who have certain birth defects. For example, children born with first arch syndrome have a tiny jaw and nonfunctioning ears with no malleus or incus bone. Missing are structures that normally would have formed from the first arch.

The arches are the road map for major chunks of the skull, from the most complicated cranial nerves to the muscles, arteries, bones, and glands inside. The arches are also a guide to something else: our very deep connection with sharks.

OUR INNER SHARK

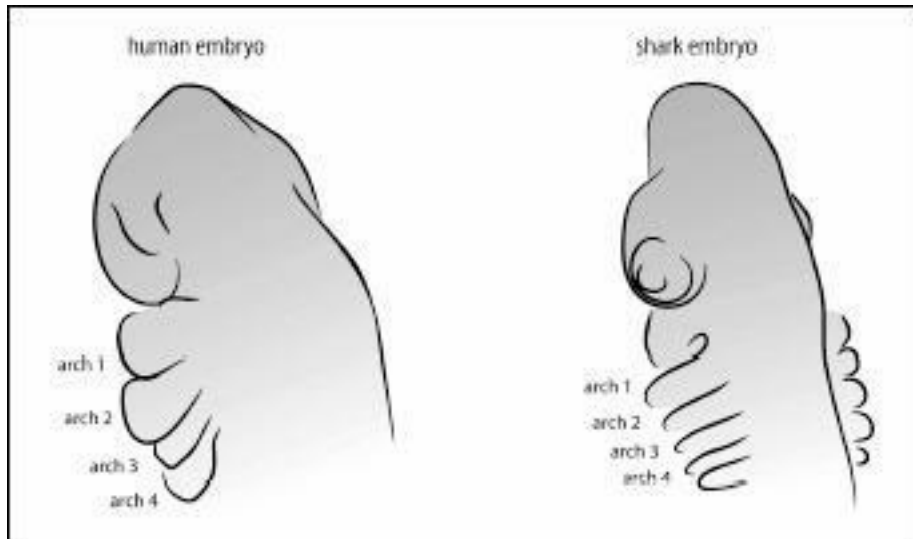
The take-home message of many a lawyer joke is that lawyers are an especially voracious kind of shark. Teaching embryology during one of the recurring vogues for these jokes, I remember thinking that the joke is on all of us. We're all modified sharks—or, worse, there is a lawyer inside each of us.

As we've seen, much of the secret of heads lies in the arches, the swellings that gave us the road map for the complicated cranial nerves and key structures inside the head. Those insignificant-looking swellings and indentations have captured the imagination of anatomists

for 150 years, because they look like the gill slits in the throat regions of fish and sharks.

Fish embryos have these bulges and indentations, too. In fish, the indentations ultimately open up to form the spaces between the gills where water flows. In us, the indentations normally seal over. In abnormal cases, gill slits fail to close and remain open as pouches or cysts. A branchial cyst, for example, is often a benign fluid-filled cyst that forms in an open pouch inside the neck; the pouch is created by the failure of the third or fourth arch to close. Rarely, children are born with an actual vestige of an ancient gill arch cartilage, a little rod that represents a gill bar from the third arch. In these instances, my surgical colleagues are operating on an inner fish that unfortunately has come back to bite us.

Every head on every animal from a shark to a human shares those four arches in development. The richness of the story lies in what happens inside each arch. Here, we can make a point-by-point comparison between our heads and those of sharks.



The gill region of a developing human and a developing shark look the same early on.

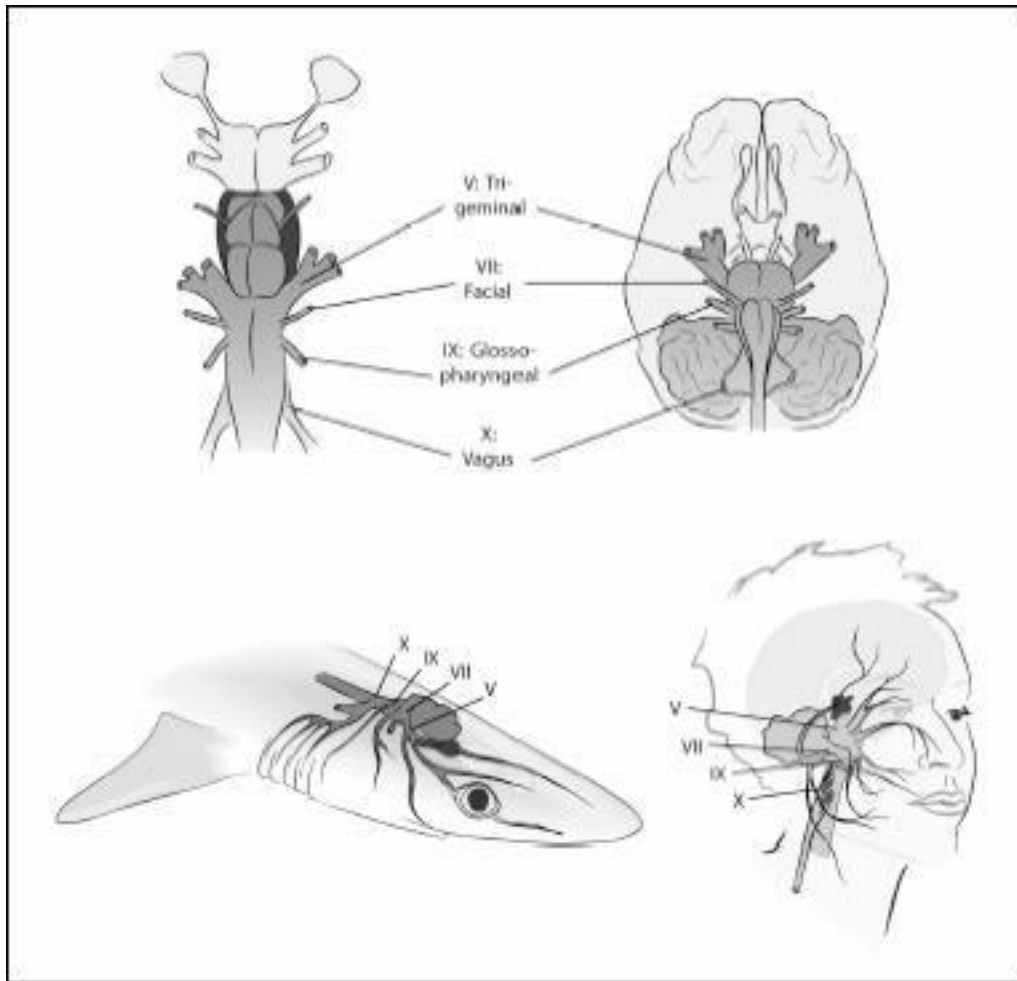
Look at the first arch in a human and a shark, and you find a very similar state of affairs: jaws. The major difference is that humans' first arch also forms some ear bones, which we do not see in sharks. Unsurprisingly, the cranial nerve that supplies the jaws of humans and sharks is the first arch nerve, the trigeminal nerve.

The cells inside the second gill arch divide, change, and give rise to a bar of cartilage and muscle. In us, the bar of cartilage breaks up to form one of the three bones of our middle ear (the stapes) and some other small structures at the base of the head and throat. One of these bones, called the hyoid, assists us in swallowing. Take a gulp, listen to music, and thank the structures that form from your second arch.

In a shark, the second arch rod breaks up to form two bones that support the jaws: a lower one that compares

with our hyoid and an upper one that supports the upper jaw. If you have ever watched a great white shark try to chomp something—a diver in a cage, for example—you have probably noticed that the upper jaw can extend and retract as the shark bites. The upper bone of this second arch is part of the lever system of bones that rotate to make that possible. That upper bone is remarkable in another way, too. It compares with one of the bones in our middle ear: the stapes. Bones that support the upper and lower jaws in sharks are used in us to swallow and hear.

As for the third and fourth arches, we find that many of the structures we use to talk and swallow are, in sharks, parts of tissues that support the gills. The muscles and cranial nerves we use to swallow and talk move the gills in sharks and fish.



At first glance, our cranial nerves (bottom right) appear different from those of a shark (bottom left). But look closely and you will find profound similarities. Virtually all of our nerves are present in sharks. The parallels go deeper still: equivalent nerves in sharks and humans supply similar structures, and they even exit the brain in the same order (top left and right).

Our head may look incredibly complicated, but it is built from a simple and elegant blueprint. There is a pattern common to every skull on earth, whether it belongs to a shark, a bony fish, a salamander, or a human. The discovery

of this pattern was a major accomplishment of nineteenth-century anatomy, a time when anatomists were putting embryos of all kinds of species under the microscope. In 1872, the Oxford anatomist Francis Maitland Balfour first saw the basic plan of heads when he looked at sharks and saw the bulges, the gill arches, and the structures inside. Unfortunately, he died soon after in a mountaineering accident in the Swiss Alps. He was only in his thirties.

GILL ARCH GENES

During the first three weeks after conception, whole batteries of genes are turned on and off in our gill arches and throughout the tissues that will become our future brain. These genes instruct cells to make the different portions of our head. Think of each region of our head as gaining a genetic address that makes it distinctive. Modify this genetic address and we can modify the kinds of structures that develop there.

For example, a gene known as *Otx* is active in the front region, where the first gill arch forms. Behind it, toward the back of the head, a number of so-called *Hox* genes are active. Each gill arch has a different complement of *Hox* genes active in it. With this information, we can make a map of our gill arches and the constellation of genes active in making each.

Now we can do experiments: change the genetic address

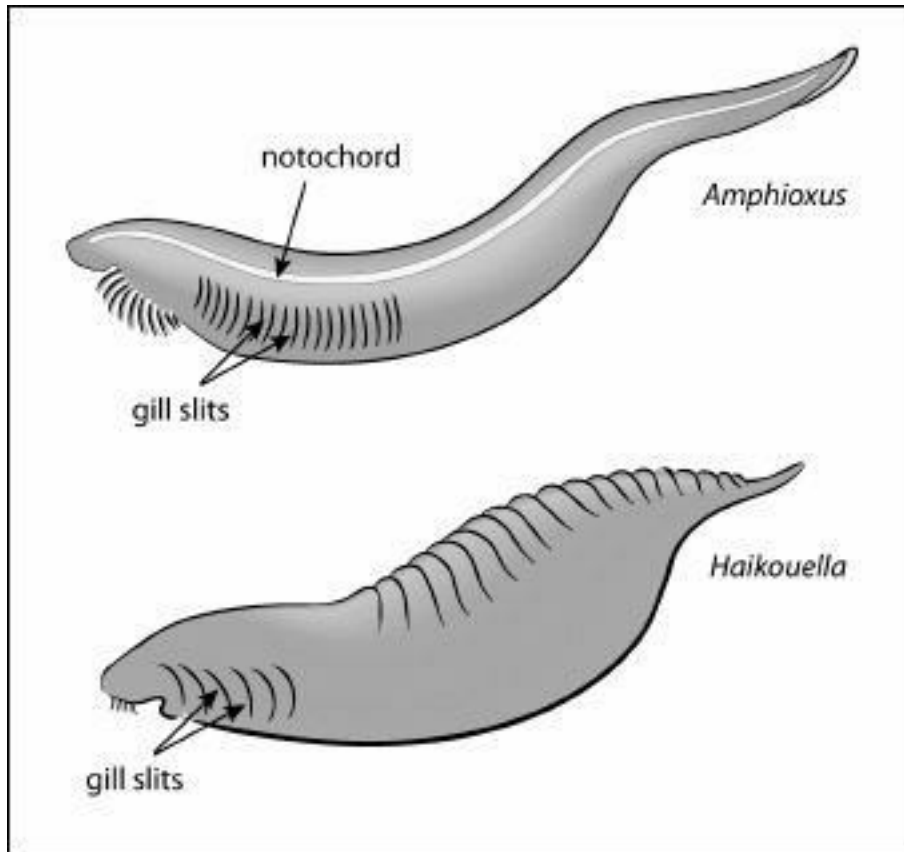
of one gill arch into that of another. Take a frog embryo, turn off some genes, make the genetic signals similar in the first and second arches, and you end up with a frog that has two jaws: a mandible develops where a hyoid bone would normally be. This shows the power of the genetic addresses in making our gill arches. Change the address, and you change the structures in the arch. The power of this approach is that we can now experiment with the basic design of heads: we can manipulate the identity of the gill arches almost at will, by changing the activity of the genes inside.

TRACING HEADS: FROM HEADLESS WONDERS TO OUR HEADED ANCESTORS

Why stop at frogs and sharks? Why not extend our comparison to other creatures, like insects or worms? But why would we do this when none of these creatures has a skull, much less cranial nerves? None of them even has bones. When we leave fish for worms, we get to a very soft and headless world. Bits of ourselves are there, though, if you look closely.

Those of us who teach comparative anatomy to undergraduates usually begin the course with a slide of *Amphioxus*. Every September, hundreds of *Amphioxus* slides appear on screens in college lecture halls from Maine to California. Why? Remember the simple dichotomy between invertebrates and vertebrates? *Amphioxus* is a worm, an

invertebrate, that shares many features with backboned animals such as fish, amphibians, and mammals. *Amphioxus* lacks a backbone, but like all creatures with backbones, it has a nerve cord that runs along its back. In addition, a rod runs the length of its body, parallel to the nerve cord. This rod, known as the notochord, is filled with a jelly-like substance and provides support for the body. As embryos, we have a notochord, too, but unlike *Amphioxus*'s, ours breaks up and ultimately becomes part of the disks that lie between our vertebrae. Rupture a disk and the jelly-like substance of what was once a notochord can wreak havoc when it pinches nerves or interferes with the ability of one vertebra to move along the next. When we injure a disk, a very ancient part of our body plan is rupturing. Thanks a lot, *Amphioxus*.



The closest relatives to animals with heads are worms with gill slits. Shown are *Amphioxus* and a reconstruction of a fossil worm (*Haikouella*) over 530 million years old. Both worms have a notochord, a nerve cord, and gill slits. The fossil worm is known from over three hundred individual specimens from southern China.

Amphioxus is not unique among worms. Some of the best examples are not in the oceans of today but in ancient rocks of China and Canada. Buried in sediments over 500 million years old are small worms that lack heads, complex brains, or cranial nerves. They may not look like much, being small smudges in the rock, but the preservation of these fossils is

incredible. When you look under a microscope, you find beautifully preserved impressions that display their soft anatomy in fine detail, occasionally even with impressions of skin. They show something else wonderful, too. They are the earliest creatures with notochords and nerve cords. These worms are telling us something about the origin of parts of our bodies.

But there is something else we share with these little worms: gill arches. *Amphioxus*, for example, has them in abundance, and associated with each arch is a little bar of cartilage. Like the cartilages that form our jaws, our ear bones, and parts of our voice box, these rods support the gill slit. The essence of our head goes back to worms, organisms that do not even have a head. What does *Amphioxus* do with the gill arches? It pumps water through them to filter out little particles of food. From so humble a beginning comes the basic structures of our own head. Just as teeth, genes, and limbs have been modified and their functions repurposed over the ages, so, too, has the basic structure of our head.