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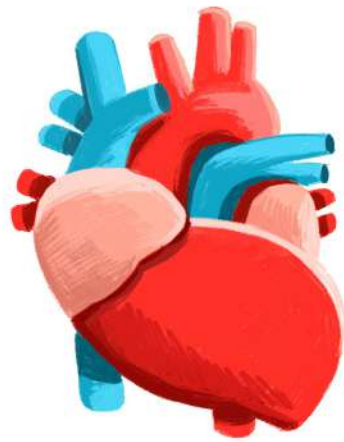

A NATURAL HISTORY *of the* HEART

BILL SCHUTT

Author of Cannibalism

ILLUSTRATIONS BY PATRICIA J. WYNNE

PUMP

ALSO BY BILL SCHUTT

Dark Banquet: Blood and the Curious Lives of Blood-Feeding Creatures

Cannibalism: A Perfectly Natural History

ALSO BY BILL SCHUTT AND J. R. FINCH

Hell's Gate

The Himalayan Codex

The Darwin Strain

PUMP

A Natural History of the Heart

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illustrations by
PATRICIA J. WYNNE

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First Edition

For Elaine Markson (*Bill Schutt*)

and

Ted Riley (*Patricia J. Wynne*)

HEART (*n.*)

1 A hollow muscular organ that pumps the blood through the circulatory system by rhythmic contraction and dilation. In vertebrates, there may be up to four chambers (as in humans), with two atria and two ventricles.

2 Used to refer to a person's character, or the place within a person where feelings or emotions are considered to come from.

3 The firm central part of a vegetable, especially one with a lot of leaves.

4 Courage, determination, or hope.

5 A shape consisting of two half circles next to each other at the top and a V shape at the bottom, often colored pink or red and used to represent love.

6 One of the four suits in playing cards, represented by a red heart shape.

7 The central or most important part.

Hearts cannot be broken, they're small squishy things.
—Jeff Heiskell

I am reminded of the advice of my neighbor,
"Never worry about your heart till it stops beating."
—William Strunk Jr. and E. B. White,
The Elements of Style

Contents

PART 3: From Bad to Better

PUMP

Most things in life come as a surprise.
—Lykke Li

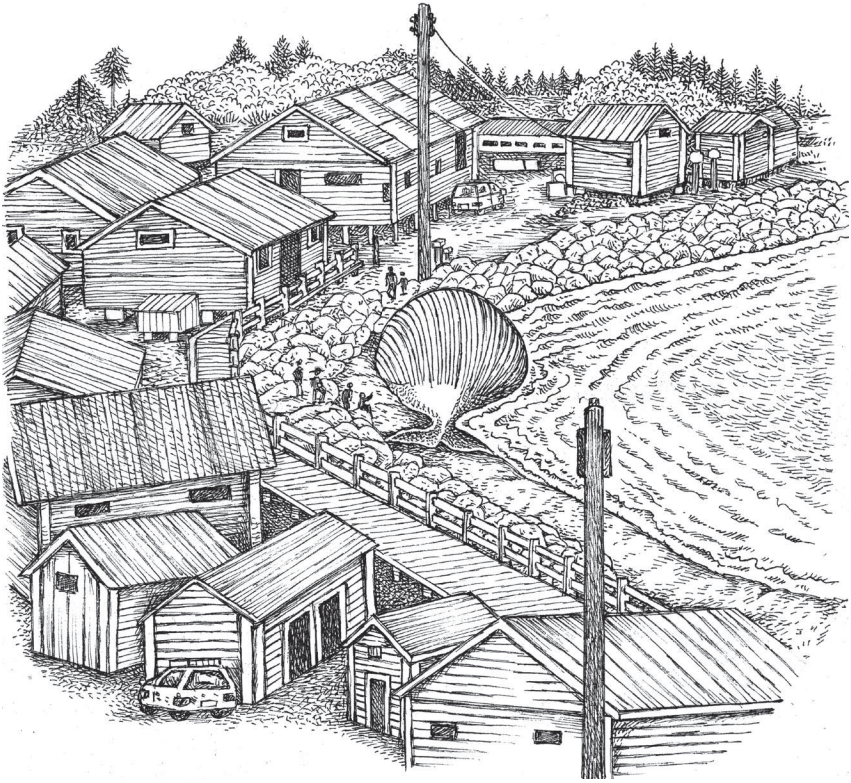
PROLOGUE

A Small Town with a Big Heart

In mid-April 2014, a sharp-eyed resident of Trout River, Newfoundland, looked out into the Gulf of Saint Lawrence and saw something peculiar. What had first appeared as a small dot on the horizon was growing larger and larger. By the time the giant thing washed ashore, the media had descended, and so, too, had the ungodly stink, which someone described to me as "a sickly perfume smell combined with the reek of decaying flesh." And, indeed, this was more decaying flesh than anyone had ever seen before—around a hundred tons of it.

Soon the tiny fishing village was buzzing with reporters and gawkers as word of mouth gave rise to sensational headlines. The chatter between locals turned from bewilderment and disgust to health concerns, the potential for lost income, and even the threat of a horrific explosion. Stranger yet, something almost identical was taking place just up the coast, in the small town of Rocky Harbour.

Canadian winters are often frigid, but the winter of 2014 had been the coldest in memory. For the first time in decades, the Great Lakes had frozen over and their outlet to the Atlantic Ocean, the Gulf of Saint Lawrence, had a heavy buildup of sea ice. The high winds and currents had also piled up ice in the Cabot Strait, turning the gulf's widest channel



to the sea into a bottleneck. But if the inhabitants of Trout River and Rocky Harbour were struggling through the harsh weather conditions, a far more desperate struggle was taking place roughly two hundred miles to the south—in the Cabot Strait itself.*

In the late winter and early spring, blue whales (*Balaenoptera musculus*) typically begin to leave the Atlantic Ocean and enter the Gulf of Saint Lawrence to feed on tiny crustaceans called krill. The largest animal known to have lived on Earth,† a blue whale can reach one hundred feet in length and can weigh up to 163 tons. By way of comparison, this is equivalent

* Located between Nova Scotia and Newfoundland, the Cabot Strait is an important international shipping lane, named after Italian maritime navigator Giovanni Caboto. After exploring coastal North America in 1497, he was subsequently referred to as John Cabot by the English, who had commissioned his flag-planting exploits.

† The largest organism is a humongous fungus (*Armillaria ostoyae*) living in Oregon and covering an area of nearly four square miles.

to twenty African bull elephants or about sixteen hundred average-sized adult human males. Despite their enormous size, blue whales were not hunted for their oil-rich blubber until 1864. The reasons for this were related to the great speeds they can attain—up to thirty-one miles per hour—and their tendency to sink when slain. Whalers preferred the three species of *Eubalaena*, since their bodies have a higher blubber content and tend to float after death. Thus, they were christened "right wales"; they were the *right* whales to throw harpoons at. Things went horribly wrong for blue whale populations after faster, steam-driven whaling ships began using the newly invented harpoon cannon, and more than 380,000 blue whales were slain between 1866 and 1978. Most countries don't allow whale hunting anymore, but the blue whale's propensity to sink after death remains an inconvenience to those attempting to study its anatomy.

In March 2014, Mark Engstrom, senior curator and deputy director of collections and research at the Royal Ontario Museum (ROM) in Toronto, received a call from his friend Lois Harwood. Harwood, who worked for Canada's Department of Fisheries and Oceans (DFO), wondered if Engstrom had heard the news that nine blue whales feeding in the Cabot Strait had died. Apparently, she said, they were unable to escape a massive ice floe, had gotten trapped in the ice, and perished. This was tragic, especially because blue whales were critically endangered, and the loss of nine individuals meant the loss of something like 3 to 5 percent of the total North Atlantic population.

Harwood knew, though, that Engstrom was looking to obtain specimens of every whale species found in Canadian waters. She told him that three of the whales hadn't sunk, possibly because they had been buoyed by the thick ice. Engstrom became even more interested after Harwood put him in touch with Jack Lawson, a researcher with the DFO who had been tracking the dead whales by helicopter for the past month. He told Engstrom that he expected the trio of whales to wash up on the shore sooner or later—and in April, they did.

"The thing is, the whales drifted ashore in these three tiny villages," Engstrom told me during my visit to the ROM in 2018. "Trout River doesn't really get the normal tourist traffic. It's sort of a struggling community. The mayor told me one day he looked out and he could see the whale in the water and he said, 'Oh, please, God, don't let that thing come ashore here.' He said the next morning there it was, on the *only* stretch of beach they have, and right underneath their *only* restaurant—this giant dead blue whale, stinking to high heaven."

I asked Engstrom what happened next.

Engstrom laughed. "Then it started to bloat."

"That must have lightened things up," I offered.

"Not really," he said. "By then, they'd all seen YouTube videos of whales exploding."

Videos of whales detonating from an accumulation of gases have been making the rounds on the internet for years. At last count, they numbered over two hundred and included one pitching "The Exploded Whale Song." My personal favorite, though, depicts a fifty-six-foot, sixty-ton sperm whale that beached in Taiwan in 2004. Local university-scientist types quickly decided to take advantage of the unexpected opportunity by carrying out an autopsy on the megacorpse. They also decided that it would be best to do this at their labs, and so a massive effort was undertaken to move the thing. Three cranes, fifty workers, and thirteen hours later, the whale was driven off, strapped to the open bed of a tractor-trailer. But on the way through the busy streets of Tainan City, the putrefying giant exploded spontaneously. The blast spewed thousands of pounds of rotten blood, blubber, and entrails onto cars, motor scooters, and shops. It even soaked some unfortunate onlookers.*

"But blue whales don't do that," Engstrom assured me, just as he had

* The event left such an impression on me that I immediately posted a newspaper photo of the postexplosion carnage outside my office door at LIU Post, labeling one car owner's particularly bad parking spot.

previously tried to assure the freaked-out and unconvinced residents of Trout River. He told the townsfolk that unless people decided to jump up and down on the dead behemoth or cut it open, the tissue breakdown would likely allow the accumulating gases to escape slowly, like from an old balloon. "Which is what eventually happened," he said.

Engstrom explained that most of the questions he got from the reporters on the scene in Newfoundland were related to one of two topics: smell and size. "How big is the heart? We hear it's as big as a car." He and his team heard the heart-size question so many times that, finally, one of his technicians responded with a question of his own. "Why don't we try to save the sucker?"

Engstrom was immediately intrigued by the possibility, though he knew that his team had to move quickly. One of the three whales had drifted into an uninhabited cove and had broken up in the tide during a storm. The second specimen was currently impersonating the Goodyear Blimp for whale-bomb-wary crowds in Trout River, a situation that did not bode well for the preservation of its internal organs.

But Engstrom knew that the last and smallest whale (seventy-six feet), the one that had come ashore at Rocky Harbour, lay partially submerged in the cold water—potentially slowing down the process of organ decomposition. He asked ROM colleague Jacqueline Miller, a mammalogy technician assigned to the Rocky Harbour recovery team, if she could salvage the heart.

The expert anatomist responded immediately and enthusiastically, "Yeah, we can save it." Later, she confessed to me that she wasn't quite sure *what* they would find when they opened the whale up, or if it would be salvageable. But the prospect of preserving a blue whale heart was exciting enough that she was eager to try.

Miller and seven other intrepid researchers began by "flensing" the Rocky Harbour whale carcass—whaling-speak for removing the flesh and soft tissue from tail to head. Once the muscles surrounding the

heart- and lung-containing thoracic cavity had been removed, members of the recovery team got their first look at the megapump—something no researchers had ever seen before. Instead of a typical mammalian heart, the specimen more closely resembled a four-hundred-pound flesh-colored soup dumpling. Undaunted by the heart's resemblance to a gargantuan Chinese appetizer, they took a further look through the gore and were completely thrilled to see that although the heart had collapsed into a six-foot-wide blob, it had *not* decomposed.

"It was still pink," Miller told me, although she also remembers some mildew and a bit of necrotic (i.e., dead) tissue. "It had a lot of elasticity, and it still held a lot of fluid."

Several years later, in 2017, Miller would be invited to necropsy a North Atlantic right whale (*Eubalaena glacialis*) after a mass mortality event during which seventeen whales had died mysteriously. Her hope was to recover a cetacean heart from an additional species.* But even though that particular whale had been dead for less time than the Newfoundland blues whales, it turned out to be the wrong right whale. The heart had already decayed into an unsalvageable mess. The episode, which took place during the summer, led Miller to realize how fortuitous it had been that the Rocky Harbour specimen had died in the winter and spent three months in ice water. "I think we were just lucky," she said.

Miller, whose graduate school studies had focused on mice and other pint-sized mammals, got in and got dirty. She and her rainwear-clad colleagues worked with flensing knives and machetes to sever the vena cava and the aorta, the great vessels leading to and from the blue whale's heart, respectively. Then they attempted to free the organ from the gigantic animal's body. But after positioning themselves inside the creature, Miller and three associates discovered that, try as they might,

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* *Necropsy* comes from the Greek for "corpse" or "the dead" (*nekros*), while the *-opsy* part (also derived from Greek) means "sight," thus referring to the visual inspection of a dead body. *Autopsy* (from Greek, "seeing for oneself"), when used in the context of dead bodies, is reserved for postmortem examination of human bodies.

they could not maneuver the heart through the space they had cut for it between two of the ribs. Even after detaching the heart from the lungs by cutting through the pulmonary arteries and veins, it wouldn't budge. Eventually, after forcing several ribs apart, the four researchers were able to shove what turned out to be a 386-pound heart from its original home into a nylon mesh bag spacious enough to package a Volkswagen Beetle.

With the aid of a front-end loader, a forklift, and a dump truck, the blue whale heart was transferred to a refrigerated truck and shipped out to a facility where it was frozen at −20°C. It would remain on ice for an entire year before a team of experts could be assembled to carry out the next phase of the project: preservation.

This process, Engstrom explained, would include restoring the heart to its original shape. This was necessary because, unlike a human heart would do, the blue whale's heart had collapsed like a deflated beach ball after its great vessels were severed. Engstrom told me that, although no one was quite sure, this was likely an adaptation to the great pressure experienced by blue whales during deep dives.

Preservation efforts began with the specimen being placed into a tap water bath to thaw. The heart would need to be filled with preservative to halt decomposition, stiffen the muscles, and kill any bacteria that might have survived the trip to the freezer. First, though, the team searched for appropriately sized objects to plug the dozen or so severed blood vessels coming off the organ. The cork job was necessary so that they could fill the interior chambers of the heart with preservative without having it flow back out. It would also allow the researchers to reinflate the specimen, remedying the unsightly collapsed-balloon look that the mighty heart had assumed since its removal.

Ultimately, the items they chose as plugs ranged from soft drink bottles, for the smallest vessels, all the way up to a five-gallon bucket, which fit quite nicely into the giant caudal vena cava. This particular mega-vein was responsible for carrying oxygen-depleted blood from the whale's body

and tail to its right atrium, one of the heart's two "receiving chambers."* The right atrium also received blood from the only slightly smaller cranial venae cavae, which returned blood from the whale's massive head region. In two-legged creatures like humans, the equivalent vessels are known as the inferior vena cava and the superior vena cava, respectively. As in all mammals, the venae cavae transport carbon dioxide–rich and oxygen-poor blood back to the heart, which then pumps it to the lungs.

During the initial preservation effort, Jacqueline Miller and her team used seven hundred gallons of everyone's favorite embalming agent, formaldehyde. This tissue fixative has been known to be a carcinogen since the early 1980s, and though most people remember its distinctive smell from biology class, our most common exposure results from the chemical's nearly undetectable inclusion in building materials like particleboard, plywood, and fiberboard. Although the whale preservation crew diluted their formaldehyde into a somewhat more biologically friendly solution known as formalin (generally around 40 percent formaldehyde), the liquid was still, in scientific parlance, some particularly nasty shit.

"The funny thing," Miller told me, "is that in a typical lab, you risk getting splashed by formalin. Here, the risk was falling into a vat full of it."

The heart sat in formalin for five months, undergoing the process of fixation, during which all tissue decay ceases. The formerly pink organ also took on the beige color typical of similarly fixed specimens. But although it could have remained in the same solution for decades, Mark Engstrom and his colleagues decided that sticking it in the equivalent of a giant bottle of poison would not do justice to the great heart. Instead, after consultation with a pair of conservators versed in the art of preserving large specimens, a decision was made to "plastinate" it. Plastination is a unique process of specimen preservation invented in 1977 by the decidedly weird German anatomist Gunther von Hagens. Known affectionately as

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* *Atrium* is Latin for "entrance hall."

Dr. Death, von Hagens created the controversial *Body Worlds* exhibit, which consists of dozens of skinned and plastinated human bodies, posed in a variety of positions, each chosen to better illustrate a range of anatomical systems.*

Since the researchers at the ROM were not trained or equipped to carry out the complex procedure by themselves, they shipped the whale heart to the Plastinarium, a *Body Worlds* gallery and plastination facility in Guben, Germany. Otherwise known as Gubener Plastinate GmbH, the former cloth factory is staffed with von Hagens–trained experts, each eager to satisfy their customers' every plastination need. Though they were used to dealing with museum specimens of many shapes and sizes, the blue whale heart would be their largest undertaking ever.

During the initial steps of the process, all of the water and soluble fats are slowly drawn out of the specimen and replaced by acetone, an organic compound that is as toxic to humans as it is flammable. In the very definition of "Don't try this at home," the ROM's blue whale heart required a total of six thousand gallons of the stuff. The heart sat in acetone for eighty days at freezing temperatures, the cold expediting the loss of water from the cells and its replacement with the poisonous solvent.

The staff of the Plastinarium then put the heart through a process known as forced impregnation, during which the acetone was replaced by liquid plastic, specifically a silicone polymer. To achieve this, they placed the organ in a vacuum chamber and gradually lowered the air pressure. This environment caused the acetone to vaporize within the cells, drawing the polymer in behind it to fill the empty space. With most of the cell mass now occupied by liquid polymer, the process had literally transformed the formerly living tissue into plastic. The Plastinarium

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* In January 2011, in a macabre chapter to a story many had considered more than a bit macabre to begin with, the then sixty-five-year-old von Hagens revealed publicly that he was terminally ill. He also expressed a desire to have his body skinned and plastinated after his death. The current plan is for the plastinate version of von Hagens to "greet" visitors as they enter one of the permanent *Body Worlds* exhibitions. Reportedly, Dr. Death will be wearing his trademark black fedora.

employees then employed a curing agent to harden the silicone, a step that took an additional three months.

Once fully firm, the blue whale heart was shipped back across the pond in May 2017, to become the centerpiece of an elaborate exhibit that was constructed at the Royal Ontario Museum to highlight the amazing specimen. For size comparison purposes, the heart was displayed alongside a Smart car, while from the adjacent ceiling stretched the fully articulated skeleton of the Trout River whale specimen. Now weighing in at 440 pounds, the plastinated blue whale heart would never decay or smell, and the enormous pump would be viewed by hundreds of thousands of museum visitors during its four-month-long star turn in Toronto.

Pump is a story about hearts and the circulatory systems associated with them. Big hearts, small hearts, cold hearts, and even nonexistent hearts. It is also the story of some of the notable structures, fluids, findings, and foul-ups associated with them. The history of our attempts to understand the function of the heart and circulatory system is long and, until relatively recently, riddled with errors. For example, among the medical communities of the seventeenth and eighteenth centuries, there was a belief that blood carried within it the essence of its owner's personality. Terms like "blue blood," "bloodthirsty," "cold-blooded," and "hot-blooded" are linguistic vestiges from a very different world. Armed with the knowledge of just *how* different that world was, it will be easier to understand why the history of cardiovascular medicine has no shortage of strange stories and bizarre treatments.

Pump is certainly not a textbook, nor is it my goal to cover every type of heart and every facet of every circulatory system. Instead, I will wander through these broad topics, making interesting stops along the way. For those of you who have gone exploring with me before, there will be quite a few of these side trips, most of them with a zoological or historical

perspective. Some of these seemingly tangential stops will be necessary to better explain poorly understood or misunderstood concepts, while others will help explain how hearts and circulatory systems work—covering topics like diffusion, the blood-brain barrier, and Mothra.

Hearts and their related circuitry show a serious degree of variation in invertebrates like insects, crustaceans, and worms—and there are good reasons for that. There exist far fewer differences in creatures that come equipped with a backbone, whether fish, fowl, or farmer. But in addition to exploring some prime examples of cardiovascular diversity across the animal kingdom, we'll learn how some of these creatures are now saving lives and providing answers to difficult questions about cardiac health and the ailing human heart.

Pump is also the story about what happened when one relatively new species of mammal decided that the heart was something far more than an organ keeping everybody alive—that it was no less than the center of emotion and the seat of the soul. Where did *that* belief come from? Why does it cross so many cultural boundaries? Why does it persist? And just as importantly, is there any truth to the link between hearts and minds?

By the end of this journey, you will gain a new appreciation for the degree to which the heart plays a vital role in the natural and human world, both as the engine that drives the circulatory system *and* as the mysterious organ at the core of human culture and human nature itself. From a hollow cluster of cells with a unique ability to shorten its length to the golf cart–sized heart of the blue whale, from beliefs about the origin of love and the soul to early cardiac medicine, futuristic therapies, and beyond—my hope is that you will never think about these topics in quite the same way again.

In fact, it's my heart's desire.

PART 1

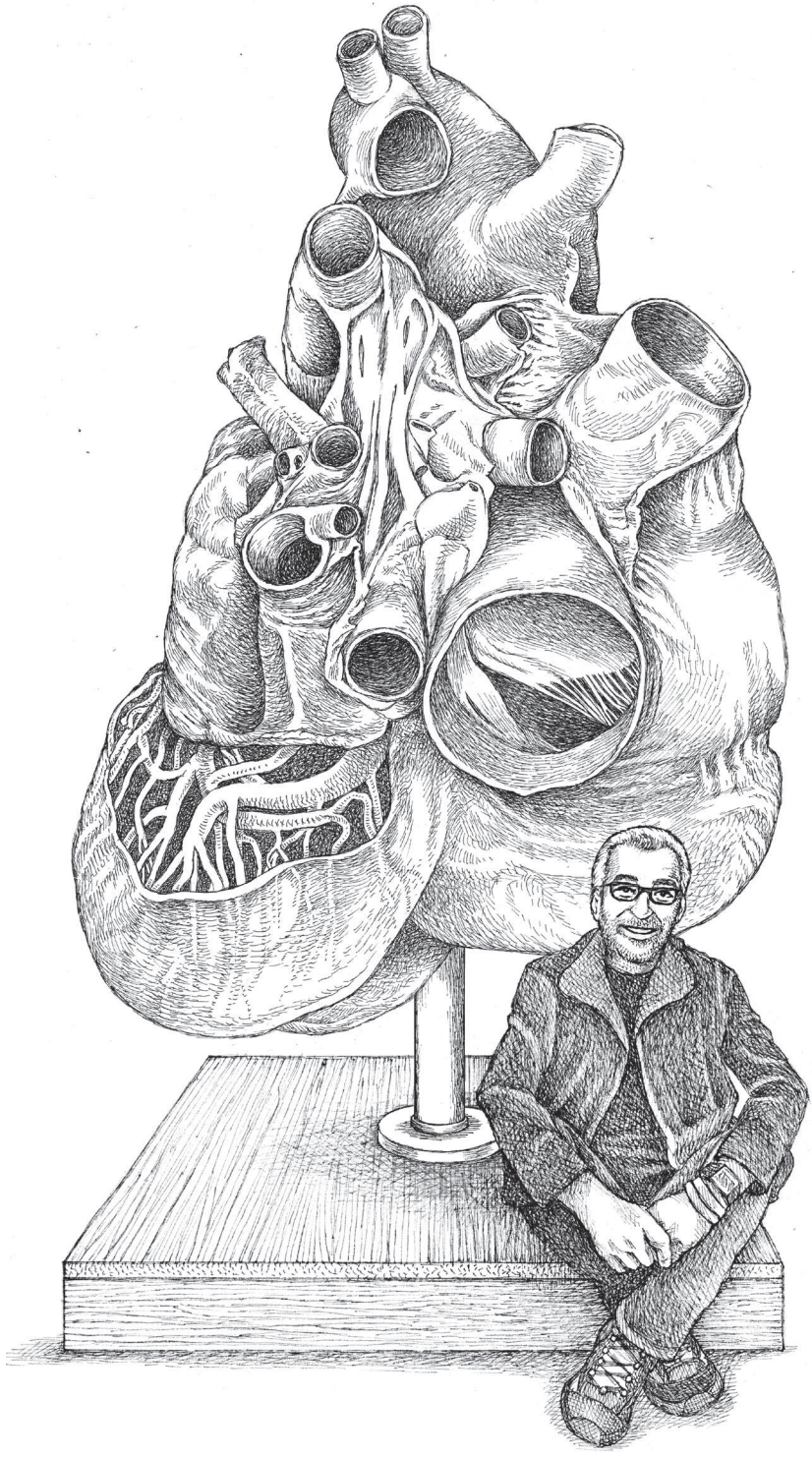
Wild at Heart

One size does not fit all.
—UNKNOWN (POSSIBLY FRANK ZAPPA)

[1]
Size Matters I

IN AUGUST 2018, I traveled to Toronto's Royal Ontario Museum with artist Patricia J. Wynne to examine the famous blue whale heart. Patricia and I have been friends and officemates at the American Museum of Natural History since the mid-1990s, and she has illustrated every paper, book chapter, and book (fiction and nonfiction) that I've ever written. Although the blue whale exhibit had already closed and the specimen was being stored at an off-site facility, researcher Bill Hodgkinson had uncrated the heart in preparation for our arrival. In a room the size of a small aircraft hangar, the preserved whale heart sat perched upon a two-inch-thick stainless-steel rod, giving it the appearance of having been skewered from below. The bottom end of the skewer was secured to a wooden floor stand while the business end had been connected to a metal armature, invisible to viewers, that served as the heart's permanent internal scaffold.

Because the specimen's official dimensions are forty-two inches from top to bottom by thirty-eight inches in width, I was quite surprised to find it looming over me at a height of what I estimated to be well over six feet. The explanation for the added height was the massive blood vessels situated atop the plastinated organ. The most prominent of these was the



great arch of the aorta and its offshoots, a pair of carotid arteries that had once carried oxygenated blood from the left ventricle of the heart to the animal's head. If the previously mentioned atria can be envisioned as the heart's receiving chambers (the left atrium and the right atrium receiving blood from the lungs and the body, respectively), then the ventricles are the heart's pumping chambers—the right ventricle pumps oxygen-poor/CO_2-rich blood to the lungs while the left pumps oxygenated blood out to supply the body.

During the blue whale heart's lengthy preparation period, a special type of colored silicone polymer had been injected into the blood vessels, and so veins and arteries could now be differentiated, because veins were blue and arteries were red. The multicolored heart was really quite beautiful, and I was immediately drawn to a porthole-shaped section that had been cut through the right ventricle by plastination expert Vladimir Chereminsky. The window allows viewers to peer inside the chamber, where, among other things, they can see the odd-looking arrangement of inch-thick muscle strands that line its walls. These strands are known as trabeculae carneae (meaty ridges) by anatomy types and medical professionals, and smaller versions can be seen in many mammals, including humans. The ridges increase the surface area of the ventricular walls as compared to a smooth wall, packing more muscle fibers into a limited space. This is important because the extra muscle translates to stronger ventricular contractions, which propel blood out of the heart. Additional functions of this odd-looking chamber surface remain to be explored.

The right and left atria of the whale heart also contract, and their thinner walls reflect the fact that their job is less difficult: pumping blood into their adjacent ventricles instead of out to the body. Located between the atria and ventricles are the aptly named atrioventricular (AV) valves. Through Chereminsky's porthole, museum visitors could see the blue

whale's right AV valve, which appeared to have the diameter of a toddler's toy drum. In humans, the corresponding valve spans about three-quarters of a square inch, about the diameter of a marble, and is more commonly known as the tricuspid valve, due to its three flap-like valve cusps.*

The AV valves regulate blood flow from the atria to the ventricles, but equally important is their job preventing blood from reversing direction and heading *back* into the atria when the ventricles contract. Vital to this role, and clearly visible within the blue whale heart, are a dozen or so tough fibers known as chordae tendineae. Colloquially known as the heartstrings (since they resemble pieces of string), these cords are composed primarily of a structural protein called collagen.† With one end of the chordae tendineae firmly anchored to the floor of the ventricle and the other end attached to the valve cusp, the cusps are prevented from extending into the atria when the ventricles contract—effectively sealing off the two chambers.

To visualize this, picture a dog with its collar fastened to a long leash, with the nondog end staked to the ground. The dog (standing in for the valve cusps) can travel only so far before the leash (the chordae tendineae) pulls tight, preventing the dog from advancing past an open gate. In humans, the terms "ventricular prolapse" or "prolapsed valve" are used to describe medical conditions in which one or more of the AV valve cusps bulges into an atrium (think of the dog's leash that has been stretched from the pup's constant tugging, allowing it to advance beyond the gate). Since this prolapse breaks the seal separating the atrium and the ventricle, some of the ventricular blood "regurgitates" back into the atrium when the ventricle contracts, instead of leaving the heart, as it

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* On the left side, the bicuspid valve is named for its two cusps. Confusing the issue, it is also known as the mitral valve, due to its *supposed* resemblance to a miter, the ceremonial headwear worn by bishops. Thankfully, there are no hat-derived alternative names for the tricuspid valve.

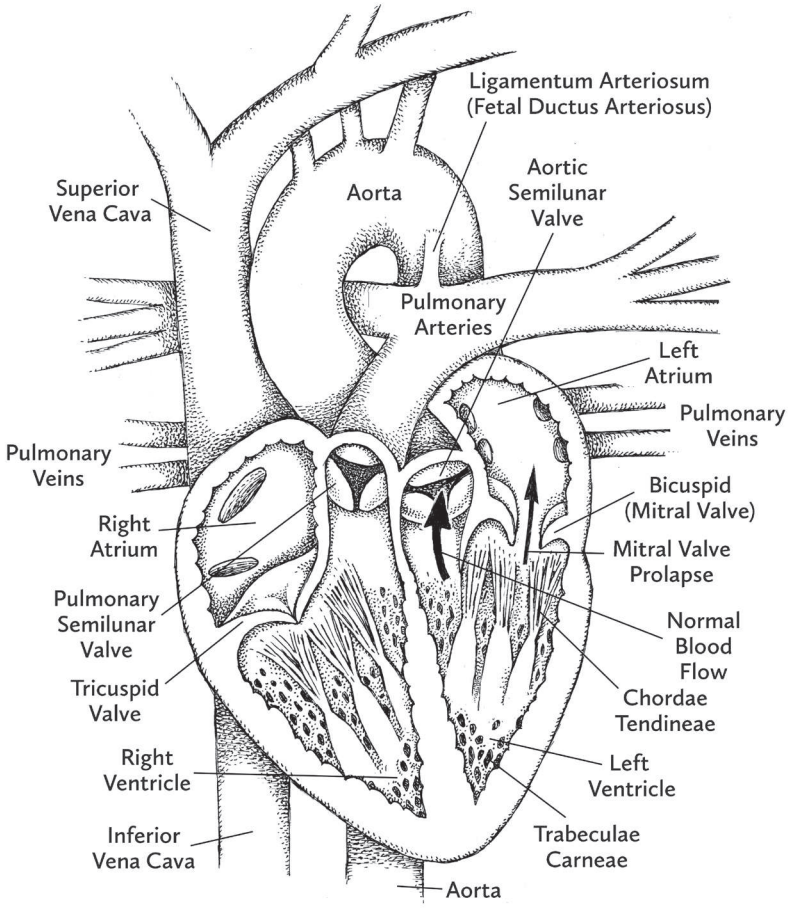
† Wound into fibers, collagen is the most abundant protein in mammals. It is commonly found in tendons, ligaments, and the skin. Collagen also give bones their varying degrees of flexibility.

would normally. These so-called "floppy" valves can result from previous heart attacks, infections like bacterial endocarditis (frequently found in intravenous drug users), or rheumatic fever, a now-rare consequence of untreated strep throat or scarlet fever. Mitral valve prolapse can also be congenital in nature.

Valve problems can also be a consequence of aging. As the heart valves stiffen and lose their flexibility, they lose their ability to efficiently seal off the heart chambers. With some of the blood moving backward into the atrium with each heartbeat, less blood is pumped out of the heart, and so it has to work harder (by increasing its rate or contracting harder) to compensate. The extra effort can put added stress on the heart, which can lead to serious problems. These become especially apparent if the heart reaches a point at which it can no longer provide sufficient oxygen- and nutrient-rich blood to the body.

Once blood passes through the AV valves, filling the right and left ventricles, it must next pass through the semilunar valves, named for their half-moon-shaped cusps. As the ventricles contract, blood rushes through them into two large arteries. On the right side is the pulmonary trunk, which sends deoxygenated blood to the lungs via the pulmonary arteries that branch from it. On the left side, ventricular contraction pumps oxygenated blood out through the aorta, whose branches distribute it to the rest of the body. Though their anatomy is different from the AV valves before them—no chordae tendineae here—pulmonary and aortic semilunar valves also prevent the backflow of blood, here from the pulmonary artery and aorta back into the ventricles.

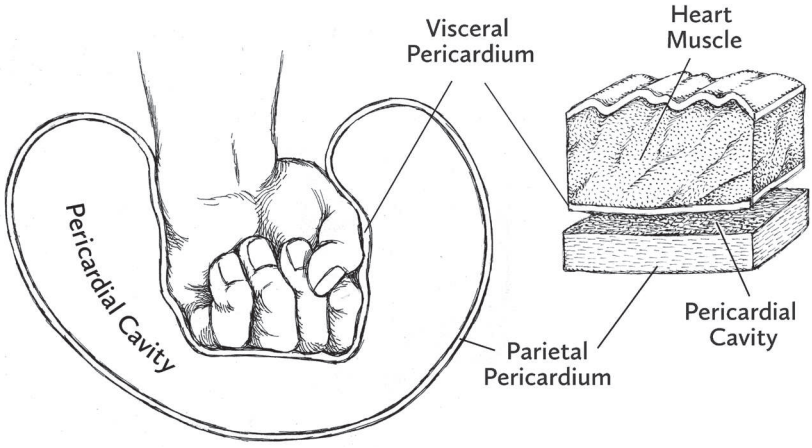
In humans, slight valvular abnormalities are often symptom-free and don't require treatment. In more serious cases, a prolapsed valve can cause irregular heartbeat (arrhythmia), dizziness, fatigue, and shortness of breath, and surgery may be required to fix it. Until the early 2000s, valve repair or replacement required complicated open-heart surgery. Now, though, transcatheter valve replacements can be accomplished through



small incisions, or even no incisions at all, as a result of major advances in cardiac catheterization—a process whose history is as interesting as any fiction writer could have dreamed up. But more on that topic later.

To give viewers a look at the blue whale's heart just below its surface, plastination-meister Chereminsky also removed a section of the whale's visceral pericardium. This is the thin, protective layer of the heart that lies atop all that muscle. It's also the *inner* layer of the saclike pericardium, which lubricates and cushions the heart while holding it in place. To visualize the relationship between heart and the pericardium, picture a Ziploc storage bag containing a bit of water. Push your fist (the heart) into the side of the bag so that the bag wraps around your fist. The bag of

water is the pericardium, and the part of the bag plastered against your fist is the visceral pericardium. The space inside the bag is the pericardial cavity, partially filled with its supply of pericardial fluid. To complete the metaphor, the part of the Ziploc bag farthest from your fist is the parietal pericardium, and it is attached to the surrounding walls of the chest cavity. This connection anchors the heart in place while cushioning it from external shocks. It's worth noting that the pericardium does not *contain* the heart, but rather is wrapped around it.



Having observed the plastinated whale heart, inside and out, I left my friend Patricia at the warehouse to sketch the specimen while I set off for the ROM to interview some of the people responsible for its recovery and preservation. But beyond the story of how this one-of-a-kind specimen came to be, I was most interested in what Jacqueline Miller, Mark Engstrom, and their colleagues learned from it that they had not known before.

I asked Miller about the plastinated heart's odd shape. Typically, the mammalian heart is conical, coming to a single point at the bottom or apex. I had been struck by the fact that in blue whales the apex of the heart is split. Miller explained that this bifurcation is a characteristic of

rorquals, a name used to group the largest of the baleen whales.* Another unique characteristic, she told me, is that this particular heart is flatter and wider than most mammalian hearts.

"The typical terrestrial mammal has a spiral heart—a heart in which the connective tissue and muscle fibers are oriented so that they spiral around the left and right ventricles," added Engstrom. "When the heart contracts, the overall action is more like wringing out a towel."

But in rorquals, the fibers run straight from the top of the heart (the base) to the bottom, rather than in a spiral.

"I think what's happening is that when they do deep dives, their heart collapses," Engstrom told me.† "It's still beating, but it collapses due to the pressure."

Because of this, and as Miller and her team discovered back in Rocky Harbour, once the heart had been severed from its moorings and removed from the body, it had collapsed "like an enormous spongy bag," according to Miller, thus requiring reinflation during the preservation process.

Adding to the list of things the researchers at the ROM had learned about blue whales, Engstrom mentioned how many times over his career he had been asked about the actual size of the world's largest heart.

"I was getting tired of the question," he admitted. "And I really wanted to be able to say 'It's *that* big' and then point to it."

For decades, in both popular and scientific literature, it was written that a blue whale heart would be the size of a sedan and weigh at least a metric ton.‡ Miller told me that in preparing to extract the heart, she and her colleagues had read about how "you'd be able to swim down one of the greater vessels, presumably the caudal vena cava, which is the largest vessel on the blue whale heart."

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* "Baleen" is the arrangement of bristles inside the mouths of certain whale species into a filter-feeding device. Composed of keratin (the stuff that makes up our nails and hair), it is used to trap krill after large gulps of water are taken in and then forced out of the mouth.

† While the dive record for a tagged blue whale is 315 meters (1,033.5 feet), a Cuvier's beaked whale (*Ziphius cavirostris*) holds the record for dive depth by a mammal, at 2,992 meters (or 1.86 miles)!

‡ 1 metric ton = 2,204.6 pounds.

As I looked over the impressive vasculature attached to the ROM specimen, it was easy to see that even the largest blood vessel wasn't wide enough for a human to swim through, though I figured an otter or a migrating salmon could make the journey with relative ease.

Indeed, Miller told me, once the heart had been preserved it was significantly *smaller* than they had thought it would be. And this wasn't an undersized blue whale by any stretch. So *why* was it so much smaller than anticipated?

The answer turned out to be that blue whale hearts are simply not as large as the hearts of most other mammals. While quite humongous by human standards, a blue whale's heart apparently makes up only around 0.3 percent of the animal's total body weight. For comparative purposes, the relative size of the heart in both mice and elephants has been calculated to be about 0.6 percent.

Interestingly, some of the world's smallest animals have disproportionately large hearts. For example, the masked shrew (*Sorex cinereus*) is one of the smallest mammals in the world, weighing in at around five grams,* but its heart makes up about 1.7 percent of its body weight, which is approximately three times larger than one would predict for a typical terrestrial mammal, and nearly six times the relative size of a blue whale heart. Birds, meanwhile, tend to have relatively larger hearts than mammalian hearts, due to the metabolic demands of flight. In hummingbirds, the smallest of which can weigh as little as two grams (less than a dime), the heart-to-body weight numbers are even more extreme, with the heart reaching 2.4 percent of body weight. Relatively speaking, this means that hummingbird hearts are *eight times* larger than those of a blue whale.

It is thought that the reason for possessing a relatively large heart relates to the lifestyles of the small and hyperactive. For example, hummingbirds

* The smallest mammal in the world is the Kitti's hog-nosed bat (*Craseonycteris thonglongyai*) from Thailand and Myanmar. Also known as the bumblebee bat, it weighs in at barely two grams.

can beat their wings at eighty times per second, and shrews are such nonstop hunters that during my mammal-trapping days as a PhD student at Cornell University I was taught that they would starve to death if not removed from a live trap within an hour. The manic behavior of these tiny animals causes an extremely high cellular demand for both energy and oxygen. These metabolic requirements are met in part by increasing heart rate, thus also increasing the frequency at which oxygen-rich and nutrient-laden blood is pumped to the body. The resulting heart rate numbers are truly astonishing. Hummingbird heart rates can reach 1,260 beats per minute, while shrews hold the vertebrate record at 1,320 beats per minute—roughly seven times the maximum heart rate of a thirty-five-year-old human.

Though these are eye-popping numbers, the increase in beat frequency is not unlimited, and researchers believe that there *is* a maximum rate at which a heart can beat. For a shrew, one heartbeat lasts forty-three milliseconds—that's forty-three *thousandths* of a second. During this split second, the heart needs to fill with venous blood, contract and eject the arterial blood, and relax in preparation for the next filling cycle. All of that can occur only so fast—and if shrews aren't at the upper limit of heart rate, then they're awful damn close. So if the physical design of the heart limits it to something like a maximum of fourteen hundred beats per minute, then the only way to pump *more* blood is to increase the size of the heart. That way, the larger chambers are able to receive and pump a relatively greater measure of blood with each beat.* This explains the comparatively enormous heart size of creatures like shrews and hummingbirds. But as we'll soon see, increasing heart size among the ubersmall also has its limits.

Before leaving blue whale hearts, though, and whale hearts in general, it should be emphasized that there is much, much more to learn: How

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* An average-sized man has about five liters of blood. At rest, cardiac output is approximately five liters/minute, so the average time it takes our blood to take a full circuit of the body (from heart to lungs, back to the heart, out to the body, and back to the heart) is approximately one minute.

exactly do these hearts collapse, and how can their owners survive when they do? Other diving mammals, like seals, reduce their heart rates and cut off blood flow to different regions of their body. Do blue whales possess the same oxygen-saving adaptations? Initial research indicates that this could be so, since a recent study by biologist Jeremy Goldbogen and his colleagues at Stanford University found that blue whale heart rates can drop to as low as two beats per minute.* On the anatomy side of things, other serious questions remain, some as simple as identifying the blood vessels in the confusing assemblage sprouting from the now-famous ROM specimen. Until more research can be done, much of the physiology of the rorqual heart will remain in the realm of hypothesis and conjecture.

* Goldbogen and his team used suction cups to attach a heart rate monitor to a single blue whale, and were able to monitor the animal's heart rate for nearly nine hours. They did not seek to determine if blood flow was redirected to specific regions of the body during the dramatic drop in heart rate that they recorded.

The Microbe is so very small
You cannot take him out at all.
—Hilaire Belloc

[2]

Size Matters II

For those of you who have a body of less than one millimeter across, nothing much in this book applies to you. Why's that, you ask? The answer is that much of what has come before in this book and much that follows is about the heart. By definition, a heart is a hollow muscular organ that receives circulatory fluid from the body before rhythmically pumping it back out again. Collectively, the pump, the fluid, and the vessels through which the fluid travels are referred to as a circulatory system . . . and you don't have one. Because of your minuscule size, nutrients and oxygen can be distributed to your cells (or cell, if you're small enough to have only one), and waste products can be removed from them, by a simple exchange with the external environment, which for most of you probably consists of water.

That exchange is known as diffusion, which is a vitally important process for all living things, whether they're microbes or blue whales. Basically, diffusion occurs when molecules—like oxygen, or nutrients, or waste products—exist at different concentrations on either side of a barrier. Imagine that you've just cleaned your room by cramming everything into your closet and forcing the door shut. There is a higher concentration of stuff inside the closet than outside, with the closet

door acting as the barrier. If you were to cut a hole in the door, anything smaller than that hole would have the potential to escape and tumble out, always moving from an area of higher concentration (your closet) to an area of lower concentration (your room). So now, instead of bumming out whenever you open your closet door and stuff falls out, you can think of the mini avalanche as your belongings following their concentration gradient.

But what does your closet have to do with circulatory systems? As previously touched upon, the answer relates to one of the system's key functions, which is to deliver nutrients and oxygen from outside the body to the cells and tissues inside the body. Conversely, circulatory systems also function by helping transport potentially harmful stuff, like toxins, cellular waste products, and carbon dioxide, *out* of the body before it can cause problems.

Organisms less than a millimeter wide are generally composed of a single cell. In these microbes, both the good stuff moving in and the waste moving out pass through tiny pores in the cell membrane, a barrier that separates the inside of the cell from the outside. These gaps are the equivalent of the hole in our metaphorical closet door. Like junk from a closet, the movement of material follows its particular concentration gradient. If there is more oxygen outside the microbe than inside, then it diffuses *into* the organism. Nutrients, including carbohydrates and sugars, also diffuse in. And when waste products accumulate at a higher concentration inside the microbe than outside . . . Well, you get the picture.* Finally, as in the closet example, some substances are prevented from crossing the cell membrane. As a result, the cell membrane is said to be "semipermeable." This property explains why cell structures like

* The back-and-forth movement described above takes place with little or no energy expenditure by the cell, making it a "passive" process. Material can also be moved in either direction if engulfed by the cell (as is seen in organisms like amoebas) or packaged by it in tiny membrane-bound bags called vesicles, which can be ejected from the cell. Both of these "active" processes require an input of energy, as would moving a substance across a membrane *against* its concentration gradient.

organelles (the nucleus and mitochondria, for example) remain inside the cell: basically, because they can't fit through the pores.*

Now I know what a few of you are thinking—or *would* be thinking if you had a central nervous system. "Some of us are a whole lot wider than a millimeter, and we don't have any of that circulatory-system junk you just mentioned. So explain that one, Mr. Science."

Well, all right, but I'm going to make this quick.

It *is* true that some of you—flatworms (a.k.a. platyhelminths), for example—can form chains up to eighty feet long, and, yes, you're all doing ever so well without a circulatory system—too well if you ask me. But like every other living creature, the twenty thousand or so species belonging to Team Flatworm exist and thrive because they have adapted to the specific demands of their environments (so-called selection pressures). For some flatworms, this resulted in the evolution of folded bodies, or of long threadlike shapes. Just as a walnut has more surface area than a smooth ball of the same size, a flatworm with a folded body has more surface area for gas, nutrient, and waste exchange than a smooth flatworm of the same size and shape. Extending that concept to the closet door example, an accordion door would have more surface area than a flat door, allowing for more holes to be cut in it.

But there's more to the success of flatworms than just shape. Notably, there are no high-activity sprinters here. No speedy swimmers or fliers either. Instead, their lives are pretty much fulfilled once they hook their headlike scolex to the lining of someone's colon. Others while away the hours lying low in a streambed, or maybe in the shade of some moist leaf litter. It's a lazy existence, and as a result, these couch potatoes need less energy and oxygen to get them through the day.

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* In addition to size constraints, some substances exhibit other physical properties that prevent their movement across the membrane. An example of this might be a molecule with an electrical charge that repels it if it gets too close to a similarly charged membrane.

But, hey, guys, don't take this the wrong way. Though you lack circulatory and respiratory systems, and many of you live parasitic lifestyles and infect three hundred million people per year and defecate out your mouths, please know that none of this is meant to make you feel bad.* It's just that this book isn't about you—so we'll talk later, okay?

All right. Are they gone? Cool.

Now for those of you who are a bit thicker around the middle than our minuscule friends and who might live somewhere other than in someone else's intestine or under a layer of pond scum, you should know that there were real problems during your evolutionary journey from single-celled organisms into dung beetles, leeches, and insurance salesmen. Perhaps the most serious issue was the fact that diffusion does not work well over large distances. In fact, it's a no-go for pretty much anything wider than a millimeter. As a consequence, diffusion alone is extremely ineffective for moving vital substances and waste products in creatures with beefy three-dimensional bodies, composed of layers hundreds and even thousands of cells thick.

You might ask, how then did organisms evolve to become as large as they are?

That's a tough one.

I should start off with the caveat that, given the small size and the squishy-bodied nature of the extremely ancient organisms involved, the fossil record for this sort of thing is relatively scanty. That said, scientists think that the first multicellular life-forms, the metazoans, evolved somewhere between 770 and 850 million years before present (BP). By 600 million years BP, a new line of metazoans had evolved, sporting identical right

* Although most of the more than twenty thousand members of the phylum Platyhelminthes regurgitate undigested food, some species have an anus, or even several, situated on their backs. The problem for other species is the fact that tapeworms (cestodes), and especially the flounder-shaped flukes (digeneans), are internal parasites that cause serious diseases, like schistosomiasis, in humans and their livestock—nowadays primarily in Africa.

and left sides, rather than radial (a.k.a. circular) shapes. Their embryos also added a third layer to what had previously been a double-layered, embryonic body plan. The more ancient setup consisted of an outer ectoderm, which developed into structures like skin, nervous tissue, the mouth, and the anus, and a more deeply situated endoderm, fated to become the inner lining of the digestive and respiratory systems. The newly evolved third layer, known as the mesoderm, was found between the other layers and served as a source of new building blocks for larger and more complex organisms. Eventually, it would give rise to muscle, connective tissues like cartilage and fat, structures like bones, and a not-inconsequential assemblage of tissues that would become known as the heart.

The next-highest level of organization in a multicellular body is the tissue. Each type of tissue is made up of different cell types, as well as substances collectively known as the extracellular matrix, found outside and between those cells. Together, the cells and the matrix work in a tissue to carry out a specific function or functions, such as supporting the body against the pull of gravity or helping move liquids from place to place. There are but four tissue types: connective tissue (like blood, bone, and cartilage), epithelial tissue (which covers body surfaces and lines cavities like hollow organs and blood vessels), nervous tissue (neurons and their support cells, the glia), and muscle tissue. Within muscle tissue, there are three subtypes: smooth muscle (involuntarily controlled), skeletal muscle (voluntarily controlled), and cardiac muscle, which is, happily, also involuntary, thus freeing us from the bother of remembering to keep our heart beating.

The next organizational level of the body is the organ. Your organs each carry out at least one particular function, and often many more. Each organ is composed of at least two different types of tissue, and some of the larger organs, including the heart, can be composed of all four types. Though the heart, kidney, and liver are more readily recognized as

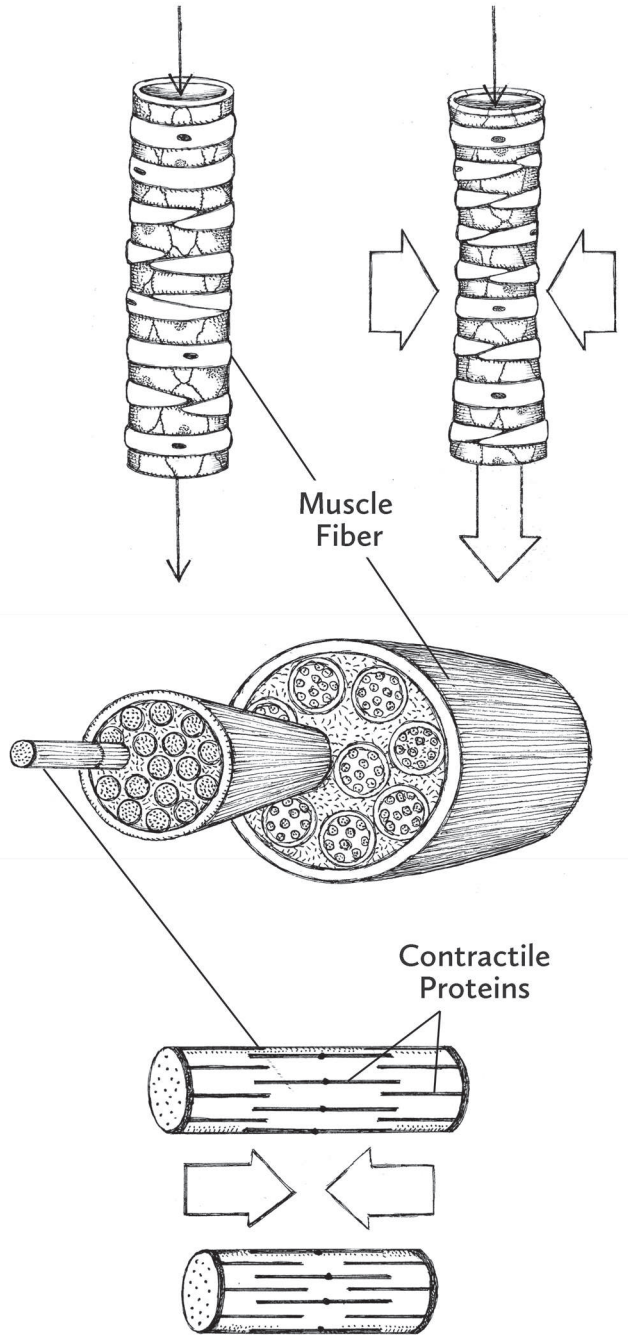
organs, blood vessels actually fall into the category as well, since veins and arteries are composed of epithelial, connective, and muscle tissue, and carry out the function of transporting and distributing blood.

At the top of this hierarchy of body organization are organ systems like the circulatory and digestive systems. These are made up of multiple organs involved in some general function or functions. In the case of our circulatory system, the organs consist primarily of the heart, arteries, capillaries, and veins involved in transporting blood throughout the body.

Like other organs, most blood vessels are made up of layers of cells. Muscle cells, more often referred to as muscle fibers or myocytes, form an internal layer bounded on either side by connective and epithelial tissue. When those muscle fibers contract, the liquid within the vessel is compressed and moves—picture your fingers squeezing the center of an elongated water balloon. Scientists believe that this is how water, and eventually blood, began to be transported from place to place within organisms that were growing increasingly larger over evolutionary time.

How did this process unfold? One hypothesis is that approximately half a billion years ago, some of the cells derived from the newly evolved mesoderm of some unknown organism developed the ability to shorten their lengths—that is, to contract. For this to happen, at some point the contractile proteins within a cell would have had to line up next to each other. Once provided with an energy source, these proteins (like the actin and myosin found in human muscles, including the heart) would have slid past each other in opposite directions. If millions of these molecules did this simultaneously, it would have contracted the cells they were found in, and so, too, the whole structure around those cells. Then when the contractile proteins slid back to their previous positions, the cells would have relaxed and returned to their precontracted length.

Half a billion years ago, though, the first contractile cells would have been far simpler than our own muscle cells (a.k.a. myocytes or


Muscle
Fiber
Contractile
Proteins

myofibers). Additionally, they couldn't have evolved in blood vessels, since neither blood nor the vessels that transport it existed back then—though water certainly did, and it was primarily within water that material could move into and out of an organism. Even now, contractile proteins are found inside normal body cells, where they form a vital part of the cell's internal transportation system. Scientists believe that in some ancient creatures, cells containing ancient contractile proteins may have accumulated into tubes, thus forming primitive circulatory systems. These contractile tubes would have enabled the movement of water and the material contained in that water—and, *much* later, blood—from place to place within increasingly larger organisms. With innovations like contractile circulatory systems in place, the new blobs on the block would have branched off relatively quickly* into myriad forms, like segmented worms, mollusks, and, after a while, even chordates—a subset of which, the vertebrates, makes up the vast majority of this book's readership.

Along the way, those critters equipped with adaptations like these would have outcompeted many of the organisms that lacked such systems, driving them to extinction. Though not all of them. Corals, jellyfish, and comb jellies had already split off from the rest of the invertebrates before the evolution of the muscle-producing mesoderm. Though they never inherited muscle tissue from their ancestors, members of the phylum Cnidaria developed their own evolutionary advantages, like toxins and stinging cells to ward off predators. They also evolved contractile epithelial cells that act like muscle cells. Because of this, they were able to survive and thrive.

Though they were certainly revolutionary, circulatory systems did not evolve in a vacuum. Blood vessels are all well and good, but a significant reason for the success of organisms possessing circulatory systems was

* Well . . . quickly as in over the course of a hundred million years or so.

that they had coevolved other organ systems, notably the respiratory system. Evolving and functioning in tandem, these two systems solved the problem of moving large amounts of gases into and out of the body—and as a result, they enabled organisms like chordates to cope with the energy costs associated with increasingly complex behaviors and processes.

Most respiratory systems consist primarily of gas exchange mechanisms, like gills or lungs. Their main function is to facilitate the uptake of oxygen, which is essential for the life-sustaining chemical reactions that occur within the body. These reactions are known as metabolic processes, and they're collectively referred to as an organism's metabolism. One of the most important of these processes is the release of usable energy from the food we eat. As the process of digestion reaches completion, the nutrients in our food are broken down into smaller molecules, like carbohydrates, fats, and proteins. Through a process known as cellular respiration, the sugar glucose (a carbohydrate) can be converted into adenosine triphosphate (ATP), the energy currency of the cell. Muscle fibers and other cells have the ability to break the chemical bonds holding ATP together, and that energy can then be used to fuel things like repair, growth, and muscle contraction. Crucially, the chemical reactions involved in this molecular breakdown and energy release require oxygen. Enter stage right: gills and lungs.

There's more, though. Besides releasing energy, cellular respiration also releases carbon dioxide (CO_2) as a by-product, and this stuff is toxic to many organisms. As a result, the body constantly needs to get rid of CO_2 before it accumulates to harmful levels. Most circulatory systems, therefore, play the dual role of carrying oxygen from the gills or lungs to the cells of the body while simultaneously carrying the waste biproducts of metabolism back to the gills or lungs, where they can be removed from the body. (As a point of emphasis, although many people think that we breathe faster during exercise because of an increased requirement for

oxygen, it is as much the need to eliminate excess carbon dioxide that gets us huffing and puffing.)

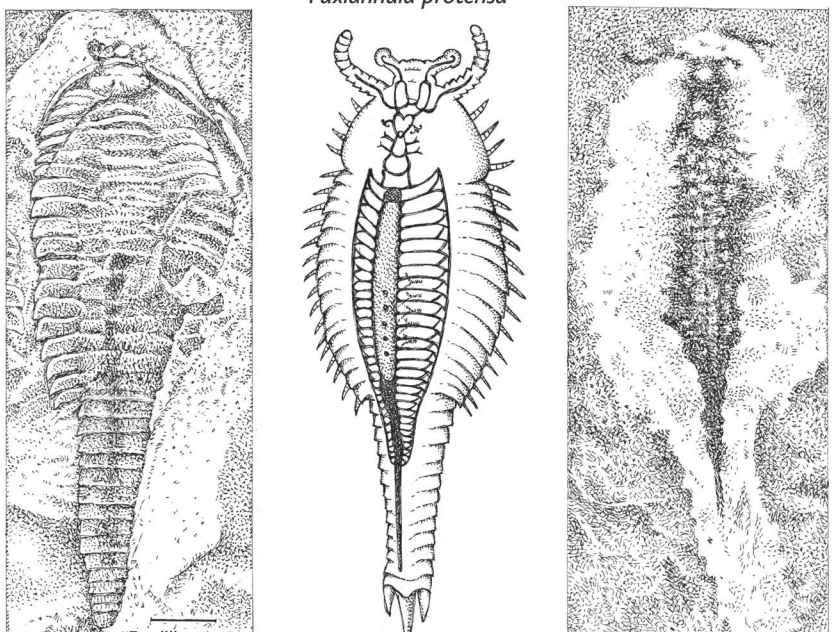
As respiratory systems were evolving, so, too, were circulatory systems, enabling the movement of a fluid called blood* around the body. The earliest evidence for this dual system dates to approximately 520 million years ago and an arthropod called *Fuxianhuia protensa*, first discovered at the Chengjiang fossil site in southwest China.

Passing through a series of vessels known as arteries, capillaries, and veins, blood back then, as it does now, likely functioned to deliver nutrients, gases, and waste to and from each cell in an organism's body. As importantly, this arrangement allowed these deliveries and pickups to be made *far* from the outer surface of the organism. While diffusion is still the name of the game when it comes to moving these products into and out of body cells, nutrients, gases, and waste now travel through the blood vessels to get there, instead of having to seep their way in and out, cell layer by cell layer, to and from the external environment.

Now jump ahead half a billion years from *Fuxianhuia protensa*, and envision five hundred million tiny saclike alveoli (roughly 0.2 millimeters in diameter) at the end of the bronchial tubes, deep inside your lungs. Each alveolus is surrounded by a meshwork of capillaries, tiny blood vessels with diameters approximately one-tenth that of a human hair. These are the microscopic sites of gas exchange between the respiratory and circulatory systems. Both the alveoli and capillaries have extremely thin walls, one cell layer thick, which enables the rapid exchange of gases. But although they might be tiny, when taken together the alveoli cover a surface of roughly one hundred square meters, allowing the large amounts of air we breathe in to be processed. As we inhale, oxygen diffuses out of the alveoli and into the alveolar capillaries, where it is carried by increasingly larger blood vessels back to the heart (the left atrium this time) and, when

* The invertebrate version of blood is known as hemolymph. When discussing invertebrates, the two terms are used interchangeably, as will happen throughout this book.

Fuxianhuia protensa

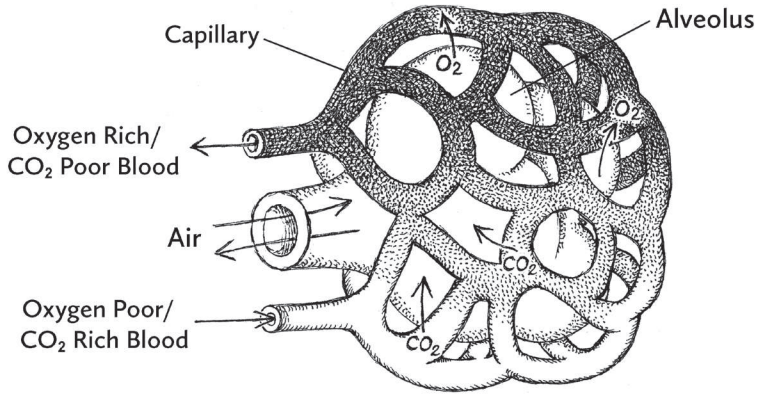


the left ventricle contracts, out to the body. CO_2 moves in the opposite direction, out of the alveolar capillaries and into the alveoli, to be exhaled back out into the environment.

Okay, demonstration time. Ready? Take a breath . . . then breathe out.

That was it. Now read the above paragraph again because that's exactly what happened during this exercise.

This interplay between the circulatory and respiratory systems is one of the many ways in which the organ systems of the body do *not* function like separate chapters in a textbook, which regrettably is how many of us first learned about them. Because this mindset is detrimental to a real understanding of how biological systems work, it is something that I continually warned my Human Anatomy and Physiology students about. I told them that organ systems interact: they cooperate, they depend on each other, and they are basically useless by themselves.



Unfortunately, this loss of synergism does sometimes occur. It is characteristic of diseases like emphysema, where a failure in one system sets off a chain reaction in the others. Emphysema is a degenerative and incurable respiratory disease, characterized by the systematic breakdown of alveoli in the lungs. This results in a reduction in their number, coupled with a loss of their function—which is to serve as the tiny middlemen between the atmosphere we breathe and the circulatory system that moves oxygen and carbon dioxide around the body. The causes of emphysema can range from having a rare inherited deficiency of a lung-protecting protein, to inhaling occupational dusts and chemicals, to the primary reason—smoking cigarettes. Regardless of the cause, the end result is that along with the respiratory system, a key function of the circulatory system is compromised, since the blood returning from the emphysema-stricken lungs is unable to deliver enough oxygen to the tissues and organs of the body for them to function normally.

Eventually, as organisms grew more diverse and more complex, so, too, did their circulatory systems. One evolving feature was the pump

that propelled the oxygenated and nutrient-packed circulatory fluid out to the body before returning it, oxygen- and nutrient-depleted and ready for another go-round. Of course, the pump in question is the heart.

As we will now see, the heart is not a single structure shared across the entire animal kingdom. Circulatory pumps evolved separately in different animal groups. They often look and work very differently, and as such, some of the resulting organs don't check off enough boxes to merit the label "heart." What they do share relates to their function, and that's due to a phenomenon known as convergent evolution.

Sometimes, organisms will appear to have a similar adaptation—like the tapered (a.k.a. fusiform) body shapes of sharks and dolphins. These animals are not closely related, since dolphins are mammals and sharks are fish. The key here is that the adaptation was *not* passed down from a single common ancestor of those creatures but, instead, evolved twice or, as it often happens, on multiple occasions (tuna also have roughly the same shape, as do torpedoes) in very different groups of organisms. The explanation for this phenomenon is that fusiform bodies are perfect for generating speed, and this makes them precisely the right shape for fast-swimming predators from very different branches of the evolutionary tree.

Blood feeding in the animal kingdom is another example of convergence, with animals as different as leeches, bedbugs, and vampire bats sharing a suite of similar vampiric adaptations that include stealth, small size, sharp "teeth," and salivary anticoagulants.*

Like fusiform bodies in aquatic predators or vampiric stealth, circulatory systems appear to have evolved on numerous occasions in

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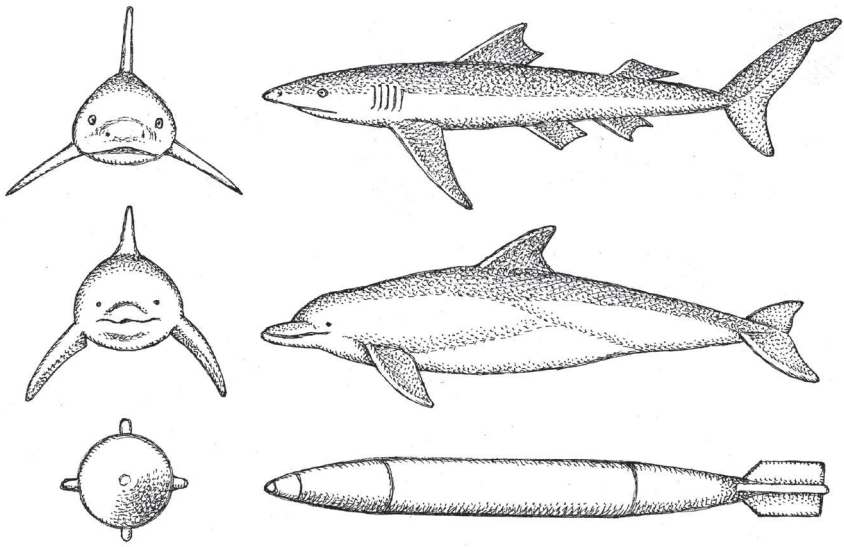
* Probably the most famous examples of convergence are the wings of insects, pterosaurs, birds, and bats. Each of these airfoils evolved separately yet perform a similar function, allowing their owners to overcome the force of gravity and fly. Gills are also convergent; these gas-exchange organs have apparently evolved multiple times in both invertebrates and vertebrates.



different invertebrate groups. Circulatory pumps and their associated vessels perform what is essentially the same job, and because of this they exhibit similarities even when their owners are not closely related. Their multiple evolutionary origins can also explain why the invertebrate circulatory systems we'll be examining next show such a high degree of variation in form. There are single hearts, multiple hearts, and no hearts, as well as circulatory systems that are either open or closed—the latter a distinction we'll be exploring soon.

Conversely, evolutionary origins also explain why there is less variation in vertebrate organ systems. Most scientists think that all vertebrate circulatory systems can be traced back to a single common ancestor, likely a type of jawless fish that lived about five hundred million years ago.* As a result, some of that ancient vertebrate's adaptations can be seen in all living vertebrates—though many other aspects of these structures

* Interestingly, there are specific regulatory genes (small sections of the genetic blueprint) that are shared by both insects *and* vertebrates. This points to the *possibility* of an ancient shared ancestry for *all* circulatory systems.

have changed over evolutionary time. The changes, like the evolution of two-chambered hearts in fish and four-chambered hearts in mammals, crocodiles, and birds, enabled these creatures to meet the demands of the very different environments they inhabit. Still, though, the basic blueprint for the ancient vertebrate circulatory system—arteries, veins, and the presence of a chambered heart—remains in existence today. But more on that later.

I'm different. I have a different constitution,
I have a different brain, I have a different heart.
—Charlie Sheen

I bleed Dodger Blue!
—Tommy Lasorda

[3]

Blue Blood and Bad Sushi

About a hundred feet from its older but perfectly serviceable-looking twin, the new boat launch cut a fan-shaped swath of granite stones and concrete through Monument Beach.

"Did the locals put up a fight before they built this thing?"

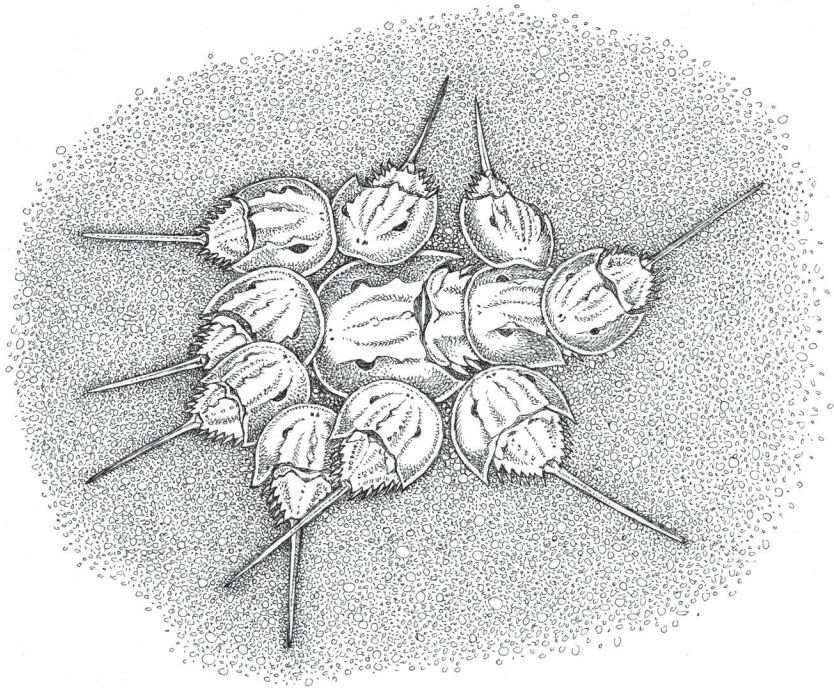
The question came from my longtime friend invertebrate biologist Leslie Nesbitt Sittlow, and it was directed at Dan Gibson, a fit seventysomething neurobiologist at the Woods Hole Oceanographic Institution in nearby Falmouth, Massachusetts. Leslie and I had met Gibson about five minutes earlier, after hightailing it down from Great Bay, New Hampshire, another coastal environment we had barnstormed during a book research-related New England field trip.

Gibson was currently searching for something in the sand. "I live a couple of miles from here," he replied, "and by the time I heard anything about a new boat launch, they'd already built it."

Getting back to the business at foot, Gibson gestured toward a small half-moon-shaped depression in the sand. Using the open end of a plastic pitcher, he began carefully lathing away thin layers until he'd reached five or so inches below the surface. Then he shot us a grin and reached into the hole. After probing with an index finger for a few moments, the scientist scooped out a cluster of tiny bluish-gray spheres.

The eggs belonged to *Limulus polyphemus*, one of four extant species of horseshoe crabs. From the Yucatán Peninsula to Maine, these claw-bottomed domes are a familiar sight during their annual late spring/early summer pilgrimages from deeper water into coastal shallows. The females follow the tides in, hunkering down to lay their eggs in hollows they scratch out of the sandy substrate. Gibson explained that horseshoe crabs are quite particular about where they deposit their eggs, since nests needed to be water-covered at high tide but dry and warmed by the sun at low tide. We also knew from our previous day's observations in Great Bay that horseshoe crab males are 20 to 30 percent smaller than the females that they swarm like a convention of rude helmets. Each of the males had jostled for position, attempting to mount a female and latch a pair of club-like appendages onto her shell. Thus situated, he would be in prime position to deposit his milky-looking sperm onto the walnut-sized egg masses on the female's underside. Eventually, two to five clusters, totaling up to four thousand eggs, would be laid during a single high tide, after which everyone would head back into deeper water, presumably to wait for the next tide-initiated love-in. Gibson told us that by the time the season ended, a female horseshoe crab would have deposited somewhere around eighty thousand eggs.

Although the annual mating swarms draw crowds of the curious to beaches all along the Atlantic coast, Leslie and I were actually there to investigate the horseshoe crab's cardiovascular system, particularly its



heart and the unique qualities of its blood. And despite the crab-orgy detour, our trip had a more serious tone—namely a major threat to the survival of these ancient creatures, related to the very same aspects of horseshoe crab biology that had drawn us to coastal Massachusetts.

After showing off his find, Dan Gibson carefully placed the egg cluster back into the hole he had dug. Then, with tiny spherical search images neurologically inserted, Leslie and I were handed our own pitchers and instructed to locate additional nests. After scanning the broad concrete ramp that extended out into the shallows for what looked to be a hundred feet or more, we quickly decided to move off in search of a sandier locale. I could see that the longest stretch of Monument Beach was adjacent to a large parking lot. It was just before noon, and the lot currently held a dozen or so cars, inside of which were folks who had stopped by for a bite of lunch or a smoke with an ocean view.

What Leslie and I *didn't* see on the beach were horseshoe crab nests—at least not very many of them, and none where we had been instructed to look, on the beach adjacent to the old boat launch.

When we met up with Gibson a few minutes later, he was looking frustrated. He explained that not only had the launch builders covered fifty yards of prime spawning beach with softball-sized rocks and concrete, but that the previously prime nesting spot had become much harder to reach.

"The border along the old ramp was a calm place for the crabs to approach and lay their eggs, while the rest of this beach is more open to choppy waves. The crabs coming in from deeper water usually swim parallel to the shore until they can find the perfect spot," he told us. "The only way they'll find that old stretch of beach now is if they approach it head-on. If the crabs are moving parallel to the shore, they'll run into the new boat ramp instead."

Horseshoe crabs, though, are famously resilient. With their 445-million-year fossil record—dating back to roughly 200 million years before the first dinosaur—they are the sole survivors of a once-diverse class of arthropods that also includes trilobites, arguably the most famous of ancient invertebrates. You would be hard-pressed to come up with a group of animals that has been around as long as the horseshoe crabs, and because of this, they are commonly referred to as "living fossils."

The pessimistic predictions of horseshoe crab researchers like Gibson are, then, especially troubling. Unfortunately, in addition to habitat destruction, a number of other factors, including one related to the horseshoe crab's own unique cardiovascular system, are threatening to end their spectacular longevity record.

Horseshoe crab eggs, and the miniature larvae that emerge from them around two weeks after fertilization, are an important food source

for fish and for migratory birds like the endangered red knot (*Calidris canutus*), a chunky-looking member of the sandpiper family. As a result, the vast majority of horseshoe crab eggs and larvae never survive the approximately ten years it would take for them to develop into sexually active adults. In fact, horseshoe crab expert John Tanacredi told me that he believes that something like one in three million eggs produces a larva that survives to adulthood.

When Europeans came to the New World, they found Native Americans using horseshoe crab parts for food and fertilizer, and for tools like hoes and fishing spear tips. As colonies of settlers sprang up along the East Coast, they harvested horseshoe crabs in numbers that seem almost unbelievable today. In 1856, for example, more than one million horseshoe crabs were collected from a single mile-long stretch of New Jersey beach. This type of population-straining harvest continued well into the twentieth century, with workers stacking the crabs into chest-high walls extending across vast stretches of waterfront, awaiting transportation to fertilizer factories.

That industry, which was centered along the Delaware Bay and coastal New Jersey, finally collapsed in the 1960s due to declining crab populations and the increasing popularity of alternative forms of fertilizer. Unfortunately, the mass collection of horseshoe crabs did not end. Sometime around 1860, American eel fishermen had discovered that chopped-up horseshoe crabs were terrific bait for their eel traps—especially jumbo-sized females laden with eggs. And horseshoe crab harvesting was still rampant in the mid-twentieth century, when some commercial fishermen began to turn to oversized snail relatives called whelks for an alternative source of income. The problem was that whelks also enjoy hacked-up horseshoe crabs, and so crab populations were threatened anew as whelk fishermen sought bait for their pots.

Today, many eel and whelk fishermen still consider horseshoe crabs to be their bait of choice, and the bait industry continues to reduce horseshoe crab populations by around seven hundred thousand individuals per year. But while the American horseshoe crab fishery is fully regulated (at least in theory), there exists a growing problem with poachers and the inability of officials to control the number of animals harvested.

In Asia, the three remaining horseshoe crab species* are under even more serious threat of extinction, and the reasons extend past the eel pot and onto the dinner plate. In places like Thailand and Malaysia, horseshoe crab eggs are considered an aphrodisiac, and so there are restaurants where their roe is the main item on the menu.

But consuming the egg masses, which are usually boiled or grilled, does come with a few drawbacks. For one, people die from eating horseshoe crab roe. Their deaths are somewhat less than gentle, and are almost certainly related to an important aspect of our own circulatory system.

Tetrodotoxin is a deadly nerve-blocking agent that is at least an order of magnitude (i.e., ten times) more lethal than black widow spider venom. Although its infamy stems from its presence (when poorly prepared) in arguably the most dangerous of exotic cuisines, fugu or puffer-fish flesh, several outbreaks of tetrodotoxin poisoning have been traced back to the consumption of horseshoe crab roe. Tetrodotoxin is extremely dangerous because after digestion it accumulates in tissues like muscles and nerves. Although the exact mode of tetrodotoxin's entry into the nervous system is still unknown, its lethality is due, at least in part, to its ability to bypass the protective blockade known as the blood-brain barrier (BBB).

The BBB is regulated in part by a class of starburst-shaped cells called astrocytes. Astrocytes are one of several different types of

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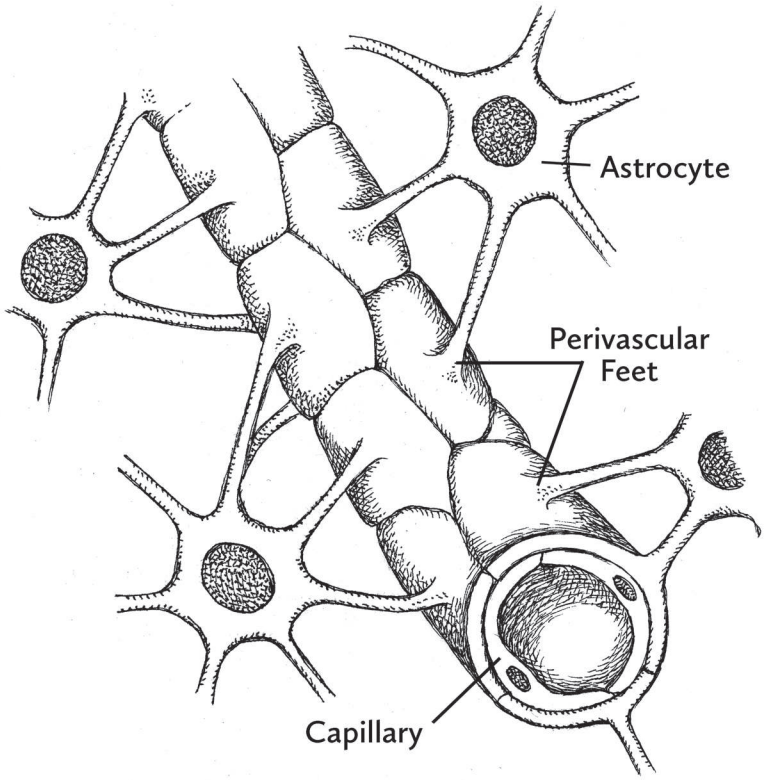
* *Tachypleus gigas*, *Tachypleus tridentatus*, and *Carcinoscorpius rotundicauda*



glial cells (or neuroglia) that assist, support, protect, and repair the superstars of the nervous system—the neurons. Among several other duties, astrocytes can be found latched on to capillaries in the brain. As in the rest of the body, these vessels supply oxygen and nutrients to tissues while carrying away waste products and carbon dioxide. In the brain, however, the astrocytes restrict that back-and-forth movement, allowing the passage of only *some* substances (like oxygen, glucose, and alcohol) out of the tiny vessels. As for how that works, the astrocytes have footlike structures, appropriately called perivascular feet, which act as a barrier, covering the capillary walls. Mostly that's a good thing, since they prevent harmful materials like bacteria and certain chemicals from exiting the circulatory system and doing damage to the delicate neural tissues of the brain.

Unfortunately, the blood-brain barrier also prevents beneficial substances like antibiotics from leaving the blood and entering the brain, which explains why *any* infection of the brain can turn into a life-threatening situation.

"A significant hindrance to treating neurodegenerative diseases at the moment is that most drugs can't cross the blood-brain barrier," wrote Kelly McNagny, a professor in the Department of Medical Genetics at the University of British Columbia.

There are additional elements of the blood-brain barrier besides astrocytes. Notably, these include "tight junctions," seams that form between adjacent cells in the inner lining of blood vessels. If these seams loosen, the consequences can be devastating. For example, studies have shown a probable link between a bacterium associated with periodontal disease and the development of Alzheimer's disease. Some researchers believe that *Porphyromonas gingivalis* evades the BBB and invades brain tissue, possibly slipping through gaps in the tight junctions or hitchhiking inside white blood cells whose roles require that they exit the circulatory system. Experiments on mice have shown that once inside the brain, *P. gingivalis* bacteria release toxic substances called gingipains, which disrupt the functioning of essential proteins, damaging neurons and worsening the effects of Alzheimer's. The infection also causes the accumulation of two distinctive proteins, amyloid and tau, which have historically been considered signs of Alzheimer's—although there is now a growing suspicion that these sticky masses, or plaques, are actually a defense mechanism against *P. gingivalis* and not themselves a cause of Alzheimer's disease. This ongoing research is a potential game changer, since Alzheimer's is the sixth leading cause of death in the United States, killing more people than breast cancer and prostate cancer combined.*

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* In 2018, the latest year for which data from the CDC were available as of this writing, 122,019 deaths in the United States were attributed to Alzheimer's disease. With COVID-19 deaths far surpassing that number in 2020, Alzheimer's will likely drop a notch, to number seven.

Among the substances that *can* be delivered across the blood-brain barrier is tetrodotoxin, and people who consume horseshoe crab eggs need to know that its presence in roe is unpredictable. It is believed that the crabs ingest certain bacteria that produce the neurotoxin by consuming contaminated shellfish or decayed matter. Symptoms of tetrodotoxin poisoning generally start with a slight numbness of the lips and tongue, not a unique sensation when consuming spicy Thai food. A pins-and-needles numbness of the face might be the first clue to diners that something has gone terribly awry. The real buzzkill follows quickly, in the form of headache, diarrhea, stomach pain, and vomiting. As tetrodotoxin spreads throughout the body, walking becomes difficult as the chemical begins to block the nerve impulses that lead to contraction of voluntary muscles like those of the limbs. Tetrodotoxin can also interrupt the spread of electrical signals through the myocardium, the heart's thick layer of cardiac muscle. As we'll see later, this is the electrical system responsible for the heart's coordinated contraction and relaxation—the heartbeat itself.

Eventually, around 7 percent of those who fall victim to tetrodotoxin poisoning die, reportedly conscious and quite likely completely aware that consuming a week-old California roll, or even a chopstick, would have been a better choice than the horseshoe crab roe or fugu that became their last meal.*

But beyond facing the possibility of being eaten, ground up as fertilizer, or chopped up as bait, horseshoe crabs also face a unique threat to their survival.

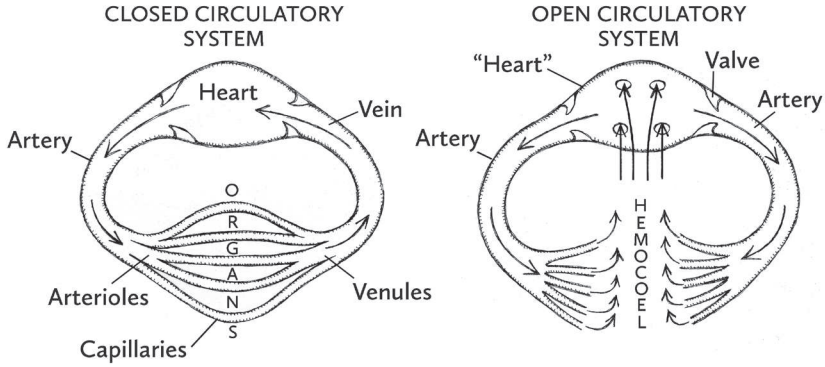
The American horseshoe crab, *Limulus polyphemus*, and its three Indo-Pacific cousins are not really crabs at all. Like true crabs, however,

* Because victims can remain conscious through the paralyzing effects of tetrodotoxin, an ethnobotanist named Wade Davis suggested in 1983 that voodoo practitioners had used it to turn people into zombies to toil as slaves on Haitian plantations. His claim was subsequently hammered into the ground like a tent peg by some science types, who happened to know a thing or two about tetrodotoxin and its *actual* effects.

they *are* arthropods, members of a massively diverse phylum of animals, which includes insects, spiders, and crustaceans, that share the presence of jointed exoskeletons. Crucially for the horseshoe crab, they also share *open* circulatory systems. These are significantly different from the *closed* circulatory systems found in blue whales, humans, and the roughly fifty thousand other species of mammals, fish, amphibians, reptiles, and birds. As we'll soon see, some invertebrates, like earthworms, octopuses, and squid, also have closed circulatory systems, though they are very different from those found in creatures burdened with a backbone.

In closed circulatory systems, blood leaves the heart via large arteries, which branch into a series of increasingly smaller arteries and even-smaller arterioles. The arterioles enter and thread through organs and muscle tissue before they, too, split into even-smaller vessels called capillaries. These tiny tubes make up approximately 80 percent of the total length of the circulatory system, and it is within dense networks known as capillary beds that the mutual exchange of substances between the blood and the body takes place. As discussed earlier, oxygen from the lungs or gills and nutrients absorbed from the digestive system pass through the thin capillary walls and into the surrounding tissues. Meanwhile, metabolic waste products, like carbon dioxide and ammonia, diffuse into the blood, to be carried back toward the heart, first by tiny venules and then by increasingly large veins.

In gilled vertebrates like fish, some salamanders, and all amphibian larvae, the now-deoxygenated blood gets pumped through the gills, where the carbon dioxide diffuses into the surrounding water and a new batch of oxygen diffuses back in. As you may have noticed as a non–water breather, a pretty major tweak to this gas exchange system occurred somewhere down the line to allow for the exchange of oxygen and carbon dioxide with the air instead of water. The nature of this tweak? Lungs. There will be more on this particular story later.



Whether oxygenated by gills or lungs, however, one thing closed circulatory systems have in common is that blood is always confined to a closed loop. Not so for most invertebrates, including the horseshoe crab. In their open circulatory systems, fluid (called hemolymph, rather than blood) also leaves the heart through arteries.* But instead of flowing into capillaries, the hemolymph spills out of the vessels and into body cavities called hemocoels, where it bathes the organs, tissues, and cells it comes into contact with. There, the hemolymph drops off nutrients through diffusion while simultaneously picking up waste products. Many of these open circulatory systems also exchange oxygen and carbon dioxide, although as we'll see in the next chapter, insects are a significant exception to this rule.

Although gills are forever linked in our minds to fish, they are the respiratory organs found in many invertebrates, including horseshoe crabs. This is another example of convergent evolution: though vertebrates and invertebrates evolved separately, both use diffusion to draw oxygen into the familiar-looking arrangement of gill membranes that often resembles the overlaying pages of a book. In non-insect arthropods, oxygenated

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* When describing open circulatory systems, the term "artery" is used more for convenience than for scientific accuracy. Circulatory system purists require that card-carrying arteries have an inner lining of epithelial tissue called the endothelium, which is not present in open circulatory system vessels. For our purposes, the term "artery" is purely functional and describes a vessel that carries a circulatory fluid *away* from the heart (while veins carry blood *toward* the heart).

hemolymph leaves the gills and heads back to the heart via the circulatory system. And in horseshoe crabs, by this point the hemolymph has undergone an additional transformation. It has turned from milky white to a beautiful powder blue.

The "blue blood" of horseshoe crabs and invertebrates like cephalopods, clams, lobsters, scorpions, and tarantulas is due to the presence of a copper-based protein called hemocyanin. Carried in the hemolymph in a dissolved form, the hemocyanin latches on to oxygen whenever it comes into contact with it. When copper oxidizes, it turns blue—and so, too, hemolymph turns blue as it leaves the gills, having undergone the same chemical reaction that gives the copper-plated surface of the Statue of Liberty its famous blue-green tint.

With the exception of the blue bloods mentioned above, the oxygen-carrying molecule in pretty much every other creature with a circulatory system is hemoglobin. Here, though, the oxygen binds to an atom of iron, rather than copper. And unlike hemocyanin, hemoglobin is not free-floating in the blood. Rather, it's carried by a specialized type of cell called an erythrocyte, which spends its roughly four-month life span toting hemoglobin around the circulatory system.* Because the erythrocytes contain iron instead of copper, when they oxidize, they don't give off blue light. Instead, they emit red light. If these cells sound familiar, it's because they're also called red blood cells. And if the oxygen-related color change rings a bell, that's because it's the very same oxidation reaction that occurs when an iron fence is exposed to atmospheric oxygen and turns rusty red.

So why, you might ask, don't humans and other vertebrates have blue blood? The answer likely relates to body size and oxygen-carrying efficiency. Larger bodies require more oxygen, and hemoglobin is better

* Hemoglobin is also found in some non–red blood cells, like the previously mentioned astrocytes in the brain.

equipped to provide it: each hemoglobin molecule can carry four oxygen molecules, while hemocyanin can carry only one. So over time, organisms with blood containing hemoglobin were able to evolve into larger-bodied creatures than those utilizing hemocyanin.

We interrupt this chapter for a hemoglobin-related public service announcement: A *serious* problem for humans is that hemoglobin is much more strongly attracted to molecules of carbon monoxide (CO) than it is to oxygen (O_2). This makes even small amounts of this odorless, colorless gas, which is released by things like car engines, gas appliances (like heaters), and woodstoves, *especially* dangerous. In fact, the potential presence of carbon monoxide is so dangerous that if you don't have a carbon monoxide detector in your house or apartment already, or if you know of a loved one who doesn't have one, then take a break from reading this book and go purchase one.

I'll wait . . .

Okay, where was I?

In closed circulatory systems like ours, blood returning from the body enters the heart directly, by way of large veins like the superior and inferior venae cavae. This occurs during the portion of the cardiac cycle known as diastole, when the ventricles relax after contracting and forcing their contents out of the heart during the phase called systole. Since horseshoe crabs have open circulatory systems and don't have veins, oxygenated blood leaving their gills must enter the heart differently, first flowing into a reservoir surrounding the heart called the pericardial cavity.*

Once blood fills the pericardial cavity, how does it get into the horseshoe crab heart? To start, the heart itself is suspended within the

* Readers should note that this is *not* how the pericardial cavity in a closed circulatory system (like that mentioned earlier) works. In fact, any blood found within it would be a deadly serious problem.

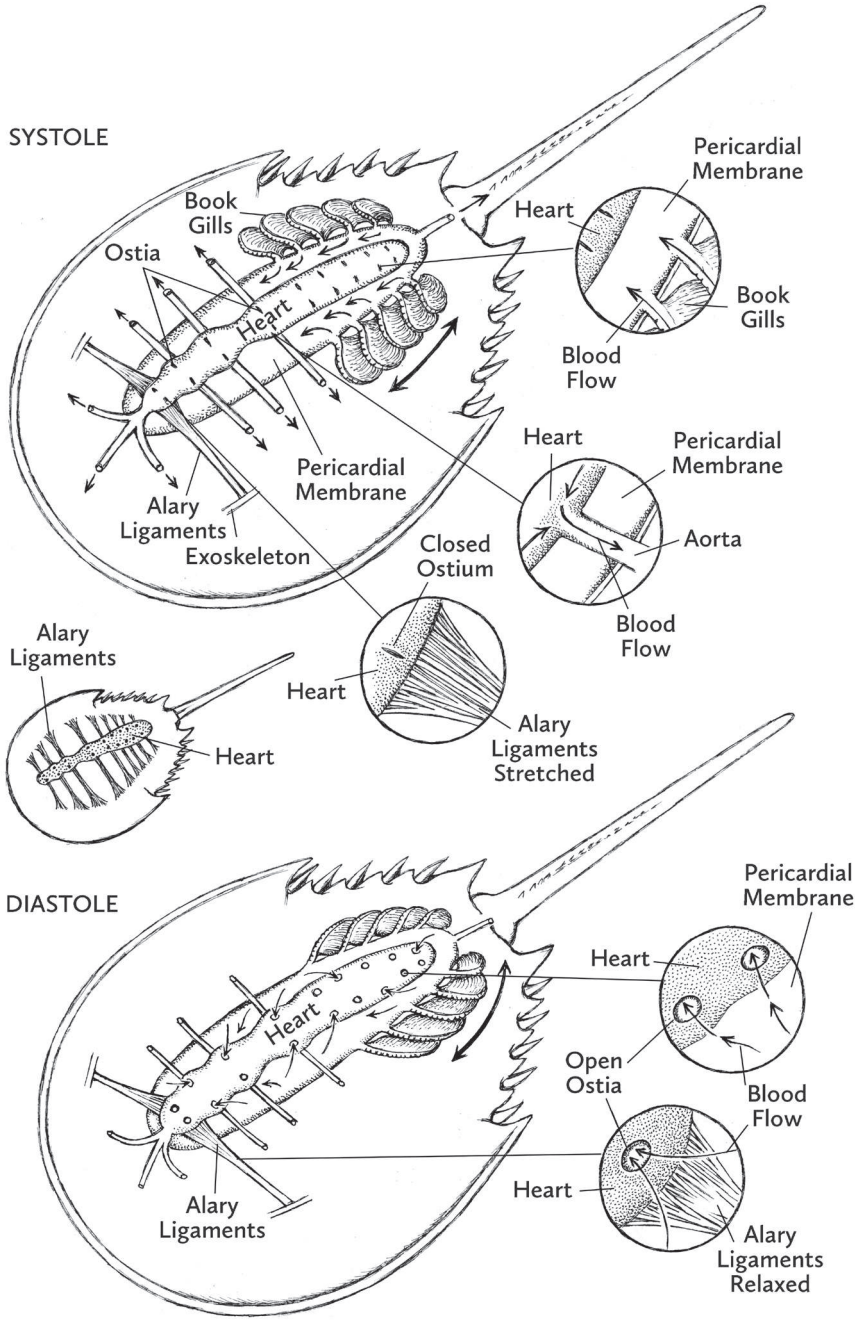
pericardial cavity by a series of elastic bands called alary ligaments. These stretchy bands run along the length of the heart, and they anchor the outer walls of the heart to the inside of the crab's exoskeleton, or shell. As the heart contracts (during systole), the alary ligaments are stretched like rubber bands, causing them to store elastic energy. Once the heart has contracted and ejected its contents, it relaxes (diastole) and the ligaments' elastic energy tugs the heart back open to its precontraction volume.

Simultaneously, as the volume increases, pairs of valve-like apertures in the heart, called ostia (singular ostium), reopen. The blood that has gathered in the pericardial cavity flows through the ostia, refilling the empty heart—moving from the higher pressure of the pericardial cavity to the lower pressure of the newly emptied organ. Then the process of filling and emptying the pericardium and the heart repeats.

A neat system, to be sure, but as horseshoe crab expert and University of New Hampshire zoology professor Win Watson explained to Leslie and me, horseshoe crab circulation gets an assist from the action of another organ system, and in a manner that turns out to be quite familiar. This discovery started with the observation that horseshoe crabs' so-called book gills fan back and forth in a rhythm that is synced with the movement of blood into the pericardial cavity.

As Watson described the mechanics, I thought back to a paper on galloping horses that I had read during my PhD work at Cornell back in the 1990s. In that study, functional morphologists Dennis Bramble and David Carrier had suggested that during the gallop (a pace during which all four feet are off the ground at the same time), the accompanying backward-and-forward movement of a horse's liver within the abdominal cavity turned that massive organ into a "visceral piston," which assisted in the process of breathing, and thus the efficient exchange of oxygen and carbon dioxide.

Bramble and Carrier hypothesized that as the bulky liver slides backward (see horse figure A), it pulls the dome-shaped diaphragm, to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Pericardial Membrane
Aorta
Blood Flow
Closed Ostium
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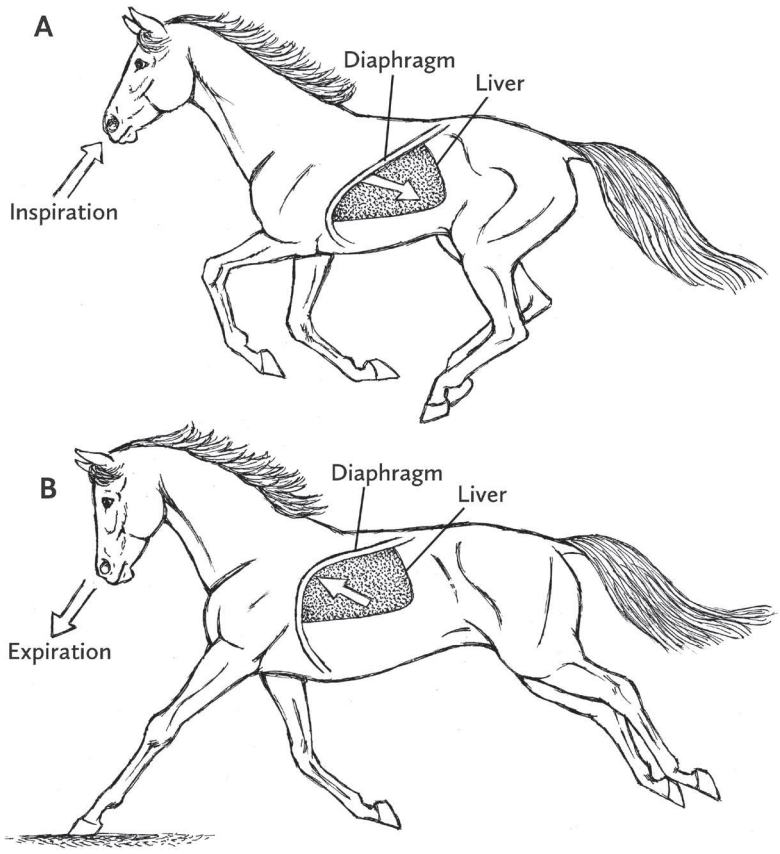

which it is attached by a ligament, backward as well. Since the diaphragm makes up the rear wall of the thoracic cavity (the sealed chamber surrounding the lungs and heart), the volume of that space is increased by the diaphragm's movement. Physics tells us that when a space gets larger, the air pressure within that space decreases—here meaning that the atmospheric air pressure outside the horse is suddenly higher than the pressure inside the thoracic cavity. Air rushes into the mouth and nose to equalize the pressure, thus helping to fill the lungs as the horse inhales.

Sound familiar? That volume-pressure relationship is exactly what helps empty our heart of blood during ventricular systole, when the contraction of the ventricles causes an increase in pressure that forces blood out of the heart. During ventricular diastole, the exact opposite

happens. Here, as the ventricles relax, the pressure inside them drops, causing the ventricular volume to increase and allowing the chamber to fill with blood coming from the atria.

With that in mind, it should be easy to figure out how the visceral pump works during exhalation. Bramble and Carrier explained that as the horse's forelimbs stride forward (see horse figure B), the liver moves in the same direction, slamming against the diaphragm and causing it to bow forward. This *decreases* the volume of the thoracic cavity and, you got it, *increases* the pressure inside the cavity. This increase compresses the horse's lungs, the way a hand would squeeze water out of a sponge. But instead of water, here the compressed lungs squeeze CO_2-laden air back into the atmosphere.*

So why does this adaptation make sense? As we've already seen, muscle contraction requires energy. According to Bramble and Carrier, the key benefit of the visceral piston is that in a galloping horse, inspiration and expiration take place with less energy cost to the animal.

Similarly, horseshoe crab blood returning to the heart is aided by the book gills, which are already busy waving back and forth as they exchange oxygen and carbon dioxide with their watery environment. Like the backward-and-forward movements of the horse liver, the back-and-forth movements of the horseshoe crab gills drive the blood within them toward the pericardium, thus decreasing the energy that would have been required to move blood into the pericardium by a separate means.

Open circulatory systems have long been regarded as relatively simple and thus somehow inefficient. But as we've just seen in the rather complex workings of the horseshoe crab circulatory system, this is not the case. Instead, this mindset is just one more unfortunate bias against pretty

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* In humans, the pressure and volume relationships are similar, but changes in thoracic cavity volume occur primarily because of the up-and-down movement of the muscular diaphragm as it contracts and relaxes.

much any organism that doesn't wear blue jeans and carry a cell phone.*

One complex and unique feature of horseshoe crab circulatory systems in particular has to do with immunity. Invertebrates do not have the mammalian equivalent of *acquired* immunity, which is the part of the immune system in which specialized cells called lymphocytes and bits of protein called antibodies recognize and combat foreign invaders like bacteria, fungi, and other pathogens. This immune response is turned off (or "suppressed") once the invaders are gone, leaving behind memory cells, which remain in circulation and can rapidly crank up the immune response should they encounter the same foreign invader again. This is why, for example, you don't get the same strain of flu twice—your already-primed immune response destroys the pathogen before you can get sick again.

Although invertebrate immune systems are different, scientists now understand that they are quite spectacular in their own right. Horseshoe crabs, for instance, have evolved their own version of immune cells. And although they are unlike anything seen in humans, they have undoubtedly saved thousands of human lives.

The story of the Atlantic horseshoe crab's first turn toward medical relevance occurred in 1956. That's when Woods Hole pathobiologist Fred Bang determined that certain types of bacteria caused horseshoe crab blood to clot into stringy masses. He and his colleagues hypothesized that this was an ancient form of immune defense. Eventually, they determined that a type of blood cell called an amoebocyte was responsible for the clot formation.† As their name implies, amoebocytes resemble amoebas, the blobby single-celled protists that make pseudopods so popular and dysentery so unpopular.

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* Our completely off-base depiction of Neanderthals as brutish, apelike losers, fit to be driven to extinction by modern humans, comes to mind.

† Amoebocytes occur in other invertebrates (like land snails), but while these cells may also be involved in clotting and response to blood-borne toxins in non–horseshoe crabs, there has been relatively little research related to this topic.

Bang, and those who followed up his research, hypothesized that the clotting ability of the amoebocyte evolved in response to the bacteria- and pathogen-rich muck that horseshoe crabs plow through for pretty much their entire lives. Their army of blood-borne amoebocytes can wall off foreign invaders, isolating them in prisons of gelatinous goo before they can spread their infections.

As a result, horseshoe crabs are not only disease-resistant but have an impressive ability to survive *extreme* physical damage. The most lethal-looking wounds are quickly plugged with amoebocyte-generated clots, allowing banged-up individuals to carry on as if they hadn't just lost a fist-sized section of shell to an outboard motor propeller. This unique defense-and-repair system may be at least partially responsible for the horseshoe crabs' record of having been around for nearly half a billion years, a period during which they've survived a total of five planetwide extinction events.

We now know that the amoebocytes do their thing by detecting potentially lethal chemicals called endotoxins. These are associated with gram-negative bacteria, a class of microbes that includes pathogens like *Escherichia coli* (food poisoning), *Salmonella* (typhoid fever and food poisoning), *Neisseria* (meningitis and gonorrhea), *Haemophilus influenzae* (sepsis and meningitis), *Bordetella pertussis* (whooping cough), and *Vibrio cholerae* (cholera).

Oddly, the endotoxins are not themselves responsible for the myriad diseases associated with these bacteria. Nor are they protective products—released, for example, to combat the bacteria's own enemies. Instead, these large molecules form much of the bacterial cell membrane, helping to create a structural boundary between the cell and its external environment. Endotoxins are also known as lipopolysaccharides, since they consist of a fat attached to a carbohydrate. These molecules become problematic for other organisms only after the bacteria have been killed and sliced open, or lysed—something that can happen when the immune system (or an

antibiotic) is engaged to fight off a gram-negative bacterial infection. At this point, the bacterial cell contents spill out and the lipopolysaccharide components of the membrane are released into the environment.

Unfortunately, although the disease-causing bacteria may have been conquered, the sick host's problems are not over. The presence of endotoxins in the blood can cause the rapid onset of fever, one of the body's protective responses to a foreign invader. Such fever-inducing substances are called pyrogens, and they can lead to serious problems (like brain damage) if they drive body temperatures too high for too long. Further complications can also arise from the body's dangerously overblown immune response—a condition healthcare professionals have been forced to deal with during the coronavirus pandemic. In the worst cases, exposure to endotoxins can lead to a condition known as endotoxic shock, a cascade of life-threatening symptoms that range from damage to the lining of the heart and the blood vessels, to dangerously low blood pressure.

After our trip to find horseshoe crab eggs at the beach, Leslie and I accompanied Dan Gibson to the Woods Hole lab, where he prepared a microscope slide of fresh horseshoe crab blood. We were soon examining live horseshoe crab amoebocytes.

"They're all full of granules," I said, noting the sand-like particles that packed the cell interiors.

"Those are tiny packets of a protein called coagulogen," Gibson said. As their name may suggest, coagulogens cause coagulation, or clotting. "When the amoebocytes encounter even the slightest amount of endotoxin, they release their packets of coagulogen, which quickly transforms into a gel-like clot."

Because endotoxins can cause such a dangerous response in humans, in the 1940s the pharmaceutical industry began to test its products for the presence of these substances, which can also be released by accident during

the drug manufacturing process. One of the first methods developed was the rabbit pyrogen test, which became an industry standard. Here's how it worked: In what definitely sounds like a job for "the new guy," baseline rectal temperatures were taken for lab rabbits involved in the test. Next, the lab technicians injected rabbits with the batch of whatever drug was being tested, often doing so via an easily accessible ear vein. They then recorded rectal temperatures every thirty minutes for the next three hours. If a fever developed, it would signal the potential presence of an endotoxin in that particular batch.

Having discovered that horseshoe crab blood would clot in the presence of endotoxins, in the late 1960s, a colleague of Fred Bang's, hematologist Jack Levin, developed a chemical test, known as an assay, that would come to replace the laborious and controversial rabbit pyrogen test. Essentially, Levin and his colleagues sliced open horseshoe crab amoebocytes to collect the clot-forming component, a substance they named Limulus amoebocyte lysate (LAL). Not only could LAL be used to test for the presence of endotoxins in batches of pharmaceuticals and vaccines, researchers eventually discovered that it also worked on instruments like catheters and syringes, medical devices for which sterilization might kill bacteria but also could accidentally introduce endotoxins into patients receiving medical care.

While this discovery was presumably greeted by relief within the rabbit community, horseshoe crabs and their fans were somewhat less than thrilled, especially when another Woods Hole researcher quickly established a biomedical company that began extracting horseshoe crab blood on an industrial scale. Three more such companies soon sprang up along the Atlantic coast, turning the production of LAL into a multimillion-dollar industry. As a result, today nearly half a million horseshoe crabs are hauled out of the water each year, many during spawning season. Most are transported to industrial-sized lab facilities,

not in tanks of cold salt water, but in the back of open pickup trucks. Upon arrival, the crabs encounter teams of mask- and gown-clad workers, who scrub them with disinfectant, bend their hinged shells in half ("the abdominal flexure position"), and strap them to long metal tables, assembly line–style. Large-gauge syringes are then inserted directly into the horseshoe crabs' hearts. The blood, blue-tinted and with the consistency of milk, drips down into glass collecting bottles. And in a move that would make Count Dracula envious, the collection continues until the blood stops flowing, usually when around 30 percent of it has been drained.*

In theory at least, the horseshoe crabs are supposed to survive their ordeal, and once bled, by law they must be returned to the approximate area where they were collected. But according to Plymouth State University neurobiologist, Chris Chabot, an estimated 20 to 30 percent of the crabs die during the roughly seventy-two hours from collection to bleeding to return.

"It's significant that the gill-breathing crabs are held out of the water for the entire time," Chabot told Leslie and me. We were visiting the scientist and his colleague, zoologist Win Watson, at the University of New Hampshire's Jackson Estuarine Laboratory.

Also of potential significance, Chabot explained, is the fact that no one knows whether previously bled specimens suffer any short- or long-term effects after being returned to the water—or even whether they survive. (The Atlantic States Marine Fisheries Commission [ASMFC] has been formally managing horseshoe crab populations since 1998, but various policies have hampered its ability to access mortality rate numbers in horseshoe crabs harvested for biomedical companies.) With this in mind, Chabot and his research team have been trying to determine the effect that the harvesting process has on horseshoe crabs once they are returned

* It's likely that the needle interrupts the circulation of blood back to the heart—no surprise—so only the blood in the heart and the blood that gravity drags back into it can drain out.

to the water. To do this, he and his students collected a small number of specimens and subjected them to conditions mimicking those the crabs face during encounters with the biomedical industry.

Chabot and his students observed listlessness and disorientation in their subjects, which they hypothesized was due in part to the fact that after bleeding, the crab's body can't deliver as much oxygen as it requires. "It takes weeks to replenish the amoebocytes and the hemocyanin they've lost," he told us.

Chabot also explained that with many of their protective amoebocytes being lysed in a test tube somewhere, things like wound repair and a return to environments infested with gram-negative bacteria made for a pretty grim outlook for those horseshoe crabs headed home after a long day on the assembly line.

Watson confirmed that the combination of three days spent out of the water, at high temperatures, coupled with significant blood loss, can make for a lethal combination for horseshoe crabs. What's more, he added, since crabs are usually collected during the mating season, and often *before* mating occurs, any death rate would have the potential to affect the size of future generations—especially since the larger female crabs are preferentially selected during collection. And given that the crabs have slow maturation times, the extent of the problems that are brewing may not become apparent to researchers, or anyone else, for a decade. According to the ASMFC, the New York and New England regions are already starting to see a decrease in the abundance of horseshoe crabs.

Watson and Chabot both suggested that some fairly simple steps could be undertaken to improve mortality numbers, thus helping sustain horseshoe crab populations without hurting the LAL industry. The first step would be to delay the harvesting of horseshoe crabs until after the mating season. Their second suggestion was to transport specimens to and from biotech labs in cool water tanks rather than stacking them up, dry and hot, on boat decks and in the backs of trucks. This, the horseshoe

crab mavens explained, would not only prevent heat stress but also keep the thin, membranous "pages" of their book gills from drying out.

From talking to Watson and Chabot, it is clear to me that they fully appreciate the importance of LAL to the medical community and to the patients whose lives it saves. These researchers are simply trying to improve the odds for a species that has been coping with threats to its existence long before humans showed up and added pollution, habitat destruction, and overharvesting to the horseshoe crab shit list.

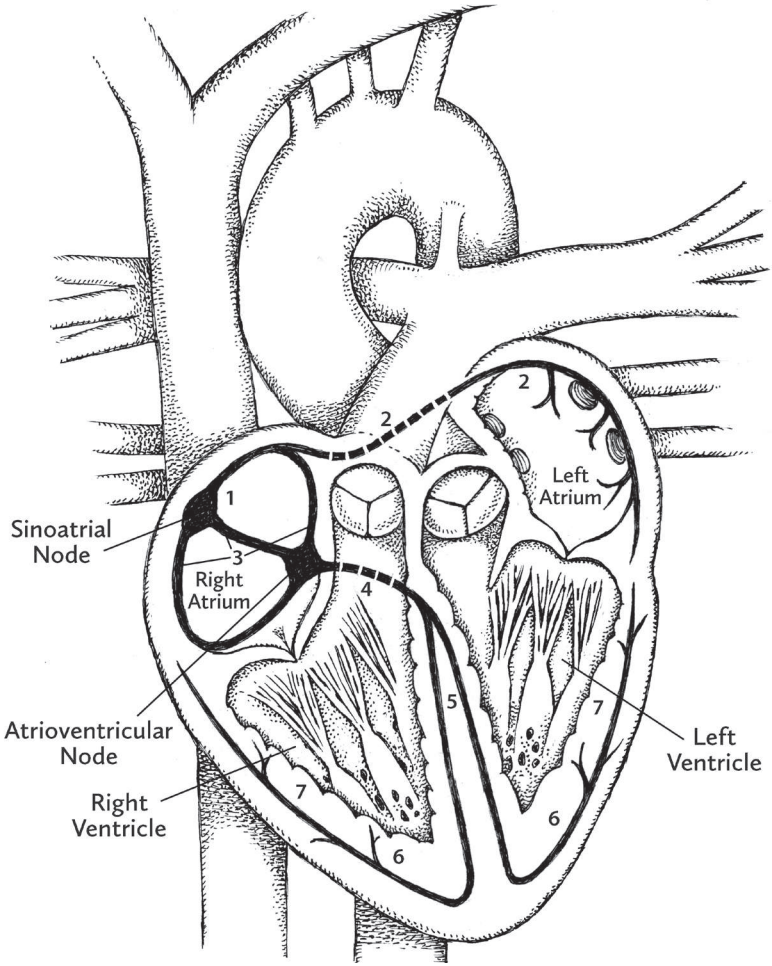
Although the steps Watson and Chabot suggested would go a long way toward improving horseshoe crab mortality, there is another harvesting-related risk. This one stems from the fact that each horseshoe crab heartbeat is initiated and controlled by a small mass of neurons called a ganglion, located just above the heart. Its job is to stimulate each section of the heart to contract in the right order in response to minute electrical pulses.

These *neurogenic* hearts are found in crustaceans like shrimp as well as segmented worms like earthworms and leeches. They differ significantly from the *myogenic* hearts seen in humans and other vertebrates, which beat without being stimulated by external structures like ganglia or nerves. Instead, the stimulus for myogenic contraction originates in small regions of specialized muscle tissue called cardiac pacemakers, located within the heart itself.

The absence of these pacemakers in neurogenic hearts may at least partially explain why Aztec art never depicts priests as holding the still-beating hearts of newly sacrificed lobsters or horseshoe crabs. That's because their neurogenic hearts would have stopped beating the moment they were severed from the ganglia controlling them.

Meanwhile, thanks to pacemaker cells, human hearts have the ability to generate a continuous sequence of electrical signals. These begin at a location in the right atrium called the sinoatrial (SA) node, and speed through the heart along highly specific routes called conduction

pathways. Moving like ripples of water after the splash of a pebble, the signals travel from the right atrium to the left atrium, both situated within the uppermost "base" of the heart. As the ripple begins to move downward toward the ventricles, another patch of pacemaker cells, called the atrioventricular (AV) node, slows down the signal, the slight lag time allowing the ventricles to fill with blood. The electrical signal from the AV node continues down toward the pointy apex of the heart. As it does, the muscles making up each ventricle are stimulated to contract in turn.



But while our myogenic heart *initiates* its own beat, a pair of nerves control the rate and the strength of contraction. These are the vagus nerve, which slows down the heartbeat, and the cardiac accelerator nerve, which . . . well, you know. They work as part of the autonomic nervous system (ANS), which goes about its considerable duties without your consent or voluntary input.

There are two divisions of the ANS. One, the sympathetic division, prepares you to deal with real or imagined threats with a host of responses, including increased heart rate and blood pressure. This is often referred to as the "fight-or-flight response." As your heart rate speeds up, your ANS also causes an increase in blood flow to your brain and leg muscles. This occurs as blood vessels supplying those areas receive a signal to start vasodilation (i.e., widening of their inner diameters). Simultaneously, blood is diverted *away* from the digestive tract and kidneys through vasoconstriction of the tiny blood vessels that normally supply them.* The reasoning here is that digesting Cheerios and producing urine becomes somewhat less important when you are suddenly confronted by a grizzly bear or the prospect of speaking in front of an audience.† Instead, the extra blood heads to the leg muscles through their wide-open capillaries—preparing you for a sprint. The blood flow is also increased to the brain, presumably enabling you to figure out what to do if running away doesn't work.

The second division of the autonomic nervous system is the parasympathetic division, which takes over during normal (a.k.a. grizzly-bear- and public-speaking-free) conditions. This is the "rest-and-repose" alternative of the ANS. It slows down the heart rate, directing blood

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* The reduction or increase in flow to blood vessels is made possible because of the respective contraction or relaxation of smooth muscle fibers embedded in and encircling their walls.

† Remember, the ANS treats perceived threats like real ones—which is also why you respond the way you do during a good scary movie.

flow to the organs slighted by the fight-or-flight response, like those that handle digestion and urine production.

Interestingly, if the nerves that control the ANS are damaged, or if their impulses are blocked (attention fugu fans), the heart does not stop beating—which would be quickly fatal. Instead the SA node takes over regulation of the heart rate, setting the pace internally at around 104 beats per minute.

The problem for a horseshoe crab getting the hypodermic Dracula treatment is that its heart has no such ability to pace itself. Its heartbeat is solely governed by the ganglion situated above it.

Watson explained that the ganglion activates motor neurons, which communicate with the heart muscle by releasing a neurotransmitter called glutamate. This chemical messenger fits like a key into neurotransmitter-specific locks found on the surface of the heart. These locks are known as receptors, and the resulting lock-and-key arrangement directs the cells making up that muscle to contract.*

"The problem is," Watson said, "that if you stick a needle into a horseshoe crab to drain its blood and you hit the cardiac ganglion by mistake, you'll likely kill the animal."

"So, workers bleeding specimens in these biomedical facilities have to take the location of the cardiac ganglion into consideration when they insert their needles, right?"

Watson shook his head. "Bill, I doubt any of them even know about it."

In an attempt to be as fair as possible, I contacted several of the major biomedical facilities that process horseshoe crab blood. After listing my professional credentials, I explained in an email that I was fully aware of the important role of the LAL biomedical industry and that I was

* Removal of the neurotransmitter (which is taken back up into the motor neurons) leads to muscle relaxation.

interested in presenting *both* the conservation and the industry sides of the story. The initial response was deafening silence.

Eventually, a former student who "knew a guy who knew a guy" was able to put me in touch directly with someone at a biomed facility. I sent another inquiry, making sure to mention my student's name. Soon after, I received a nice letter explaining that they were sorry but that company rules did not permit on-site interviews, and that for proprietary reasons nobody was permitted to see the rooms where the horseshoe crabs were being bled. The letter writer *did* assure me in no uncertain terms that the horseshoe crabs were doing well—*so* well in fact that I expected a few of them might be sending me their own follow-up notes, telling me not to worry because everything was cool.

I was also able to dig up another company's prepared impact statement, written to address the "misleading suggestions" that (1) the American horseshoe crab population was in danger and (2) that the production of LAL was a primary cause of horseshoe crab mortality. Running counter to a number of peer-reviewed scientific papers, the company's findings were that *Limulus* populations were not only stable but they were actually *increasing*. This claim likely draws on figures from the Delaware Bay, where conservation efforts *have* led to an increase in horseshoe crab populations. But the impact statement appears to ignore population declines reported elsewhere along the Atlantic coast. It also concluded that the biomedical industry had only a minor impact on horseshoe crab mortality, with an accompanying bar graph used to point the finger at the *real* culprits—the whelk and eel fisheries. There is no argument that these particular industries remain serious problems to horseshoe crabs, though their designation as the *primary* problem is troubling.

There are, however, some promising developments, as I learned from biologist John Tanacredi, the director of the Center for Environmental Research and Coastal Oceans Monitoring at Molloy College. At the site

of an old oyster hatchery on Long Island's South Shore, Tanacredi and his team maintain the only captive breeding colony of *Limulus* in the United States. In addition to this small-scale but locally popular effort, he and his colleagues are working hard to protect *Limulus polyphemus* by having it designated as a World Heritage Species by the United Nations. But even if they're successful (and the odds seem rather long), Tanacredi believes there will be local extinctions of horseshoe crabs, and possibly worse, if (1) harvesting by the bait and biomedical industries is not curtailed or at least better regulated by states, (2) their consumption as "exotic food" persists, and (3) critical habitats, especially breeding sites, continue to be destroyed through development or pollution.

Perhaps, though, the best answer to the dilemma facing horseshoe crabs originated with the work of Singaporean biologist Jeak Ling Ding in the 1980s. Ding sought to insert the horseshoe crab gene responsible for LAL's powerful response to endotoxin into the DNA of a microorganism. Similar recombinant DNA technology had already allowed drug companies to produce human insulin in large vats of yeast. Eventually, Ding and her research team were able to identify the gene behind the production of "factor C," the substance in horseshoe crab blood responsible for clot formation. They used a virus to inject factor C into cultures of insect gut cells (a popular cell type for this sort of work), which became tiny factories, cranking out the clot-generating LAL. Ding's patent for a recombinant factor C test kit was approved in 2003, but the pharmaceutical industry paid little interest. At the time, the test kit had only one supplier, and that company was still waiting for FDA approval. Because of this, the biomedical industry was apparently reluctant to switch from horseshoe crab-derived LAL, a product it had been successfully using for decades.

Recently, though, a second company has begun to produce recombinant factor C. Though the majority of biomedical companies producing

LAL have not yet adopted the new test kits, one has started offering it for sale in addition to its crab-based kits. And, in great news for horseshoe crab lovers everywhere, the pharmaceutical giant Eli Lilly has begun using recombinant factor C to quality-test its new drugs. One can only hope that this is just the beginning of what will become a full-blown transition to noninvasive technology to detect endotoxins, and that someday soon, stringing up horseshoe crabs to drain their blood will go the way of the rabbit pyrogen test.*

* In a sad setback, as drug companies scrambled to find ways to prevent or treat the coronavirus in 2020, the use of horseshoe crab blood derivatives to detect endotoxins in sterile labs skyrocketed, and kits using the new noninvasive technology were relegated to the back burner.

As an insect increases in size, demand for oxygen will increase in proportion to length cubed, but rate of supply will only increase as length squared . . . The upshot of all this is that Mothra is going to have to add a lot of tracheal tubes to maintain a sufficient oxygen supply.

—Michael C. LaBarbera,
The Biology of B-Movie Monsters

[4]

Insects, Sump Pumps, Giraffes, and Mothra

Having learned about the collegial relationship between the circulatory and respiratory systems, it might come as something of a shock that in many invertebrates, most notably the vast majority of insects, the circulatory system does *not* carry oxygen or carbon dioxide. Instead, oxygen-rich air enters the body through tiny holes called spiracles, then flows through a series of smaller and smaller tubes (called tracheae and tracheoles) until it eventually reaches the body tissues. The air takes a reverse trip as it exits, this time minus much of its oxygen and having picked up CO_2, both through the process of diffusion.

This tracheal system explains why many species of insects are able to exhibit active (and sometimes hyperactive) lifestyles without the connections between the circulatory and respiratory systems seen in other groups of animals. Interestingly, that connection may once have existed in insects, since a few species like stoneflies have the oxygen-carrying

pigment hemocyanin in their hemolymph. This suggests that some ancient (a.k.a. basal)* insects may have retained an ancestral blood-based mechanism for gas exchange that was lost later in their evolution as spiracles took over the job. Additional evidence for this hypothesis comes from a study in which the copper-based pigment hemocyanin was found in the embryonic hemolymph of a grasshopper, but not in later developmental stages.

As it happens, though, insect circulatory systems are also unusual for one additional, very unexpected reason: insects lack hearts.

How can a circulatory system possibly function without a heart? Well, like the horseshoe crab and many creatures with open circulatory systems, each insect possesses a dorsal vessel that runs along the midline of its entire body.† Here, though, the blood vessel *itself* comes equipped with ostia, the intake valves we recently saw in the horseshoe crab heart. The dorsal vessel, therefore, acts somewhat like a heart, in that nutrient-rich hemolymph enters through the ostia and is expelled by contraction of the vessel's muscular walls. Once the hemolymph leaves the dorsal vessel, it enters chamber-like hemocoels throughout the body, bringing it into contact with the head and major organs. The hemolymph is then routed toward the rear of the body, delivering nutrients to the back-end organs and waste to the excretory system. Picking up another batch of nutrients from the digestive system, the movement of the body and an assortment of auxiliary "hearts" found in the wings, antennae, and legs return the hemolymph to the dorsal vessel, which it reenters as the ostia open between contractions.

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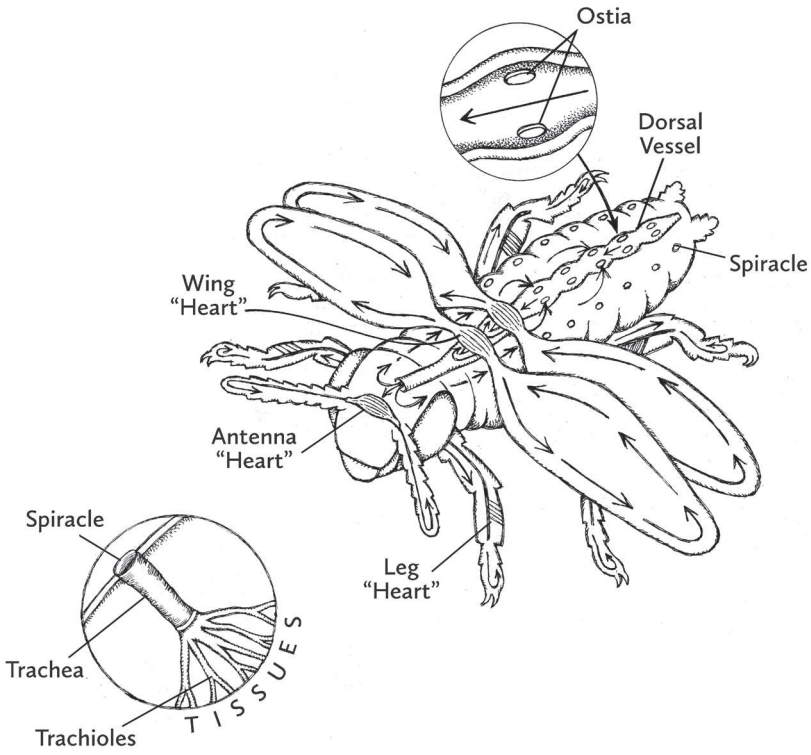
* The term "basal" implies a group near the base of the evolutionary tree of whatever group (i.e., taxon) is being discussed. Basal groups may be extinct, like jumbo-sized dragonflies at the base of the dragonfly tree, or living (i.e., extant), like the soon-to-be discussed bristletails, which are basal on the insect tree.

† Before we go on, in order to clarify the term "dorsal," please lie down on the floor and imagine that you're an insect, or an earthworm, or any four-limbs-on-the-floor species. The side of your body in contact with the floor is called the ventral surface, while the side facing the ceiling (since hopefully you're not doing this outside where passersby can see you) is the dorsal surface.



In another example of the way organ systems serve multiple purposes, as the dorsal vessel contracts, the pressure that develops within it helps maintain body shape and contributes to locomotion, reproductive behavior, molting (shedding of the exoskeleton), and hatching. This open system also plays the more traditional role of the circulatory system by supplying backup energy to the insect. It does so by carrying chemical energy from storage depots, called fat bodies, to the organs, where it can help meet the insect's metabolic needs during energy-sapping processes like flight.*

With nearly a million species known, insects display some weird variations on the highly generalized circulatory system described above.

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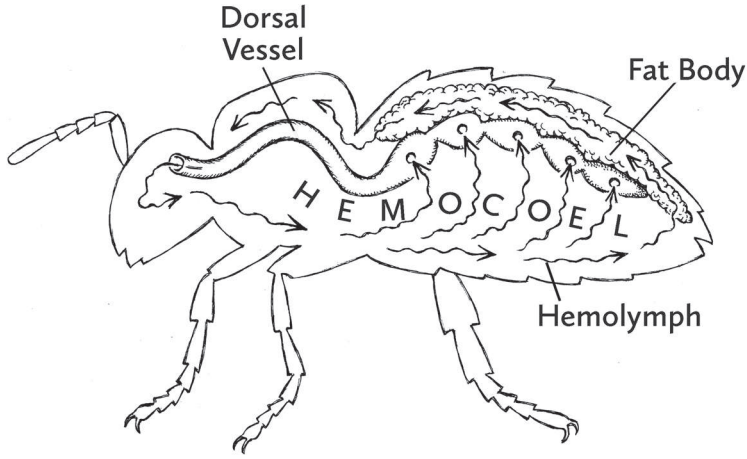
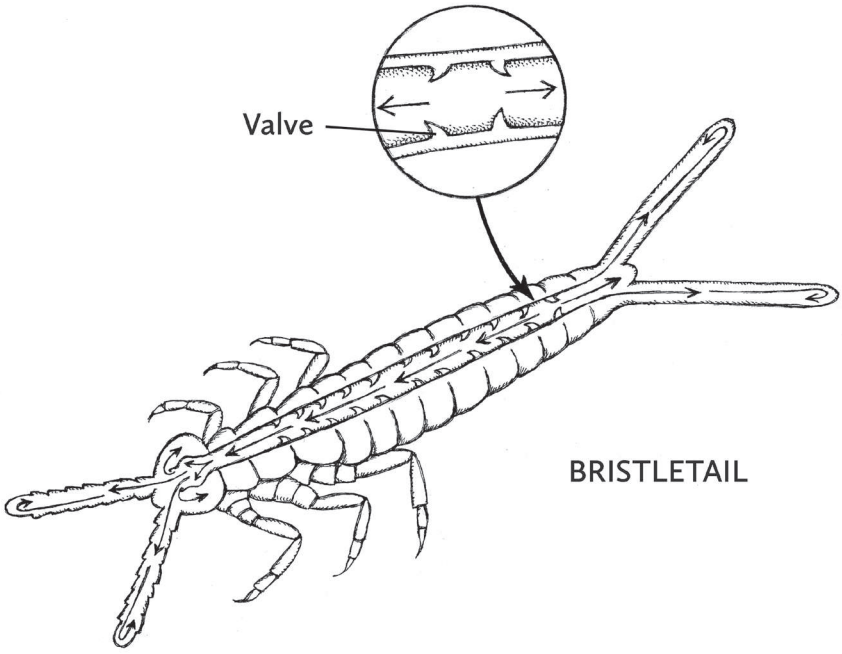
* As seen across the animal kingdom, when stored fat is needed, it is broken down into energy-rich molecules of fatty acid, which are transported by the circulatory system to the regions where they're required. There, cells break the chemical bonds holding the molecules together, using the former energy for a variety of purposes.



One such example occurs in a basal insect group called bristletails (order Diplura), which have specialized valves in the dorsal vessel that allow blood flow to alternate direction. As we touched on when discussing prolapsed valves in the human heart, backflow is usually a no-no. In bristletails, though, bidirectional flow allows hemolymph to more effectively reach both the head and tail regions. Most insects' dorsal vessels struggle to pump hemolymph to distant dead-end structures like legs, wings, and antennae, but only bristletails evolved this particular solution. More commonly, evolution provided what might appear to be a jerry-rigged response, in the form of auxiliary hearts, those previously mentioned dead-end structures. Without all of the gear typically associated with true hearts, these tiny muscle-driven pumps help drive hemolymph into hollow, elongated appendages, like wings, legs, and antennae, that would otherwise receive inadequate flow. Note: For those insect-oriented grad students looking for a research project, much about the mechanism behind these pulsatile organs remains unknown.

Once hemolymph is on the move inside an insect's open circulatory system, what keeps it from backing up? As hinted at by the bristletail tale



above, the mechanics of backflow prevention are pretty much the same as those found in animals with closed circulatory systems. It is also the same system found in many flood-prone basements.

In each case, the starting point is a pump, be it a contractile dorsal vessel, a heart, or the electric motor in a basement sump pump. As in a biological system, the sump pump converts energy (in this case, electrical energy from an outlet or a battery) into mechanical energy (in this case, through the movement within the motor, like a spinning fan). This mechanical energy can be used to do work, like overcoming the gravity keeping water in the sump pit, a hole dug into the basement floor where water can accumulate for various reasons—none of which falls under the category of "fun." If the pump is powerful enough, the water is driven through the pump, up a hose, and out into your neighbor's yard. When the electrical power is cut off or when the water gets too far from the pump, gravity tries to pull the water back toward the sump pit again. If

it's a decent pump, though, the water *doesn't* flow back down into your basement. That's because the pump has valves, which allow the water to move in only one direction—out.

So do blood vessels work this way?

Essentially, the answer is yes, although you should try to forget the parts about your neighbor's yard and the hole in your basement floor.

As previously mentioned, when compared to the hearts of vertebrates, the circulatory pumps found in invertebrates are *highly* variable in appearance and function. Blood might be pushed out into the body by peristaltic/pulsatile blood vessels (earthworms), tube-shaped hearts (horseshoe crabs), sac-shaped hearts (acorn worms), or even multichambered hearts (snails). Some invertebrates, like squid and their cephalopod pals, even have closed circulatory systems and *multiple* hearts, which vary in both anatomy and function. Though it would be nearly impossible to cover all of these systems, several of them stand out as interesting examples.

Technically, earthworms and their relatives (a.k.a. annelids, or segmented worms) do not have hearts, but rather have a series of five paired contractile vessels called aortic arches, pseudohearts, or circumesophageal vessels (so named because they wrap around the esophagus). As in insects, earthworm circulatory systems and respiratory systems do not overlap—that is, their hemolymph doesn't carry oxygen or carbon dioxide. But instead of a tracheal system for the passage of air, segmented worms exchange gases directly through their thin, moist skin, through a process known as cutaneous respiration. Note: Because earthworms breathe through their skin, they can drown in rain-soaked soil. This explains why they risk being out and about on rainy nights, much to the delight of early birds and fishermen.

In the mostly slimy-skinned animals that practice cutaneous

respiration, oxygen in the air diffuses through the skin's outermost layer, the epidermis, and into an extensive network of capillaries located in the next layer down, the dermis.* From there, the now-oxygenated blood moves into a larger, dorsal vessel that spans the length of the worm. The rhythmic contractions of the dorsal vessel propel the blood forward into the paired aortic arches. Lined up in parallel, these arches encircle the front section of the body and they contract in a synchronized, wavelike manner known as peristalsis. This is the same rippling-tube process that pushes food down your esophagus, sloshes it around in your stomach, and squeezes it through your small intestine.

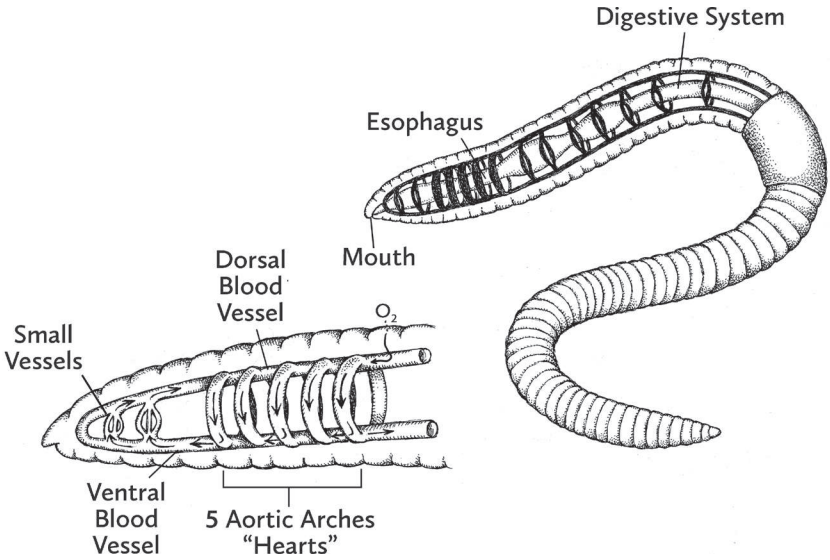
In the earthworm, peristaltic contractions drive the oxygenated blood downward and into a ventral blood vessel. From there the blood branches off into capillaries and is distributed to the body and organs. The deoxygenated blood eventually returns to the dorsal vessel through small vessels downstream of the capillaries, allowing it to circulate through the body of the worm in an unbroken loop—and making this a classic example of a closed circulatory system in an invertebrate.

Currently, there is strong support for the hypothesis that vertebrate hearts evolved from peristaltic blood vessels similar to aortic arches, although no one believes that vertebrate hearts evolved from the system currently seen in earthworms.†

While cephalopods like squid and octopuses may not have five pairs of aortic arches, they do also operate in multitudes, possessing

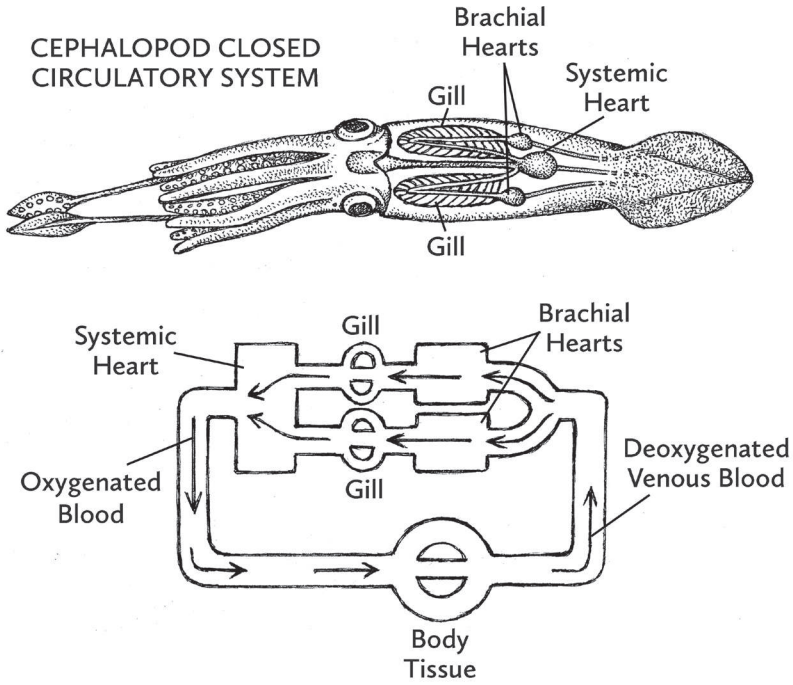
* The dermis (or dermal layer) differs from the superficially located epidermis by being richly vascularized and metabolically active. In many organisms, the epidermis functions primarily as a physical barrier against the external environment, and its uppermost cells are dead by the time they reach functional maturity. It should come as no shock that the epidermis is *extremely* thin in earthworms, and other animals that use cutaneous respiration, like frogs.

† By the way, if you're still lying on the ground since participating in that dorsal/ventral surface demonstration, please get up now.



a trio of hearts. The first two hearts, a pair of branchial hearts, receive deoxygenated blood returning from the body. Their contraction propels this blood to the gills, where it picks up oxygen extracted from the surrounding water. Leaving the gills, the oxygenated blood is routed to the third heart, a single systemic heart, which pumps it throughout the body. This highly efficient closed circulatory system likely came about as an evolutionary response to cephalopods developing their characteristically active lifestyles. Equipped with intelligence, jet propulsion, and superb predatory skills, these creatures require relatively larger amounts of oxygen than similarly sized organisms of the couch-potato variety.

At this point, a word of warning might help stomp out a common error that many nonscientists run into when looking across and within the animal kingdom. When observing the significant variation seen in the circulatory systems of insects, earthworms, and squid, it is easy to classify one as "better" than the other—and all of them as "inferior" to those systems possessed by humans. It's something that many scientists



did until the mid-twentieth century, and because of this, older scientific literature has plenty of purple prose—as man "triumphed" and humans "reached the pinnacle" of whatever topic was being discussed. But rather than considering nonhuman circulatory systems as second-rate or somehow faulty, we should think of them as *functionally equivalent*, each having evolved over hundreds of millions of years to satisfy the nutrient, waste, and gas exchange requirements of its owners and the environmental conditions in which those organisms lived or still live.

What is more, none of these organ systems are perfect. Most are just modified versions of previously existing structures, sometimes with different parts co-opted for new roles. Far more often than not, evolution does not invent; it tinkers with what is already there, tweaking some structures and fashioning new purposes for others. With this in mind,

there should be no bragging rights associated with the fact that some circulatory systems are quite complex while others are relatively simple. The key here is that all of them work.

There *are*, however, limits to what an open circulatory system can do. The reason for this is that every anatomical system must deal with the basic laws of physics and with the constraints these laws impose upon them. In other words, in evolution all things are *not* possible. For example, something shaped like a cow cannot fly because of the constraints placed on fliers by the laws of aerodynamics. In open circulatory systems, the constraints also turn out to be quite significant, particularly when it comes to size. It's due to the laws of physics that there are no eagle-sized houseflies or golf cart–sized horseshoe crabs. Large animals are simply composed of too many cells to be efficiently supplied by an open circulatory system.

As usual, this is due largely to diffusion. Closed circulatory systems have extensive interweaving capillary networks, providing a tremendous amount of surface area for the exchange of gases, nutrients, and waste between the blood and the tissues of the body. Open circulatory systems have no such thing. As we've already seen, their exchanges occur across chamber-like hemocoels. Unfortunately for any horseshoe crabs aspiring to mammoth size, the hemocoel walls don't have enough surface area to supply layer upon layer of tissues made up of millions and millions of cells.

Gravity is another constraint on organisms with open circulatory systems, and it explains why there are no creatures of this type equivalent to the giraffe. The reason is that the pumps found in open circulatory systems never evolved to be strong enough to force blood upward against the very significant force of gravity encountered by animals as tall as giraffes—or even as tall as humans.

Giraffes (*Giraffa camelopardalis*) are the tallest living mammals (up to eighteen feet for males), and in order to force blood up to their treetop-level heads, their hearts generate the highest blood pressure seen in any mammal. Normally, it's around 280/180 mm Hg, which is more than twice the blood pressure of a human, which is normally around 110/80 mm Hg. There will be more on the circulatory systems of these amazing creatures shortly, but for now let's make a stop to clear up an important, though potentially confusing, issue.

Some readers may be wondering what those blood pressure numbers I just mentioned actually mean. The first number reflects the force applied to blood vessels during ventricular contraction, while the heart is pumping blood out to the body. This is called systolic pressure. The second number represents the force applied to those same vessels while the heart is relaxed and the ventricles are filling with blood. This is the diastolic pressure. Similar to other pressure measurements, like barometric pressure, these numbers can be envisioned as the height in millimeters that a column of mercury in an open-ended U-shaped glass tube will rise against gravity when a force is applied to one end of that tube. In the case of barometric pressure, that force is generated by the atmosphere; with blood pressure, it is generated by the heart as it contracts and relaxes.

The life-threatening effects of hypertension (or high blood pressure, i.e., generally 120/80 mm Hg and above) in humans are well-known, and recent studies have shown that both systolic and diastolic pressures are important predictors of heart attack, stroke, and other bad cardiovascular juju.* But more on that later.

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* A recent study also shows a clear link between high blood pressure and the risk of dementia. But while low blood pressure might seem desirable, hypotension (<90/60 mm Hg) can also lead to problems, like confusion, light-headedness, and fainting. Extreme hypotension can result in shock and even death.

On the opposite side of the blood pressure coin from giraffes is the ocean-dwelling family known as hagfish (*Myxine* spp.). Affectionately known as "slime eels" or "snot snakes" (though they're not eels *or* snakes), hagfish are often found atop "The Most Disgusting Animals in the World" lists. This probably has nothing to do with the fact that they have the lowest aortic blood pressures of any vertebrate—between 5.8 and 9.8 mm Hg—and more to do with their feeding habits (they feed by burrowing into large dead animals) and their ability to quickly fill a five-gallon bucket with slime if molested. The hagfish can be thought of as the fishy equivalent of an "anti-shrew." That's because, unlike the constantly on-the-go shrew, the hagfish has extremely low metabolic energy requirements and a lifestyle that would make the laziest person you know seem like an Olympic gymnast who has just consumed a pot of coffee.

Given the hagfish's grim feeding habits, it comes as a bit of a surprise that this charming creature is considered an aphrodisiac in South Korea, where fishermen catch it using a technique that might be described as "somewhat less delicate than fly-fishing." To land some hagfish, you'll need to follow these angling instructions: Tie a rope to a dead cow and sink it hundreds of feet down to a mud-bottomed seafloor.* Tie the free end of the rope to a buoy. Then go home. Come back in a week or so. Haul up the corpse, then split Elsie open, and collect your low-pressure prize. Hopefully, that will consist of dozens of hagfish and pounds of their slime, a protein-based goo composed of strands that are stronger than nylon and thinner than a human hair.

Unlike giraffes and humans, hagfish and most aquatic creatures are *relatively* unaffected by gravity. Mostly, this is because the water surrounding a hagfish, or any fish for that matter, is extremely dense.

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* A hole-punctured barrel baited with rotten fish can be substituted, if your bait shop is out of cows.

Because of this the water exerts an upward force on the creature that acts in opposition to gravity, a phenomenon known as buoyancy. Because air is *less* dense than water, the benefits of buoyancy are minimal for terrestrial creatures, and so they must continually deal with the downward force of gravity. In fact, gravity explains why problems commonly arise with the return of venous blood from extremities like the legs and feet—even in humans with our normally powerful hearts. This is because blood pressure in capillary beds is much lower than anywhere else in the body, usually around 20 mm Hg or less. Physics tells us that an increase in surface area leads to a decrease in pressure, and the capillary beds have a much larger total surface area than the arteries and arterioles leading into them. What's more, without this pressure drop, the arterial blood would blow out the ultrathin walls of the capillaries it enters. The problem is that once blood *leaves* the capillary bed, it remains under low pressure—and if the capillary bed in question is in your toe, this makes it hard for the blood to fight gravity as it flows back toward the heart.

As a result, humans have evolved an additional assist to boost venous blood flow back out of the legs. It comes from the contraction of calf muscles, like the gastrocnemius and the soleus. The bellies of these muscles (that is, the thickened middle portion of the muscle) surround some of the large veins that carry blood back to the heart from the feet. When these muscles contract—for example, when you point your foot downward—they compress the veins and the blood flowing within them. This increases the pressure within these vessels (imagine squeezing an elongated water balloon again), which drives the blood upward and back toward the heart. Known as the "skeletal muscle pump," this machinery is constantly at work, since separate bundles of muscle fibers within leg muscles alternate their contractions on a regular basis and without your permission.

As you might expect, the long legs of a giraffe present plenty of circulatory system–related problems. We will return to that in a minute, though, because it's their necks, which reach lengths of up to six feet, where serious challenges related to venous return to the heart arise and are overcome. As giraffes lower their heads to drink, it's easy to imagine that there would be a danger of blood pooling in the vessels of the head and brain. Luckily, this is prevented by a series of approximately seven valves in each of the two jugular veins, which carry deoxygenated blood from the head toward the heart. Just as valves prevent water leaving your basement from flowing back into the sump pump, blood leaving the lowered giraffe head cannot flow back into that head. And to provide some extra lift for the gravity-defying blood, giraffe jugular veins have more muscle in their walls than is typical of those of most mammals, and their contraction helps move the venous blood upward when the head is down.

On the arterial side, the problems faced by the world's tallest mammal are quite different. When giraffes lower their heads, you would think that the already-high-pressure blood would get even more of a boost from gravity, and flow Colorado River rapids–style into the head. Instead, that blood, which is carried by the carotid arteries, enters a dense network of vessels at the upper portion of the neck. Known as the rete mirabile (Latin for "wonderful net"), this system increases the vessel surface area, leading to a decrease in blood pressure. If this sounds familiar, that's because it's similar to the way blood pressure drops in the capillary beds. In this case, the rete mirabile prevents the sudden increase in pressure that would occur when the giraffe lowers its head to drink—a position that can bring it a dozen or so feet below the heart. Once the giraffe raises its head, the vessels of the rete constrict, sending the blood within them off to the brain.

As I mentioned, our lanky friends face yet another problem—when it comes to their extralong legs. Due mostly to gravity, the arteries running

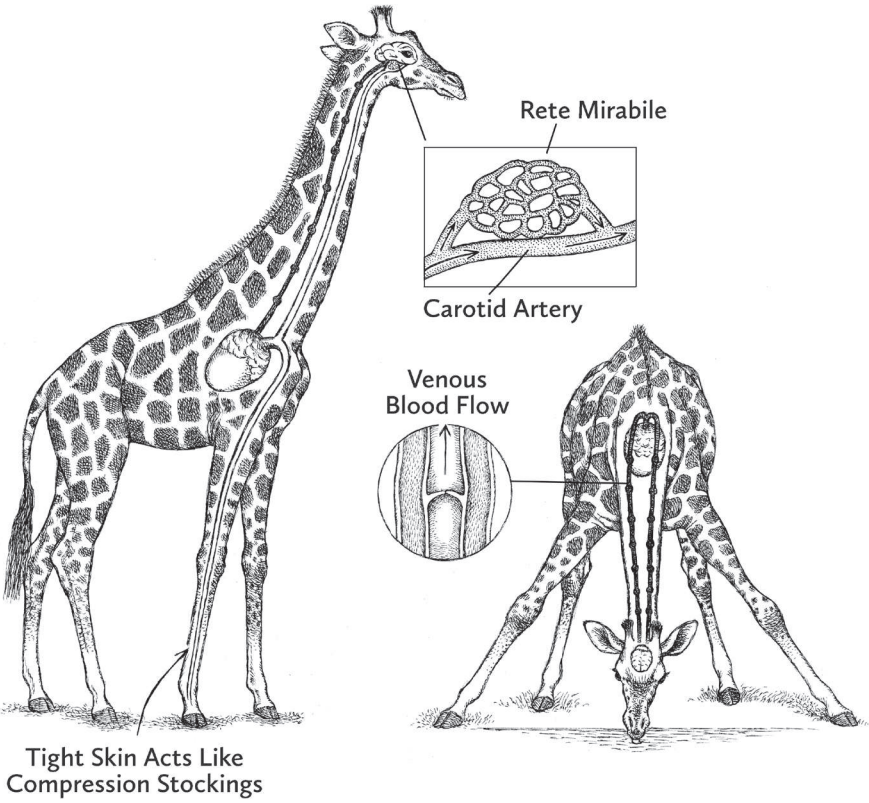
through giraffe legs can be exposed to pressures as high as 350 mm Hg. Such an immense pressure would typically leave the limbs vulnerable to edema, an abnormal accumulation of fluid, commonly referred to as "water retention." This fluid buildup occurs when plasma, the liquid portion of the blood, is forced through thin capillary walls and into the surrounding tissue. Evolution has solved this problem for the giraffe, though, in the form of thick, tight-fitting skin on their legs. This arrangement works on the same principle as compression stockings worn by humans. Both prevent edema by decreasing the flow of blood into limb vessels.*

An array of similar pressure-related adaptations can be found in other long-necked creatures, like okapis, camels, and ostriches—many serving as additional examples of convergent evolution. Clearly, there are challenges that come with being tall, and evolution has tweaked a number of previously standard anatomical features to meet these challenges.

Sticking to the topic of supersized creatures for a bit longer, we exist in a world where constraints imposed by the laws of physics dictate that many of the movie monsters of my childhood could never actually exist. Mothra, the zeppelin-sized lepidopteran, immediately comes to mind. Although the open circulatory systems found in insects work very well for the small and lightweight, we've seen that they simply do not cut it for the extralarge. But once again, there *are* exceptions.

The most spectacular outliers may be the approximately 120 species of king crabs (family Lithodidae), which can reach body weights of eighteen pounds and with a leg span of almost six feet. Another outsized aquatic outlier is the giant clam, *Tridacna gigas*, which can reach more than four feet in width and tip the scales at around 550 pounds. Their ability to

* Foot-related footnote: If an adult suddenly goes up in shoe size, it could indicate swelling caused by edema. This should be checked out by a physician since it *may* indicate a heart problem. For example, an increase in blood pressure might be forcing blood plasma out of capillaries and into the surrounding tissues, causing them to swell.



attain such size relates to their stationary (a.k.a. sessile) existence, with relatively low energy expenditure and subsequently low energy demands.*

King crabs, however, have a more active lifestyle. The key factor enabling them to grow to outsized outliers is that they live in a marine environment, where gravity is far less of a limiting factor than it is in air. In the ocean, a giant crab experiences the pull of gravity on its body, but

* Contrary to popular belief, giant clams are not dangerous to humans, since their shells close too slowly to entrap an arm or leg. And even if they were trying to snag you, they are the only bivalves unable to completely close their shells.

because of buoyancy, the total force acting to pull the crab downward has been reduced. This means that it requires less effort/energy for the crab to stand and move around in its watery environment, and its energy and nutrient requirements can be met with an open circulatory system. But because there's far less of a buoyancy effect in air, if you were to place that king crab on a beach, it would not be strong enough to support its body against the pull of gravity.

So, yes, there are some exceptions to the size rule, but such phenomena are to be expected in an animal kingdom whose diversity can surprise even the experts.*

From bristletails with two-way blood vessels to giant squid with a trio of hearts, the amazing degree of diversity exhibited by invertebrates is clearly reflected in their hearts and circulatory systems. Though the fossil record for soft-tissue structures has been less helpful than it has been for researchers studying things like shells and bones, it is abundantly clear that circulatory systems evolved on multiple occasions and in a variety of different animal groups. So while we can examine relationships between animal groups, and the workings of organs like those that make up their circulatory systems, what remains difficult to identify are the origins of circulatory structures like the hemocoel, auxiliary hearts, or, for that matter, the hemolymph that fills them.

As the chapters that follow turn back to vertebrates, the path of evolution will become easier to trace. That's because there are a far more manageable number of circulatory system models to study, and a relatively

* My favorite example of animal diversity is the existence of over 350,000 species of beetles—a fact I learned as a child, and which got me wondering about Noah's specimen-collecting skills. This was followed by questions like who got to clean up the mess left by roughly three thousand rodents (a male and female from each of the approximately fifteen hundred species)?

clear fossil record for the transitions taking place between fish, amphibians, and terrestrial vertebrates like reptiles, birds, and mammals. There are, after all, only around sixty-five thousand species of vertebrates alive today, while there are roughly five and a half times as many species of beetles. Of course, vertebrate circulatory systems still vary, with many differences having emerged in the transition from aquatic to terrestrial lifestyles. And, again, many of these adaptations will help to illustrate the constraints and trade-offs that vertebrates face—creatures, whose habitats range from inky-black ocean depths to hunting grounds a thousand feet above the earth's surface.

It is a great thing to have a big brain,
a fertile imagination, grand ideas, but the man with these,
bereft of a good backbone, is sure to serve no useful end.
—George Matthew Adams

[5]

On the Vertebrate Beat

Growing up on the South Shore of Long Island, I spent a considerable portion of my childhood and teen years fishing off neighborhood docks and beaches. Far less exciting than the blue claw crabs, blowfish, and flounder that populated my childhood were the omnipresent rubbery blobs that clung to the piers and docks near my home. They're called sea squirts, for their propensity to spurt streams of water from their funnel-like siphons, usually when they are detached from their moorings for examination, which I have been responsible for on occasion. I had no idea however, that from an evolutionary perspective, these potato-shaped orbs were more closely related to my friends and me than they were to the blue claw crabs we hunted with nets and spotlights.

"Protochordate" is an informal term used to describe several invertebrate groups, thought to be the closest relatives of the backboned vertebrates. The protochordates include a few marine species, such as the tadpole-like lancelets (a.k.a. cephalochordates) and the miniature jelly barrels known as sea squirts (a.k.a. urochordates or tunicates). While it's difficult to connect the physical appearances of adult sea squirts to blue whales or humans, scientists believe that their larvae offer a decent

approximation of what the ancestor of the first vertebrate looked like. For the purposes of our tale, we'll now learn how evolution has driven the transition of the vertebrate heart from a simple tube in our distant protochordate cousins into a diversity of forms, including the four-chambered heart seen in blue whales and the pushy bipeds responsible for their near extinction.

Looking nothing like their adult forms, larval sea squirts have tails that propel their elongated bodies, giving them a sort of headless-tadpole look that has never quite caught on with real tadpoles. Eventually, the swimmers, which were initially thought to be a completely separate species from the adults, latch on to a dock or some similar substrate. (See sea squirt figures of larval and adult stages.) Their tails are resorbed by their increasingly gelatinous-looking bodies, and they sprout a pair of in- and out-current siphons, living out the remainder of their lives filtering plankton and detritus.

While its transformation from mobile to sessile is interesting, perhaps the most fascinating thing about the sea squirt is a hypothesis about its heart. Scientists like Annette Hellbach, from the Max Planck Institute of Biochemistry, believe that the tubular heart of the sea squirt is a precursor of the vertebrate heart, particularly due to the electrical conduction system that allows both types of hearts to generate their own rhythmic beats. Hellbach and her colleagues discovered that the sea squirt heart "beats from one end to the other, stops for a short while and then starts to beat in the other direction."* The researchers also identified cells along the tubular heart that respond to heart rate–decreasing chemicals, very much like the cells found in the previously discussed cardiac pacemakers found in humans and other backboned bodies.

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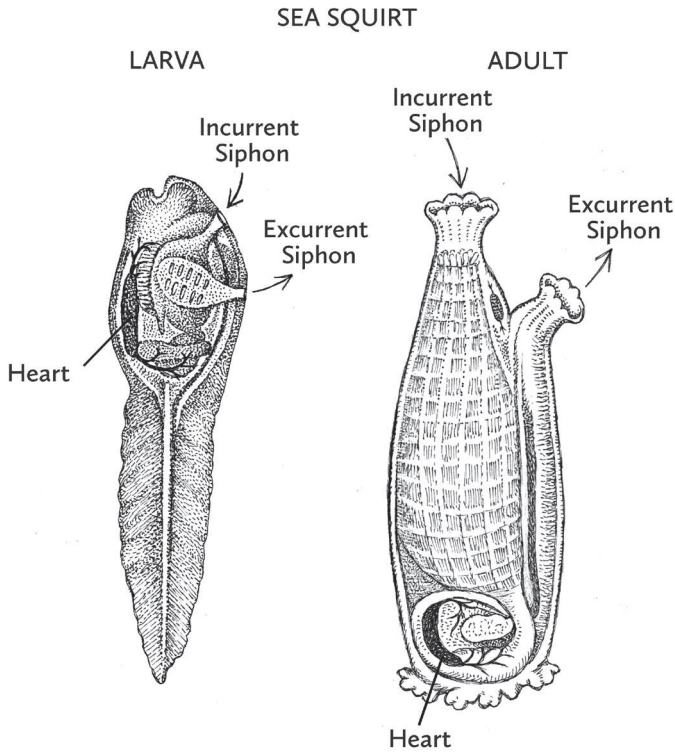
* This appears to be an alternate method to reverse the direction of blood flow than that seen in the bristletail's unique two-way valves. These adaptations promoting bidirectional blood flow would be another example of convergent evolution.



We interrupt this story for brief evolution-themed advisory: Readers should not fall into the trap of believing that the term "precursor" (as used above) implies that this species of sea squirt itself evolved into what might be considered the first backboned swimmer. Rather, the thought is that an ancient *ancestor* of modern sea squirts *may* have evolved enough adaptations (e.g., dropping the adult blob stage and evolving a support rod running down its dorsal side) that on the off chance some humans were to find its fossil half a billion years later, they might decide that the creature shouldn't be classified as a protochordate anymore—but instead that it was a chordate,* quite possibly an ancient fish.

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* Chordates are named for the presence (at some point in their lives) of a rodlike structure called the notochord, running down the dorsal length of their bodies. In vertebrates, the largest group of chordates by far, the notochord has largely been replaced by the vertebral column, with the only remaining traces of it found within the cartilaginous intervertebral disks.

Fish, amphibians, and reptiles offer a glimpse at what is perhaps the greatest natural history story ever told, one that began in the sea roughly half a billion years ago. There are plenty of great reads out there dedicated to telling this story in fascinating detail—I particularly recommend *Your Inner Fish* by Neil Shubin. Through fits and starts, cataclysms, and lucky breaks, the branching tree of vertebrate evolution took some of these creatures from aquatic to terrestrial lifestyles, from dwelling in shallow high-temperature, oxygen-depleted backwaters, to a tentative but ultimately successful colonization of the land, sea, and air. But in order for that to occur, significant evolutionary tweaks to the typical fish organ systems had to evolve—*especially* to the circulatory and respiratory systems.

Along the lines of yet another public service announcement, it would be dead wrong to assume that fish were on a march to becoming semiaquatic amphibians, and that amphibians were likewise driven to evolve the landlubber characteristics of reptiles and mammals. Similar reasoning has led some uninformed types to ask why modern chimps don't evolve into humans. In short, evolution does not work like that.

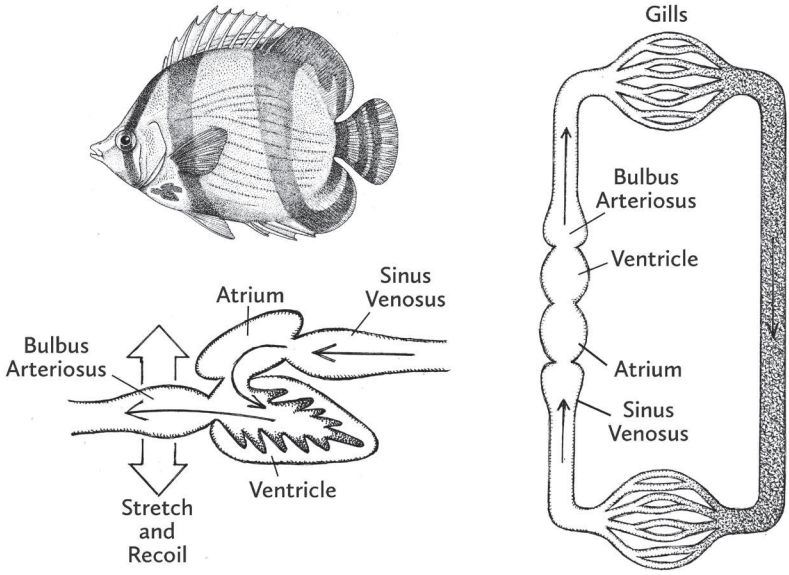
Instead, researchers believe that the way the transition from water to land occurred was that a relatively small group of fish species (known today as the elpistostegids) already had simple lungs with which they could exchange gases between their circulatory systems and atmospheric air. These lungs had themselves evolved from antigravity buoyancy bags, called swim bladders, found in basically all fish except for sharks and their dorsolaterally flattened pals, the rays and skates. Initially, lungs had enabled these ancient species to colonize swampy, low-oxygen aquatic environments. Stumpy lobe-fins helped them paddle around these shallow-water environments. They supplemented the oxygen from their gills by swallowing gulps of air, which filled their swim bladders—which

also just happened to be covered by a dense network of capillaries. Diffusion did the rest.

Then, before you could say "semiterrestrial vertebrate" (bringing us to around 375 million years ago), critters like the crocodile-headed *Tiktaalik* were making short trips onto land. They then used their previously existing stumpy fins for a brand-new purpose—walking. Similar to the way ancient horses survived and thrived because they evolved the ability to eat stuff that nobody else ate, *Tiktaalik* and its descendants would have found plenty of terrestrial snacks, with absolutely no competition from other vertebrates—since all of them were still living in the water. As with the grass-munching horses, this ability to exploit a resource (in this case, *many* resources) that nobody else could exploit became a formula for evolutionary success. Predictably, it also led to an explosion of species diversity, as some vertebrates eventually evolved from semiterrestrial amphibians into more landlocked reptiles and, later, some of the reptiles evolved into what we now classify as mammals. Most fish, though, remained fish. And with the exception of a relatively few species of walking catfish, mudskippers, and their ilk, the majority of fish species never ventured out of the pool. But what an interesting pool it turned out to be. Since those ancient times, fish have evolved into nearly every aquatic environment, from mud puddles to the deepest marine trenches.

Fish also possess the closest thing vertebrates have to an invertebrate heart, thus allowing scientists to get a glimpse of what the earliest vertebrate hearts may have looked like. Most significantly, fish hearts possess only one atrium and one ventricle. As a result, their circulatory systems are not arranged in two separate loops like other vertebrate systems, but in one continuous circuit.

Although fish hearts have only a single atrium and ventricle, they have two additional compartments through which blood exits and



FISH HEART

enters. These four chambers are arranged in a roughly straight line. The venous blood headed back into the heart from the body first enters the sinus venosus, a large collecting chamber that passes blood along into the thin-walled atrium. The atrium contracts and sends the blood on to the thick-walled ventricle, which it exits through the bulbus arteriosus, an often-pear-shaped structure composed primarily of smooth muscle and stretchy fibers consisting of the proteins elastin and collagen. When the ventricle contracts, the bulbus arteriosus fills with blood, its expandable walls s-t-r-e-t-c-h-i-n-g to accommodate the volume. Once filled, the walls of the bulbus recoil, pumping blood out of the heart and toward the gills at a *constant rate and pressure*, even when the heart is relaxing. This function is vital because of the delicate nature of the feathery, thin-walled gills. Without the bulbus, the contraction of the ventricle would lead to sudden increases in blood pressure, and the gills could be damaged.

The advantages of elastic (a.k.a. potential) energy were significant enough that they endured throughout the evolution of the mammalian heart, and several of our largest arteries are referred to as "elastic arteries"

for this reason. Like the bulbus arteriosus, their walls are rich in elastin, the same springy fibers found in places like the skin.* In mammals, an example of an elastic artery is the aorta, which stretches as it fills with blood from the contracted left ventricle. Then, as its walls recoil, the energy stored within is applied to the blood exiting the left ventricle.

Older humans (and other mammals) are often faced with a condition called arteriosclerosis, during which the large elastic arteries can stiffen and lose their elasticity. Commonly known as "hardening of the arteries," it occurs for several reasons, including fibrosis—a pathological (i.e., disease-related) response to injury in which fibrous, nonelastic tissue replaces elastic or contractile tissue in the vessels. Also imparting a negative effect on the vessels is the process of calcification—the buildup of calcium in body tissues, in this case in the form of inflexible deposits within the vessel walls. Without the help of elastic vessels, the heart must work harder to deliver blood to the body, a condition that often leads to serious health problems.

The demands of a transition to life on land, even a partial transition, eventually led to the evolution of a three-chambered heart (two atria and one ventricle) in amphibians. And even though there is some mixing of oxygenated and deoxygenated blood in the single ventricle, this tri-chambered design also carried over into the majority of reptiles.

In most amphibians, deoxygenated blood travels from the body to the right atrium. Oxygen from the gills or lungs returns to the left atrium along with blood that has been oxygenated through the process of cutaneous respiration. Because amphibians have thin, moist skin and an abundance of blood vessels located just below it, oxygen is able to diffuse out of the air through the skin and into the body. This

* So-called muscular arteries contain less elastin and more smooth muscle fibers, in a layer called the tunica media.

cutaneous respiration, plus a series of valves and flaps within the heart (that maintain a *partial* separation of the oxygenated and deoxygenated blood), more than makes up for the mixing of blood that occurs in the single ventricle. So efficient is cutaneous respiration for small vertebrates dwelling in damp environments that it is the sole method of gas exchange in the largest family of salamanders, the plethodontids, which are both lungless and gill-less.

While amphibians like frogs, toads, and salamanders have at least some aquatic stages of their lives (and some spend pretty much all of their lives in water), reptiles do not have this requirement—although some of them, like sea turtles, have reevolved aquatic lifestyles. However, by land or by sea, they all have a significant difference in the overall circulatory system function: in reptiles, lungs completely took over the role of gills. This was possible because, unlike amphibians, reptiles never go through an aquatic larval stage (like the tadpoles seen in frogs and toads). This important difference was first identified in the early nineteenth century, and, as a result, frogs, toads, and salamanders were placed into their own phylogenetic class, Amphibia, as distinct from the animals of the class Reptilia, with which they had previously been lumped.

From an evolutionary perspective, the reptilian emphasis on terrestriality wasn't a bad thing, since it meant that these critters were no longer as dependent on finding an appropriate body of water in which to mate or lay their eggs, or to have their tadpoles develop—especially since they didn't have tadpoles. This enabled them to move into habitats located farther from bodies of water, providing opportunities to exploit new types of food while decreasing the risk of running into predators. Because of this, however, reptiles lost their ancestors' moist skin, since it became vitally important to conserve the water contained in their bodies and not allow it to evaporate. As a result, their skin is most often dry, sometimes scaly, and rarely a suitable place for cutaneous respiration to occur.

As mentioned earlier, one characteristic that both amphibians and most reptiles *do* share is the presence of a three-chambered heart, where oxygenated and deoxygenated blood mix. But while this feature provides a clue to their close evolutionary ties, there are in fact a number of smaller variations between the hearts of the various "herps."* The key difference, however, between (noncrocodilian) reptile hearts and amphibian hearts is that in the reptiles, the single ventricle is at least partially divided by a wall-like septum.

As with the previous description of insect circulatory systems, please be aware that what follows is a generalization. Okay, stay with me now and hold on *tightly* to the next figure. In lizards, as the atria contract, two streams of blood (deoxygenated blood from the right atrium and oxygenated blood from the left atrium) enter the left side of the ventricle. Remember, it has a partial septum. Within the left side of the ventricle, the deoxygenated blood sticks to the right and the oxygenated blood to the left (and, yes, here's where some mixing of O_2-rich and O_2-poor blood takes place). When the ventricle contracts, the deoxygenated blood is directed through an opening in the septum and into the *right* side of the ventricle, and from there into the pulmonary artery (which is, thankfully, sitting close by) and on to the lungs. Simultaneously, as the ventricle contracts, the oxygenated blood in that chamber gets pumped out through a pair of aortae and on to the body.† *Whew!*

In one order of reptiles, the crocodilians (alligators, crocodiles, and slender-snouted gharials), there is complete separation of the pulmonary and systemic circuits. The same is true of birds—actually, a closely related class of vertebrates. Crocodilians and birds are the only known survivors

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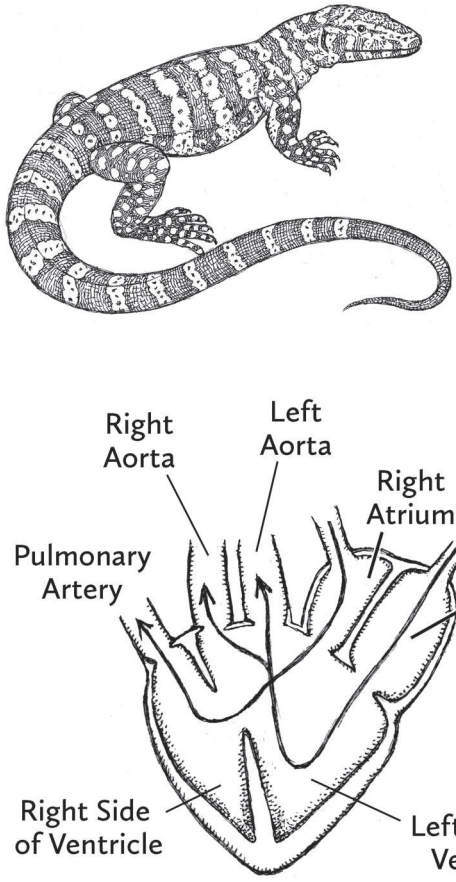
* Despite their separation by scientist types, reptiles and amphibians are still referred to as herps by much of the nonscience community. It is an abbreviated version of "herpetiles," from the Greek *herpetón*, meaning "creeping animal."

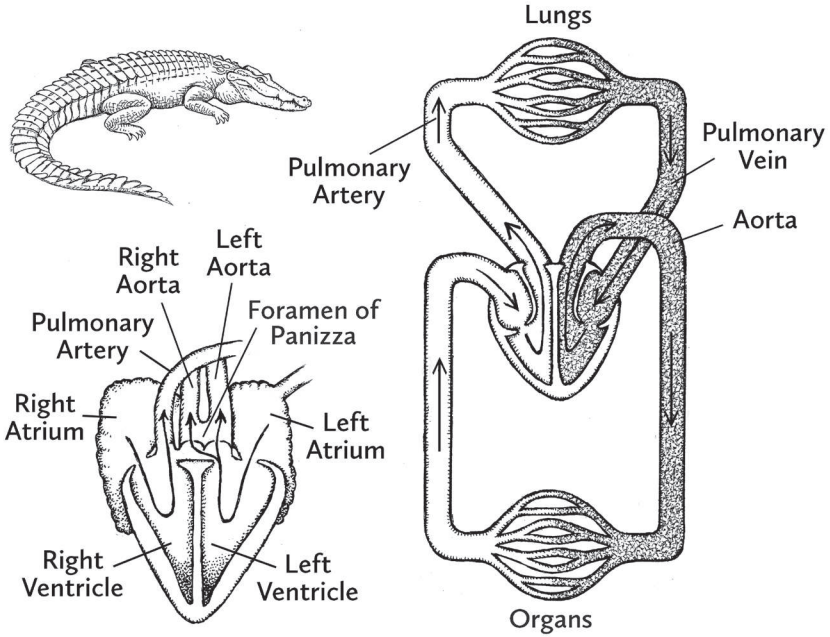
† There are slight differences in the heart and blood flow pattern in turtles and snakes.



LIZARD HEART SCHEMATIC

of the Archosauria, the group that most famously includes dinosaurs. Their four-chambered hearts are similar, though not identical, to those found in mammals.

With four chambers separated by backflow-preventing valves, and with a septum separating the left and right sides, the hearts of crocodiles, birds, and mammals form not just a pump but a pair of pumps and a pair of circuits. In the pulmonary circuit, oxygen-depleted blood returns from



CROCODILE HEART MAMMAL AND BIRD HEART

the body to the right atrium, passes into the right ventricle, and is sent off to the lungs. In the systemic circuit, the oxygen-rich blood returns from the lungs to the left atrium and passes into the thick-walled left ventricle, which contracts, propelling it out to the body. As a result, the mixing of oxygen-rich and oxygen-poor blood does not occur, and the oxygenated blood is not diluted by its deoxygenated counterpart.

In the end, though, whether vertebrate hearts have two, three, or four chambers, and whether some degree of mixing occurs between oxygen-rich and oxygen-poor blood or it doesn't, these systems work very well indeed for the creatures that possess them.

One thing that all animals share is that in order to survive, they must be well adapted to their habitats—the environments in which they live. Often, though, conditions within those environments can change—sometimes abruptly, sometimes significantly, and very often both. For

some creatures, extreme conditions are the norm: arid deserts, humid rain forests, the thin air of mountaintops, or the crushing pressure of deep oceans. Other habitats experience significant seasonal or sudden changes in temperature or water availability. The circulatory system plays a key role in the ability of animals (including humans) to cope with environmental extremes. Conveniently, many of the adaptations that allow organisms to deal with these extremes also allow us to better understand how hearts and circulatory systems work, and to see that even the most complex and efficient of these systems will fail if pushed beyond their limit. In an already compromised heart, that failure can be catastrophic.

Cold hands, warm heart.
—Traditional proverb

Call me Jack-the-Bear,
for I am in a state of hibernation.
—Ralph Ellison, *Invisible Man*

[6]

Out in the Cold

I've spent much of my thirty-year career studying bats. Though most people have, thankfully, moved beyond the stereotypical portrayal of bats as bloodsucking flying mice (only three of fourteen hundred species feed on blood, and all species are more closely related to humans than they are to rodents), to many, bats remain shrouded in mystery. One of the things most folks *do* know about these mostly nocturnal mammals is that many of them hibernate. As we'll soon see, hibernation is primarily a circulatory strategy: the energy-burning system that transports oxygen and nutrients must slow down to accommodate the often-long periods when the conditions are frigid and there is no food to be found.

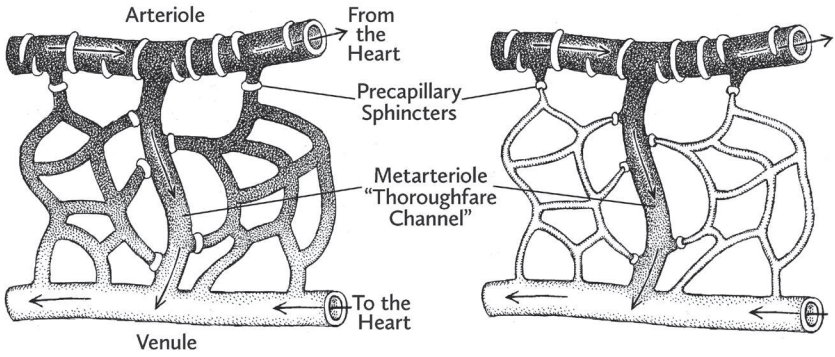
By coincidence, though, as I began to research the topic of cold adaptation in bats, I got sidetracked. Long Island and New York City were being slapped by what local meteorologists were calling "a dangerous deep freeze." Part of what earns any old freeze the label of "dangerous" are concurrent reports of people dying from heart attacks and, less frequently,

hypothermia—a condition in humans in which core body temperature falls below 95 degrees Fahrenheit.

It is not difficult to understand why someone with a heart condition might fall victim to the exertion of shoveling snow, especially the heavy, wet stuff so common in the northeastern United States, where a typical driveway can hold several tons of snow after a storm. Much of the uptick in heart attacks is thought to occur because the motion of shoveling snow, especially the lifting involved, causes the heart to beat faster and more strongly. As with any exercise, this increases blood pressure, leading to the potential for damage to what is all too often an already faulty pump. What is less obvious is the way that the cold escalates the situation.

When exposed to low temperatures, as one would experience wading into a snowdrift with a shovel, the human body attempts to conserve heat in core organs, like the brain, heart, lungs, and liver. It does this by reducing blood flow to capillary beds in peripherally located structures, like the arms, the legs, and the tip of your nose, directing it instead toward the previously mentioned essential body parts. This occurs through a process called localized vasoconstriction—that is, a closing off of blood vessels in specific regions of the body. This vessel shutdown occurs as tiny muscular valves, called precapillary sphincters, receive a message from the brain to close. As the bands of muscle constrict, the blood upstream from the valves bypasses the capillary beds, like cars on a highway driving past a temporarily closed exit. This allows the blood to bypass the capillaries (via vessels called metarterioles) and flow through the tissues without supplying them.

In the warmth of your home, something similar takes place after a meal, but in this case, blood is diverted *to* a different set of capillary beds, namely those located within the walls of your digestive tract. Here the precapillary sphincters do not get the signal to close. As a result, blood enters into the digestive system capillary beds, picking up nutrients



absorbed through the inner lining of the stomach and intestines (hello, diffusion!) and returning the nutrient-rich blood back to the heart for distribution to the body.

To be clear, though, the route the venous blood takes as it returns from the digestive tract isn't *quite* that direct. Instead, it takes a detour to the liver, via a vessel called the hepatic portal vein. Inside the liver, cells called hepatocytes remove the sugar from the blood and assemble it, building block–style, into a starch-like molecule called glycogen, which can be easily stored nearby. Only then does the still-nutrient-laden blood exit the liver and make its way, via the inferior vena cava, to the right atrium of the heart. This process is the reason that we don't overdose on sugar after eating a half dozen Twinkies.

As for the fate of the glycogen stored in the liver, it can be quickly broken down by the very same hepatocytes and returned to the blood as glucose. Generally, this happens when alarm-like chemoreceptors determine that "blood sugar levels" are too low, something that commonly occurs between meals. These structures are embedded in walls of the carotid arteries (which supply blood to the head) and the aorta. As their name implies, chemoreceptors are stimulated by changes in the concentration of chemicals (like glucose, oxygen, or carbon dioxide) flowing past them in the blood, and when the glucose level drops too far, they relay that information to the brain via nerve impulses. The brain then

initiates a suitable response (e.g., "Too much glucose . . . Store some as glycogen," or "Not enough glucose . . . Break down some glycogen").

Also carried in the blood is a waxy lipid called cholesterol. Despite its bad reputation, cholesterol has a number of vitally important functions. These include making up a significant part of cell membranes, helping to conduct nerve impulses, and acting as a building block for substances like vitamin D, sex hormones, bile (which aids in fat digestion), and the stress hormone cortisol.

Cholesterol is carried in the blood attached to lipid-transporting proteins. These come in two forms: high-density lipoproteins (HDLs) and low-density lipoproteins (LDLs). Normally, these lipoproteins can pass into and out of blood vessel walls, but LDLs sometimes get stuck, causing a buildup of fatty deposits inside those walls. These buildups are known as atherosclerotic plaques, and the disease they cause is atherosclerosis. Atherosclerosis is dangerous because the accumulation of plaque can decrease blood flow. An easy way to demonstrate this concept is to turn on your garden hose and then step on it. As you do, resistance increases within the hose, thus reducing the flow of water. What will happen if you keep your foot on the hose for several minutes? If the pressure increase upstream from your foot is great enough, the hose could split—highly dangerous in a blood vessel, since that rupture can lead to uncontrolled bleeding and even death.

So, what does all of this digestion-related information have to do with cold-weather-related heart problems?

Coronary arteries are the blood vessels that supply the heart muscle—the myocardium. Because active digestion routes blood toward the organs near your waistline, it reduces coronary blood flow. For people whose coronary arteries are already narrowed by disease, and whose hearts might be receiving barely enough blood to function under *non*stress conditions, the added stressor of physical exertion in the cold can lead

to a significant decrease in the amount of blood being delivered to the heart muscle, and therefore a dangerous drop in the amount of oxygen and nutrients it receives.*

What's more, our blood cholesterol levels are often at their worst—and most dangerous—in the winter. Cardiologist Parag Joshi and his team at Johns Hopkins looked at cholesterol levels in 2.8 million Americans between 2006 and 2013. They determined that the tendency to eat more and exercise less during cold months led to a 3.5 percent increase in LDL cholesterol (so-called "bad cholesterol") levels in men, and a 1.7 percent increase in women. Additionally, the reduced levels of sunlight during the winter months can lead to a decrease in vitamin D, which is thought to lower blood LDL cholesterol levels.

The take-home message should now be clear: *avoid overexertion in the cold*, especially if you've just eaten a big meal, since more blood is being diverted to your digestive tract, or if you've recently started eating more high-cholesterol foods like processed meat, fried food, fast food, or desserts. Best, too, for smokers to be careful, since nicotine causes resistance-increasing vasoconstriction. Oh, and no pre-snow-shoveling cocktails either, since alcohol is also a potent vasoconstrictor. Instead, when you decide to clear away what the big winter storm left in front of your house, stay warm, take frequent breaks, use a smaller shovel, and push the snow instead of lifting it. Better yet, hire a kid to clear your driveway and sidewalk.

Still determined to shovel that driveway yourself? Well, okay. But before heading out into the cold, a few more words of wintry warning. In addition to heart-related issues associated with stressful exercise in frigid temperatures,

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* According to statistics, things are worst, cardiac-wise, after breakfast. A 2011 study looking at eight hundred heart attack patients in Madrid, Spain, showed that more heart attacks occur in the morning (between 6 a.m. and noon) than at any other time. Also significant is the fact that, on average, these attacks resulted in 20 percent more tissue damage to the heart.

problems can occur if the cold conditions overwhelm the body's attempts at internal temperature maintenance. In humans, for example, once the core body temperature falls below 95°F, the body begins to lose more heat than it can replace through mechanisms like shivering and decreasing blood flow to the digestive tract and extremities. As hypothermia occurs, organ systems, like the circulatory and nervous systems, begin to shut down, and dangerous effects start to set in. These include decreases in coordination and cognition, as well as slowdowns in reaction time. The old saying "The cold makes you dumb" is actually quite apt, since judgment also becomes impaired. As the body cools down, an energy-conserving desire to stop moving sets in, and the dulled mind may be unaware of the inherent danger of falling asleep. The final stage is characterized by slow or absent pulse and respiration. Death can follow. The take-home message once again is: hire the kid (or the guy with the plow).

Most organisms can't simply throw down the snow shovel and head for their warm homes, and many have evolved unique mechanisms to deal with exposure to cold temperatures and the stresses that accompany them. For warm-blooded species, including those that *do* wield snow shovels, the body compensates for low external temperatures by working to hold internal temperatures relatively steady. Normally, our body temperature is maintained at around 98.6°F.* Primarily, this occurs as an indirect result of metabolic processes like digestion and muscle contraction, since each produces heat as a byproduct of its chemical reactions. Something very similar occurs when you turn on your car engine. Gasoline contains chemical bond energy. When mixed with air and ignited in a small space (one of your car's cylinders), a controlled explosion results and the chemical bond energy is converted into the mechanical energy that spins your

* The normal range is between 97°F and 100°F.

tires. Since no energy conversion is 100 percent efficient, some energy is lost during the process, here in the form of heat. You can demonstrate this yourself by asking someone you don't like to place a hand on your car engine a few minutes after starting it. What they feel is the energy that has been lost during the conversion from chemical to mechanical energy. You can explain this to them once they stop screaming at you.

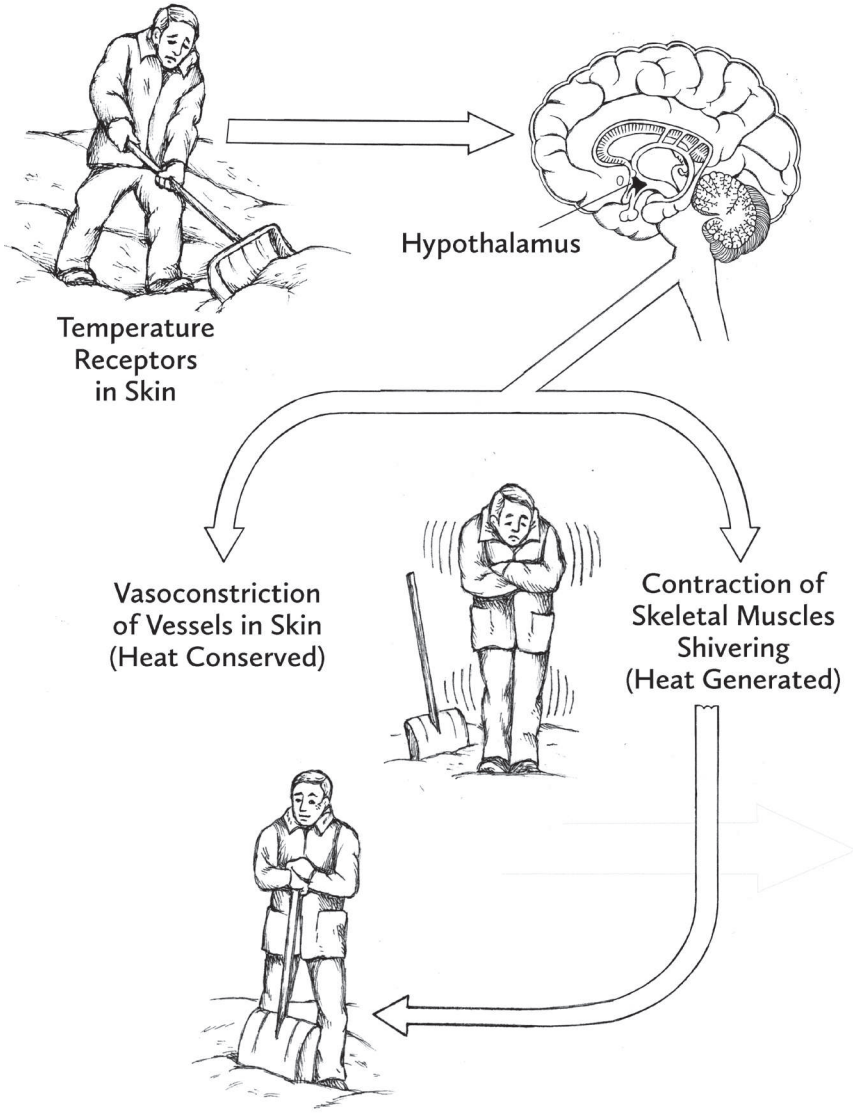
In the body, as heat is released, mostly during muscle contraction, it radiates out of the tissues where the reactions take place and into the adjacent thin-walled capillaries, warming them and the blood within. The warm blood flows back to the heart and is circulated throughout the body. As that happens, the heat leaves the blood and moves into the cooler surrounding tissues.

But what keeps the temperature of the human body constant? Why don't our bodies cool down when we step outside on a cold morning? The reasons relate to a section of the brain called the hypothalamus.

The hypothalamus is the command center for the autonomic nervous system, the portion of your nervous system that regulates most bodily functions without your conscious input. Those include the maintenance of the body's internal environment, including body temperature.

Upon receiving nerve impulses from temperature receptors in the skin, the hypothalamus acts as a sort of thermostat to keep the body temperature stable. Detecting frigid temperatures, the hypothalamus initiates the previously described shunting away of blood from the peripheral structures like the fingers and toes. It also reduces blood flow to the skin, where superficial blood vessels allow heat to be quickly lost to the environment. Additionally, the hypothalamus sets off a series of involuntary heat-releasing muscle contractions, better known as shivering.

Interestingly, some temperature receptors in the skin "learn" to ignore inconsequential stimuli, which explains why stepping into a hot shower



might be painful at first but then becomes comfortable. The phenomenon is known as thermal adaptation. Something similar occurs on a tactile level when you put on socks. Initially, the brain receives signals from touch and pressure receptors in the skin of the feet and ankles, and you feel your socks being pulled on. Very soon, though, the nervous system begins to ignore these unimportant tactile stimuli, allowing you to

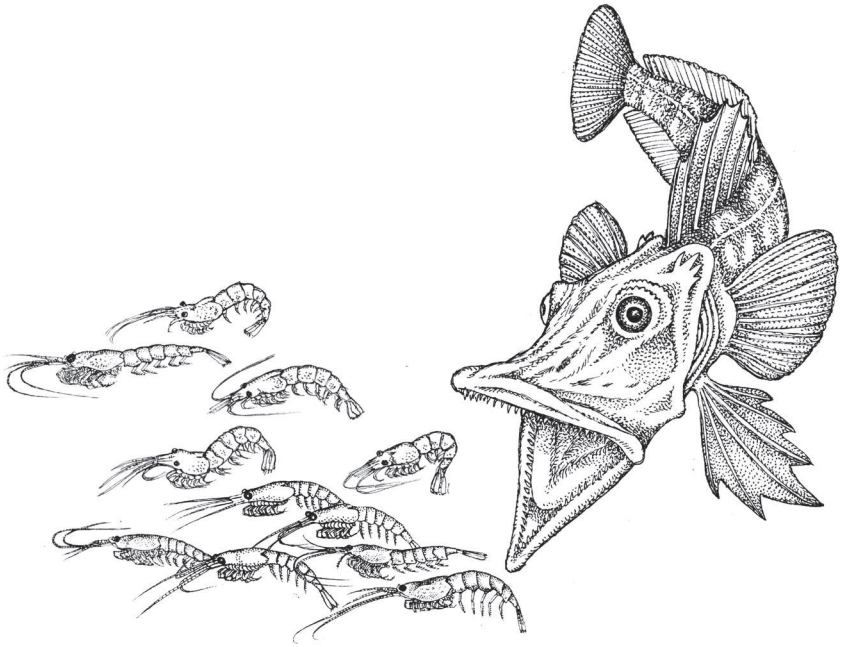
concentrate on more important things, like making sure that you've put on socks that match. Sensory adaptation can also be related to smells or sounds. Fortunately, this process has its limits. For instance, the nervous system doesn't adapt to stimuli that can be harmful, like putting on a sock with a burr inside or increasing blood pressure.

The ability to internally maintain stable body temperature is known as endothermy, and those that exhibit it, like mammals and birds, are endotherms. This ability differentiates them from ectotherms, like fish, amphibians, and most reptiles. These so-called cold-blooded creatures require externally supplied energy (usually from the rays of the sun) to keep their bodies at a temperature at which tissues and organs can function properly.

Regardless of *how* consistent body temperature is maintained, it's important that it *be* maintained. The myriad chemical reactions (that is, metabolic processes) taking place in the body can occur only when things like temperature are held within a very specific range. So how do ectotherms deal with the cold, specifically temperatures that would normally freeze their bodies and the liquids like blood found within them?

As described previously, hemoglobin is an iron-containing molecule whose primary function is to pick up oxygen in the lungs or gills, then transport it and drop it off in the tissues. And, yes, a byproduct of this oxygen/hemoglobin interaction is the distinctive red color of vertebrate blood. But for those of you who might be wondering if there's an exception to the red-blooded vertebrate rule, the answer is also yes, and that blood belongs to the Antarctic icefish (family Channichthyidae). Known to nineteenth-century whalers long before researchers snagged one in 1928, icefish are the only known vertebrates that lack hemoglobin as adults. Because of this, their blood is nearly clear.

I first heard about these unique creatures during my three-semester tenure as an undergraduate marine science major at Southampton



College on Long Island. Howard Reisman, my ichthyology professor there, taught me that icefish blood not only lacked hemoglobin, but it also contained a unique array of antifreeze proteins that allowed the fish to survive in temperatures that would normally freeze a body solid. Similar to the antifreeze in a car radiator, these substances function by chemically lowering the temperature at which freezing occurs. In the icefish, the antifreeze proteins restrict the growth of ice crystals in tissues, *including* blood, and in hollow structures like the heart and blood vessels. This opens some exciting avenues to medical researchers, who are experimenting with using antifreeze proteins to prevent damage to tissues and organs that are stored on ice before their use in transplants and related procedures.

Interestingly, this characteristic led a European food company to patent a strain of yeast that had been genetically modified to produce the very same antifreeze proteins found in icefish blood. In an amusing

twist on the original function, the company currently uses the stuff to prevent crystals from forming in ice cream. More specifically, the edible antifreeze spares frozen dessert munchers from having to deal with the crunchy ice that can form when ice cream's tiny crystals melt and then refreeze into larger, less palatable crystals. The antifreeze proteins work by latching on to the surface of the smaller crystals, thereby preventing them from clustering together into jumbo chunks.

Admittedly, my primary interest in icefish blood had nothing to do with improving mouthfeel for ice cream lovers. Instead, I wanted to know how icefish were able to evolve this weird bit of biology and still obtain enough oxygen to survive. According to University of Alaska Fairbanks icefish expert Kristin O'Brien, the explanation involves their habitat and a related quirk of physics, as well as their anatomy and behavior.

Icefish inhabit the deep waters of the Southern Ocean, also known as the Antarctic Ocean, since it encircles that particular continent. There are relatively few fish species living there and even fewer predators (mostly seals and penguins). Because of this, icefish face little or no competition for the krill, small fish, and crabs they feed upon. They are also ambush predators, which means that their movement consists of short and infrequent bursts of speed. Without much in the way of extended physical activity, their bodies require less oxygen.

The cold water itself offers the hemoglobin-free icefish an additional benefit: it holds more oxygen than warm water. This is because molecules in cold water move more slowly than in warm water. When the molecules move faster, it is easier for oxygen to break free from the H_2O molecule and escape. As a result, cold water ends up hanging on to more oxygen, which is useful for the organisms that require it.

Research suggests that the very first hemoglobin-free icefish ancestors were the result of a mistake—a genetic mutation that occurred sometime

around five million years ago. Fortunately, because of their oxygen-rich environment, this mutation didn't immediately doom the ancient fish to extinction. According to O'Brien, what it *did* do is force an extensive remodeling of the icefish cardiovascular system. This evolutionary tweakage resulted in the fish having four times the blood volume and three times the blood vessel diameter of a similarly sized red-blooded fish, as well as a heart more than five times larger than one might expect. This means that although icefish blood pressure and heart rates are low, the *volume* of blood that leaves the heart with each contraction is high. Additionally, once the blood reaches muscles and organs, extremely dense capillary beds help improve the efficiency of gas exchange. Finally, in one innovative evolutionary twist, icefish have no scales covering their bodies, and so oxygen uptake occurs not just through the gills but also directly through the skin.

So, yes, originally, perhaps icefish ancestors were lucky to have lived where they did. Now, though, they have successfully compensated for the species' lack of hemoglobin—the vital oxygen carrier found in the blood of pretty much every other vertebrate in existence.

While icefish may avoid the risk of freezing entirely through the production of antifreeze proteins, other species survive by *allowing* themselves to freeze. When temperatures plummet, the hearts of frogs like the North American wood frog (*Rana sylvatica*) can stop beating for several weeks at a time. This occurs because they're frozen solid, as are other vital organs, like the liver. Then as spring approaches and air temperatures climb, the frogs thaw out, as do their hearts, soon to resume their prerefrigerated pulsations.

I spoke to Miami University of Ohio biologist Jon Costanzo, an expert on the phenomenon. He began by telling me that while there is a great

deal of public interest in the broader topic of freeze tolerance, only a few researchers are currently working on it. According to Costanzo, the topic peaked in popularity in the 1990s, centering around the cryopreservation of human organs and tissues, but since then research has more or less dead-ended.

I flashed back to a rumor I had heard as a child: Walt Disney's body had been frozen after his death in 1966. Supposedly, it remained in a state of cryogenic preservation in a top-secret facility located beneath Disneyland's Pirates of the Caribbean attraction. I remember being disappointed to learn that, according to his family members, Uncle Walt had in fact been cremated two days after passing away from lung cancer.

But why does freeze tolerance work in wood frogs but not in woodsmen? I put the question to the frozen frog maven, who told me that most creatures' tissues are too damaged by the formation of ice crystals to defrost intact. "Imagine jagged ice crystals forming between the tissues, as well as among and inside cells," Costanzo said. "They tear everything up." So while the buildup of extracellular ice can be problematic, ice forming within the cells themselves is generally fatal.

In addition to causing structural damage from crystallization, freezing leads to excessive cell shrinkage, through loss of liquid water; messes with membranes and other cellular components; depletes energy-containing molecules; and prevents the elimination of cellular waste products, which can accumulate to toxic levels.

So how does the wood frog survive the fatal facts of frost?

"As the wood frog is chilling, it cools down to a temperature below its freezing point," Costanzo told me. "These are woodland frogs, so they've already situated themselves beneath the leaf litter on the forest floor. Of course, there are ice crystals all around, because it's cold out, and these crystals eventually permeate through the frog's moist skin."

Costanzo reminded me that the freezing of liquid water is an exothermic reaction, which means that it releases heat. As a result, the frog's body temperature actually spikes during the early hours of freezing. Its heart rate climbs rapidly as well, nearly doubling, as its heart pumps cryoprotectants out to its body. These are substances that either stop tissues from freezing (like the antifreeze in icefish blood) or prevent damage to cells when they do freeze.

One of these cryoprotectants is actually a very common substance: glucose, the high-energy sugar released into circulation by the liver. As the frog's body freezes, its liver begins breaking down starchy stores of glycogen into glucose. It does so at a tremendous rate, pumping more than eighty times the usual amount of the sugar into circulation. This rush of glucose prevents ice from forming inside cells by allowing water to leave them via a version of our old friend diffusion—this time called osmosis. The water moves from a higher concentration in the cells to a lower concentration in their sugar-saturated surroundings. This prevents the cells from swelling and rupturing when they freeze. We'll learn more about this movement of water in just a bit.

Zoologist Ken Storey has theorized that the glucose release is an exaggeration of the body's fight-or-flight response, in which stress causes the brain to signal the liver to dump glucose into the circulatory system. There, the high-energy glucose molecules can be used as an emergency energy source for things like "fighting" or "flighting." Apparently, a similar alarm goes off when wood frogs begin their transition to frog-sicles.

Recent research by Costanzo and his colleagues focused on another cryoprotectant, nitrogen, and their data suggested that some gut bacteria remain active in their frozen hosts. The bacteria release an enzyme that frees up nitrogen from any urine the frogs have in their system. As with

glucose, nitrogen is thought to protect against freeze/thaw damage, possibly because it freezes at such a very low temperature (–346°F or –210°C).

According to Costanzo, all of this previously described action occurs during the first phase of freezing. After several hours, the initial spike in body temperature subsides and the frog starts to cool down again. Eventually, its heart stops beating and the blood freezes within the vessels. The wood frog remains in this condition for most of the duration of the freezing episode, which can last anywhere from half a day during a cold snap to several months in the parts of the frog's home range that extends into the Arctic circle.

"During this time," Costanzo said, "there's no breathing and no heart function."

I asked him if anyone had determined whether electrical activity in the frozen frog brain ceases as well. A flatlining electroencephalogram (EEG) is used to indicate when someone can be declared clinically dead, and I was curious whether the waking frogs were technically zombies. Costanzo responded with a laugh. He told me that he had heard that the frog's brain flatlines when frozen, but he couldn't point to a reference that might support or refute that particular phenomenon.*

I also discovered that it isn't just circulating cryoprotectants that safeguards the wood frog from the effects of freezing. Another factor appears to be a massive redistribution of water within the amphibian's body.

Normally, water can move in and out of cells through osmosis. Since bodily fluids (like blood and intracellular fluid) are mostly water, it's vital that the levels of stuff dissolved in those fluids remain stable. Otherwise,

* Grad student research project, anyone?

the cells would dehydrate or swell as water passed in and out on its way to equalize the concentration.

In the frozen frogs, osmosis is prompted by an increase in the concentration of glucose throughout their bodies, which means there's more water inside the cells than outside. Once the water leaves the cell, though, it also seems to move outside of the organ itself, and as a result the organs dehydrate during freezing. "The liver and the heart, for example, will lose more than half of their normal water content," Costanzo told me.

"And where does all that water end up?" I asked him.

"In the coelom," the frozen frog maven answered, "the body cavity where the guts are stuffed."

I tried to envision it. "So how much water are we talking about here?"

"If you were to freeze a wood frog and then dissect it, it would look like a snow cone in there."

I remember thinking to myself that this was clearly a scientist who had seen such a frog-flavored frozen treat, and a moment later he confirmed my suspicion. With an enthusiasm that can be *fully* appreciated only by someone who has, for example, eaten a human placenta in the name of science, I listened as Costanzo described how his team had carefully scooped out and weighed the frosty frog ice to determine what percentage of the total body weight it represented.

It's worth noting that surviving dehydration isn't entirely atypical for frogs. Terrestrial frogs and toads often show a tolerance to drying out. It's possible that evolution has simply enhanced that system to improve freeze tolerance. Ultimately, Costanzo and his collaborators concluded that this process is a way for the frog to freeze a lot of its body water without risking as much organ damage, since most of the ice would accumulate outside of these vital areas. When spring rolls around and the frog thaws out, the resulting water returns to rehydrate the cells and the excess glucose returns to the liver to be processed back into glycogen and stored.

Interestingly, it's not clear to Costanzo, or to any other researchers, what exactly stimulates the heart to start beating again upon thawing. There's no particular temperature or particular time during the thawing episode at which the heartbeat kicks in. But whatever its stimulus, the reanimation process is something that did *not* occur in lab studies on a related terrestrial genus, the northern leopard frog (*Lithobates pipiens*).

"There were a couple of heartbeats after thawing," Costanzo said. "And it looked like [the heart rate] was going to pick up and take off. But then it just crapped out." He told me that there wasn't a clear explanation for the different reactions in the two genera but that it likely relates to an absence of the protective adaptations that evolved in *Rana sylvatica*.

I asked Costanzo if defrosted wood frogs appeared to suffer any ill effects. He explained that while there is no evidence that freezing affects the frogs' longevity, it *does* affect mating performance, since newly thawed frogs show little interest in the opposite sex.

In lab experiments performed on male wood frogs placed in plastic testing arenas, Costanzo and his team showed that test subjects had little interest in sex for up to twenty-four hours after thawing. And even after that, they competed badly in a lab setting against control frogs that had never been frozen. One hypothesis is that the bodies of the thawed frogs are too busy getting rid of copious amounts of glucose to deal with the rigors of mating. Another significant negative factor could be that while some of the glucose used in the freezing process is derived from glycogen stockpiled in the liver, additional glycogen comes from the breakdown of the frog's own body. This form of autocannibalism can reduce the mass of hop-generating leg muscles by up to 40 percent during hibernation.* As

* A similar effect can be seen during starvation, as the body literally feeds on itself, breaking down structural proteins in skeletal muscle and elsewhere and converting the products of that breakdown into glucose. This produces the characteristic wasted appearance of starvation victims.

a result, newly thawed male frogs may be physically incapable of chasing down females—until, that is, their limb muscles are restored to their former size and function.

The temporary dent in the thawed-out wood frogs' sex life is an example of the kind of trade-offs associated with *all* adaptations. For example, closed circulatory systems may transport more gases, waste, and nutrients, but they're more expensive (energy-wise) to maintain. Additionally, their complexity makes them more susceptible to breakdown. This is the hallmark of evolutionary biology: organisms that gain an advantage will almost certainly pay a price. Arguably, the most famous example of a trade-off relates to sickle cell disease, the most common of inherited blood disorders.

As many of us learned in high school biology class, genes are tiny sections of our genetic blueprint that control the development of one or more traits (like hair color or blood type). They come in pairs, with each gene located on one of two similar (i.e., homologous) chromosomes. Humans have twenty-three pairs of homologous chromosomes, and in total these contain somewhere between twenty thousand and twenty-five thousand genes. You may also remember that we get one chromosome in each pair— and therefore one gene in each pair—from our mother and the other from our father. This is something that occurs when one of Dad's sperm cells fuses with one of Mom's eggs to produce a single cell that multiplies, develops, and differentiates into us.

As it turns out, the genes that lead to sickle cell are a problem only if someone has two copies of the gene for the disease. And in some ethnic groups, it's incredibly common to possess *one* copy. Approximately 8 percent of African Americans carry the sickle cell trait, meaning that they have received the mutant hemoglobin gene from either their mother

or their father—but *not* both. These "carriers" typically live normal lives, with no sickle cell–related health woes.

When a person is born with *two* of the mutant hemoglobin genes, though, serious problems result due to the production of an abnormal form of hemoglobin called hemoglobin S.* Unlike normal hemoglobin, hemoglobin S forms long fibers that cause the red blood cells carrying them to twist into rigid crescent moon (or sickle) shapes. These sickle cells are able to carry less oxygen than cells containing normal hemoglobin, and as a result, less oxygen gets delivered to tissues.

The *most* significant problem is that the deformed sickle cells are not malleable enough to slip into tiny capillaries like normal red blood cells do. Instead, they end up obstructing those vessels. This logjam blocks the blood supply to certain areas of the body, like the extremities. It also stimulates pain receptors, the body's way of alerting us that something is wrong. Eventually, this blockage leads to life-threatening damage to organs, like the kidneys.†

Frequently, my anatomy and physiology students asked me why natural selection hasn't eliminated the mutant hemoglobin gene over time. Their rationale is that prior to modern medicine, carriers of the mutant hemoglobin gene were much less likely to survive to adulthood, and therefore less likely to pass on their defective genes to subsequent generations. So why then, they wondered, didn't that mutant gene disappear over time? As it turns out, the answer relates to the most severe of evolutionary trade-offs.

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* If both parents carry the defective gene, their offspring have a 25 percent chance of picking up two defective genes themselves and developing sickle cell disease.

† Sickle cell disease can manifest itself in various ways, including tissue damage and vascular obstruction. Sickle cell anemia, in which tissues do not get enough oxygen, is one such manifestation. So the two terms are not synonymous.

The first clue is that sickle cell disease is most common in people whose ancestors came from Africa, the Arabian Peninsula, the Mediterranean, and South and Central America. These are regions where the incidence of malaria is high—and as it turns out, sickle cell carriers are more resistant to malaria than people who do not carry the mutant gene. Therefore, in places where the mosquito-transmitted killer is often the number one threat to human life, having a single copy of the mutant hemoglobin gene actually *increases* reproductive fitness, since more carriers avoid dying from malaria and pass their genes on. For this reason, the mutation remains in the gene pool. Unfortunately, the cost of this particular benefit is lethally steep for those who carry *two* copies of the mutant gene and who develop sickle cell disease.

Such is the nature of trade-offs.

As we've seen, low ambient temperature (a.k.a. the air temperature of the immediate surroundings) can present a significant hurdle to survival, and this has led to some particularly notable evolutionary trade-offs. Some species seasonally migrate enormous distances to warmer climes, while others have evolved thick coats as insulation from the cold. Still others, like icefish and wood frogs, have evolved extreme responses to frigid conditions. Far more frequently, though, animals undergo winter changes that fall into the realm of torpor and hibernation, both of which present major challenges to vertebrate hearts and circulatory systems.

Torpor, a phenomenon something akin to "hibernation lite," occurs when there is a controlled and pronounced reduction in metabolic rate—the rate of energy expenditure by the body. Bouts of torpor generally last for less than a day, while hibernation can be thought of as multiday bouts of torpor, interrupted by periodic arousals.

For a long time, scientists thought that torpor was a mammalian adaptation, but recent studies point to something quite different. I spoke to Miranda Dunbar, an associate professor of biology at Southern Connecticut State University, whose research focuses on bat hibernation. She explained that many experts now see mammalian torpor as a vestige of an earlier evolutionary feature.

While mammals are endotherms, capable of generating and maintaining their own internal body temperatures, this was a relatively late-evolving feature in the vertebrates. Until roughly a quarter billion years ago, most if not all backboned creatures were ectothermic, a condition in which the regulation of body temperature depends on external sources. Like today's fish, amphibians, and reptiles, those ectotherms presumably coped with low ambient temperatures by situating their bodies to maximize the amount of heat they can gain from their environment. Anyone who has seen a turtle sunning itself on a rock has seen an ectotherm in action. The same thing can be envisioned for a chilly chameleon or a cool cobra.

As some reptiles began to evolve into what we now call mammals, newly acquired adaptations like torpor and heterothermy (the ability to adjust body temperature to match ambient temperature) stuck around. While endotherms are less affected by ambient temperature than their ectothermic kin, they need a lot of energy to power their metabolic processes and keep their body temperatures stable. When winter comes and air temperatures drop, the energy requirement only increases—at the same time that food becomes scarce.

"So," Dunbar told me, "during the winter, with little to no energy available, the animals enter into a torpid state that can be prolonged seasonally into hibernation."

I wondered how hibernation might have originated in bats, given that their ancestors apparently evolved in the tropics.

"It does seem counterintuitive," Dunbar told me, "to think that bats would be using hibernation and torpor in the tropics, but that turns out not to be the case."

She explained that in very hot climates, small mammals like bats evolved the ability to turn off the chemical reactions that would normally help them maintain stable body temperatures. Because the environment already provides a source of heat, they don't need to expend energy from nutrients to stay warm. This slowdown of metabolic processes is actually similar to what happens when bats go into torpor in colder climes. Presumably, as they moved out of the tropics, evolution simply tweaked these abilities to deal with a different temperature extreme.

Although bats are famous for hibernating in thermally stable places like caves and mines, many of them can make do almost anywhere. "We've seen them hibernating under loose tree bark and in tree hollows," Dunbar told me. "In man-made structures and even on the ground, underneath leaf litter. But probably the most bizarre example are bats in Japan that hibernate in the snow."

In a recent paper on the Ussurian tube-nosed bat (*Murina ussuriensis*), researchers noted that snow-hibernating bats were typically found only after the winter thaw had begun. In twenty-one out of twenty-two instances, they were discovered alone in small cone-shaped depressions in the melting snow. All of them were curled up in spherical or semispherical postures, which are optimal for body heat conservation. If authors Hirofumi Hirakawa and Yu Nagasaka are correct in their conclusions, this is only the second recorded instance of a mammal hibernating in the snow. Polar bears (*Ursus maritimus*) are the other, although whether they're actually hibernating is up for debate.

Male polar bears are active year-round, but although females come close to hibernation as they nestle into winter dens with their cubs, their

body temperatures never make the extreme drop normally seen during this physiological state. The tweak appears to be an adaptation that allows the females to nurse their cubs. So even though adult female bears eat nothing during this period of up to eight months, and their metabolic rates drop (e.g., heart rate can decrease from forty to eight beats per minute), true hibernation requires a drop in body temperature for an extended period. It is likely, then, that tube-nosed bats can be considered the only card-carrying snow hibernators.*

Temperature aside, this dip in metabolic rate is an important feature of hibernation, as it allows bats and other hibernators to use less oxygen and nutrients over the course of the winter. Just as the bear's heart rate drops precipitously, a bat's heart rate can go from five hundred to seven hundred beats per minute down to as low as twenty. During this time, just as in cold humans, blood is diverted from the limbs into the core of the body, to supply and warm the most vital organs. A significant difference, though, is that the hearts of hibernators have evolved to function at low temperatures and low oxygen levels that would cause fibrillation—a disastrously rapid, irregular, and unsynchronized contraction of the heart's muscle fibers—in nonhibernators like humans.

Since there's no food to be found, the nutrients that hibernators do use come from an accumulation of a substance known as brown fat, which in bats is stored in small deposits between the shoulder blades. Unlike most fat, brown fat can be broken down through a chemical reaction that produces heat *directly*, without using up energy on intermediate steps. Brown fat is also found in newborn humans. Infants are especially vulnerable to the cold, because it takes a while for a newborn's temperature regulatory mechanisms (like the ability to shiver) to get up and running.

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* A little-known fact about hibernators is that they periodically awaken—an energetically costly behavior, but necessary in some species to get rid of metabolic waste.

What's more, because babies are small, their body surface area is relatively large—the same surface-to-mass problem that bats and other small animals run into. As a result, babies can lose heat around four times faster than adults. Premature and low-birthweight babies are especially prone to temperature regulation–related problems because they have less brown fat to burn. This is part of why preemies often spend the first weeks of their life inside warm incubators.

The presence of brown fat in babies also explains their chubby phase, which lasts until most of this tissue gets burned up. In adult humans, very little (if any) brown fat remains, with small amounts generally limited to places like the upper back, the neck, and the vertebral column.

In bats and other hibernators, brown fat is rationed over the entire hibernation period, metabolized to release heat whenever the hibernator's core body temperature decreases past a certain set point. Problems can arise when hibernating animals are aroused unexpectedly by disturbances (such as inquisitive humans). Since a small portion of brown fat is burned during every arousal, there is real threat that the animals will starve to death if their fat stores are burned up before improving weather conditions allow them to seek alternative forms of energy (i.e., food).

One interesting side effect of hibernation is that it causes animals to live longer, and to age more slowly. Bats can live for over twenty years in the wild, an unusually long span for such a small mammal, the vast majority of which have extremely short life spans, typified by the pygmy shrew (*Sorex minutus*). These tiny predators weigh in at around one-fifth of an ounce and burn through their hyperactive lives in around eighteen months.

Miranda Dunbar told me that she'd recently read a study published by the Committee on Recently Extinct Organisms at the American Museum

of Natural History, which concluded that over the past five hundred years, there have been sixty-one species of mammals with confirmed extinctions.

"Of those, only three were hibernating bats," she said. "So they must be doing *something* right."

The creatures outside looked from pig to man,
and from man to pig, and from pig to man again;
but already it was impossible to say which was which.
—George Orwell, *Animal Farm*

[7]

Ode to Baby Fae

We've now learned quite a bit about animal hearts and their associated vascular circuitry. Although the anatomical differences between some of these systems appear vast, across the animal kingdom their functions are roughly equivalent—to pump blood, or its invertebrate equivalent, around the body. Our attention will soon turn inward, to our own hearts. But before we do, let's see how similarities of anatomy and function have led to additional, unexpected connections between nonhuman and human hearts.

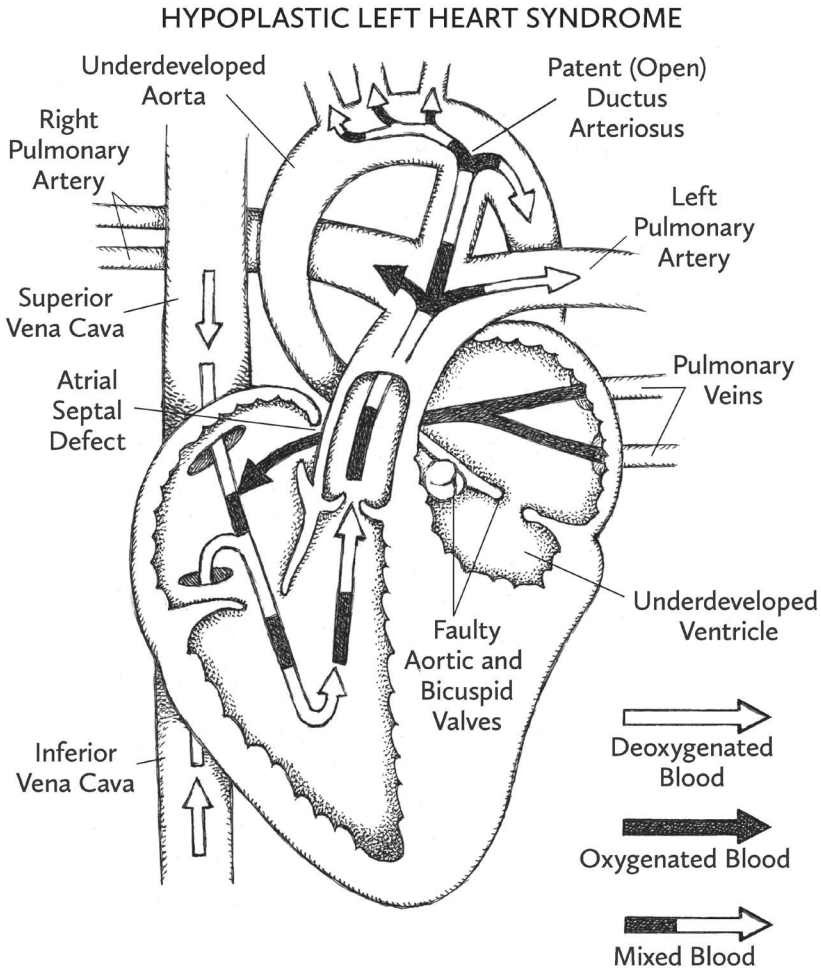
In the early 1980s, Leonard Bailey (1942–2019), a cardiothoracic surgeon at Loma Linda University Medical Center in California, began experiments in which he transplanted lamb hearts into baby goats. Eventually, his subjects not only survived to adulthood but they were able to reproduce and have their own "kids." This encouraged Bailey and his team, who hoped that they might someday use the same technique for transplants involving a very specific subset of human newborns—namely, those who had been given no chance of survival due to what were at

the time inoperable heart defects. In this case, the donor hearts would come from baboons, since they're genetically, developmentally, and physiologically similar to humans. From a cardiovascular perspective, baboon hearts are nearly identical to human hearts, and, crucially, they even have similar A, B, and AB blood types, though type O is rare.

In October 1984, Bailey's colleague, neonatologist Douglas Deming, contacted the mother of one such baby and told her that there was a transplant protocol that might save her child. After traveling from her home in Barstow, California, to Loma Linda and meeting with Bailey, the young woman initially wondered if he was a mad scientist. But after he spent long hours carefully reviewing his previous research with her, the desperate mother gave her permission for the surgery, knowing full well the potential for heartbreak.

The child who would become known to the world as Baby Fae was born on October 14, 1984, with a congenital heart defect known as hypoplastic left heart syndrome (HLHS). Invariably fatal at the time, HLHS is characterized by an underdeveloped left ventricle and faulty or completely closed mitral (a.k.a. bicuspid) and aortic valves. The symptoms include difficulty breathing and feeding, as well as the blue or purple tint to the skin, lips, and nails that is the hallmark of an inadequate oxygen supply.

The surgical team chose the most compatible of six baby baboons that were available to be donors, and on October 26, the surgery was performed at Loma Linda University Medical Center. A team of doctors removed the baboon heart in a separate ICU operating room, placed it in a bath of cold saline, and carried it to the room where Baby Fae was surrounded by a well-coordinated surgical team led by Bailey. Baby Fae's heart, which was in terrible condition, was removed, and the donor heart was placed into her chest. According to immunologist Sandra Nehlsen-Cannarella,



one of the doctors on the surgical team, it fit perfectly. Bailey and his colleagues efficiently sewed the heart into place with no setbacks. Then the big moment came as they rewarmed the baby and let the blood flow through the newly implanted heart. Moments later, it began beating.

"There wasn't a dry eye in the room," Nehlsen-Cannarella told filmmakers for the 2009 documentary *Stephanie's Heart: The Story of Baby Fae*. "We were all just choked up to hear that heartbeat." She added that nothing about the heart looked odd or reminiscent of its previous owner. "It looked like a perfectly normal human heart," she said. "A heart is a heart."

But as Baby Fae recovered and the doctors who cared for her took turns camping out in her room, something else was taking place. The story had become a worldwide media sensation, complete with hundreds of picketers at the hospital and outside Leonard Bailey's home. The protesters questioned the ethics of transplanting a baboon heart into a human, taking all sorts of angles, from pro–animal rights to anti-transplants. What's more, after reporters discovered the identity of Baby Fae's parents, they began hounding them around the clock and reporting on completely irrelevant and borderline slanderous issues related to their backgrounds. Bailey and his team were also singled out, with their sincere attempts to save a dying baby becoming buried under a barrage of claims that they had performed the surgery only for the publicity it was now generating. Thankfully, the media storm also generated sympathetic feelings among some, and Baby Fae's young mother was soon receiving hundreds of letters of support from the public.

Within a few days, Baby Fae was awake, off her ventilator, and eating. Her medical team and her parents were ecstatic. Of course, as was typical for transplant patients, she was also being treated with an immunosuppressant, a relatively new one called cyclosporine, to prevent her body from rejecting her new organ.

Near the end of the second week, postsurgery, problems began to develop as Baby Fae's body began showing signs of what Bailey and his team had first assumed was a "rejection episode." This is a common enough occurrence after organ transplants that the physicians had expected it, and they responded accordingly, stepping up immunosuppression. But when things did not improve, Bailey's team began to suspect that this was actually an autoimmune response—a situation in which the body's immune system actually attacks its own healthy cells and tissues. In this case, what they were now fighting was a body-wide shutdown of Baby Fae's organ systems.

Baby Fae passed away just shy of three weeks after the transplant, on November 15, 1984. At a press conference, Bailey opened by grieving the loss of a precious life and said, "Her unique place in our memories will derive from what she and her parents have done to give rise to a ray of hope for the babies to come."

Although the actual cause of Baby Fae's autoimmune response and subsequent death was initially a mystery, Bailey later disclosed that it was due to mismatched blood type between the human patient and the baboon donor—Baby Fae had type O blood, and the donor baboon had type AB. Bailey called this "a tactical error with catastrophic consequences."

"If Baby Fae had the type AB blood group, she would still be alive today," he told the *Los Angeles Times* in 1985.

He explained that the decision to perform the transplant was based on the mistaken belief that blood type incompatibility wouldn't be much of a problem, and could be circumvented by the use of immunosuppressant drugs. Unfortunately, this turned out to be a tragic error for reasons that will be discussed more fully in an upcoming chapter on blood transfusions.

Despite the tragedy of Baby Fae's death, her case was the beginning of what Sandra Nehlsen-Cannarella referred to as a "revolution in transplantation." Baby Fae's story served to inform the public about the fate of infants with fetal heart abnormalities, and so it also drove home the desperate need for organ donors of all ages. As a result of an increase in neonatal heart donations, Bailey's team soon moved away from what he termed trans-species transplants (and now more commonly known as xenotransplants) and on to neonatal human-to-human transplants. He was able to perform 375 human-to-human heart transplants at Loma Linda University Children's Hospital between 1984 and 2017.

Other researchers carried on xenotransplant research, however. And although primate hearts are indeed similar to human hearts, scientists

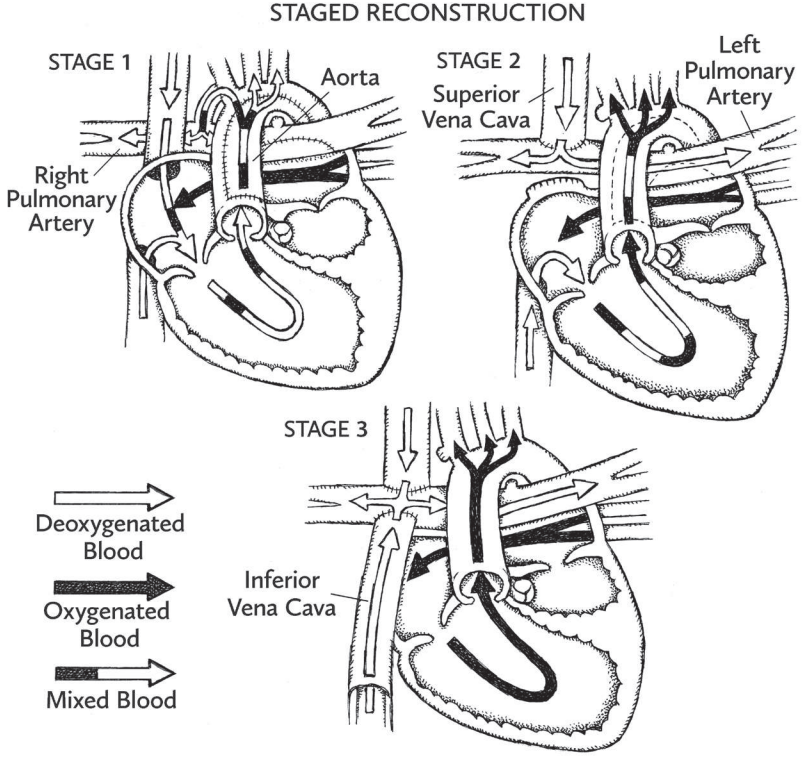
ultimately determined that they were not a good donation option. The primary reason is that primates (including baboons, chimps, and gorillas) do not produce many offspring, thus limiting any potential supply of their organs.

What researchers *did* decide was that pigs would work. Not only are their hearts very similar to human hearts in size, anatomy, and function, but female pigs can produce large numbers of piglets. While there is a problem with tissue incompatibility, that issue is being addressed by efforts to genetically alter experimental pigs using the genome editor CRISPR. Not only can this engineering technique be used to prevent pig organs from being rejected by the human immune system, it can also strip out the genetic sequences that lead to porcine endogenous retroviruses (PERVs) that could potentially be transmitted to humans.* Recently, researchers have started transplanting these genetically modified pig organs into nonhuman primates, and there is an expectation that preclinical studies would begin in 2021 or soon after.

Today, the prognosis for newborns suffering from hypoplastic left heart syndrome has improved tremendously from 1984. In addition to the options of human-to-human heart transplants and immunologically safe xenotransplants, a series of three remarkable heart surgeries (together known as a staged reconstruction) can be performed.

During the first step in the procedure, which takes place within several days of birth, the right side of the heart, which usually receives deoxygenated blood before sending it on to the lungs, is surgically converted to carry out the role normally performed by the left side of the heart—that is, receiving oxygenated blood from the lungs and pumping it out to the body. Doctors use surgical patches, grafts, and other

* Transmission of primate viruses to humans would be a similar concern if baboon hearts had continued to be transplanted.



modifications* to ensure that enough blood gets sent to the lungs that the newborn can survive until the second procedure.

In the second stage of the surgery, which occurs within six months of birth, the superior vena cava is reconfigured to bypass the heart completely, bringing deoxygenated blood directly from the upper body to the lungs. This partially frees up the right side of the heart for its new job.†

Finally, when the child is between one and a half and three years of age, the inferior vena cava is remodeled. As a result of these surgeries,

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* More specifically, a connection is formed between the left atrium and the right atrium, and the aorta is connected to the right ventricle.

† The superior vena cava (which brings deoxygenated blood from the upper body to the right atrium) is disconnected and attached directly to the pulmonary artery (which normally brings deoxygenated blood from the right ventricle to the lungs).

all deoxygenated blood returning from the body is sent directly to the lungs, and the right ventricle can fully take on the role of the left ventricle, pumping oxygenated blood out the aorta to the body!

As amazing as lifesaving surgical procedures like staged reconstruction are, just as incredible is the prospect of using a ready supply of genetically altered pig hearts and other organs to help eliminate the long and often fatal transplant waiting lists that currently exist.

So how did our knowledge of the heart advance so far?

As readers will soon see, the short answer is: we were slow learners.

PART 2

What We Knew and What We Thought We Knew

A NOTE FROM THE AUTHOR

Ancient interpretations of the anatomy and physiology of human organ systems are as surprising as they are variable. They can also be quite confusing. A primary reason for this is the fragmentary nature of ancient medical texts and papyri. Some of them are tattered pieces of much larger works. Others are compendiums of information written by multiple authors, sometimes working in different centuries and often contradicting each other.

What's more, none of this information can be accessed directly: all of the information available to us comes by way of modern translations. Many of these works describe intricate structures, like veins, arteries, and nerves, and complex conditions, like angina and myocardial infarction, and the job of a translator is subjective, an attempt to accurately interpret words from an ancient language and rephrase them in another. Doubtless, not everything makes it through as originally intended.

There is also the inescapable fact that ancient physicians and scholars got a lot wrong. They were employing rudimentary instruments, when they had them, and working within stringent social and religious boundaries. What's more, many of them were not locked into specializations, as are those of us who work in the sciences today. The ancient scholar-physicians wrote poetry, commented on political and social issues, and were experts in other fields of science, like physics and math. Given these differences, it is far wiser to appreciate the things that the ancient physicians got right rather than judge what they got wrong. We can also take some of these mistakes as a reminder of the dangers inherent in lockstep reasoning. Recycled by scholars, teachers, and physicians, without critique or revision, ancient medical knowledge was taught and practiced by rote, and, as a result, much of it went uncorrected for centuries.

All we know is still infinitely less than
all that remains unknown.
—William Harvey,
Exercitatio anatomica de motu cordis
et sanguinis in animalibus

[8]

Heart and Soul: The Ancient and Medieval Cardiovascular System

When the ancient Egyptians prepared human bodies for burial, they removed each of the organs in turn. The heart, known as *ab* (sometimes *ib*) and *haty*, was treated with reverence during embalming procedures, for it was believed to hold a record of all of the deceased's good and bad deeds. It was preserved in a jar, or placed back inside the body so that it could be weighed in the afterlife against a feather of Ma'at, the goddess of truth and justice, who would judge whether its owner had lived virtuously.* The brain, on the other hand, experienced no such funerary weigh-in. Instead, it was unceremoniously yanked out of the nose with a hook and discarded—a clear indication that the ancient Egyptians thought little of its function or importance.

If we place ourselves into the mindset of the ancient Egyptians, the heart as the seat of the soul makes perfect sense. Writing on the topic in

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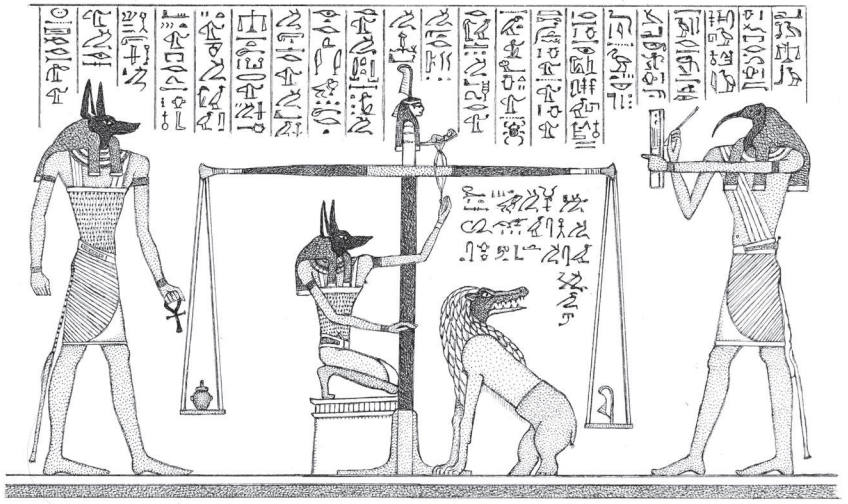
* If the heart weighed less than the feather of Ma'at, the deceased went on to live forever in the afterlife. If it weighed more, it was immediately eaten by a monster named Amam ("The Devourer"), waiting at the base of the scale.



1978, University of Cambridge historian Roger K. French rationalized it this way: Living things were warm. They breathed, and they moved, both innately and in response to external changes. The heart, too, was warm, and it moved. That movement was innate, could be related to breathing, and clearly reacted to external changes—speeding up, for example, when a person was placed in danger. "The heart and its associated vessels were central to the physiology of the living body in Egypt," French wrote. "The pulse was the heart 'speaking' through the vessels; the vessels carried from the heart the secretions and humours necessary to every part; the vessels were responsible for pathological conditions; and they carried the 'breath of life' and the 'breath of death.'"

For those philosophers looking for the seat of the soul or souls, the heart was the answer.

Some modern translations of the Egyptian *Book of the Heart*, originally dating from around 1555 BCE, indicate that Egyptian physicians may in fact have had an impressive grasp of heart-related pathologies, like heart attacks and even arterial aneurysms. In such aneurysms, weakened arterial walls balloon out dangerously. Generally, they occur in medium to large arteries, with the most commonly affected vessels being the thoracic

and abdominal aortae, and the iliac, popliteal (behind the knee), femoral, and carotid arteries. Arterial aneurysms are often called "silent killers" because of their asymptomatic nature and due to the fact that ruptured aortic aneurysms (and a closely related condition known as aortic dissection) kill 75 to 80 percent of those stricken. An aortic dissection is a tear in the inner lining of the aorta resulting in a leakage of blood, which then accumulates between the tunics (layers) of the artery. The buildup of pressure leads to a high risk of rupture. It's believed that 90 percent of deaths from ruptured aortic aneurysms and aortic dissections could be prevented through ultrasound screening, which can detect the bulging vessels before they rupture.*

Historian and author John Nunn sounded a word of caution, however, regarding the ancient Egyptians' knowledge of aneurysms and other such specific maladies, explaining in his book *Ancient Egyptian Medicine* that medical papyri "are difficult to interpret in terms of modern concepts of cardiology," due both to differences in conceptual frameworks and to the difficulty of translating hieroglyphs with precision.

But although the ancient knowledge of aneurysms remains conjectural, on more firm ground is the belief by Egyptian physicians that air drawn in through the nose passed through the lungs and into the heart, where it was pumped out to the body in arteries, creating the peripheral pulse. Admittedly, the concept sounds strange, but Nunn pointed out that, if for air we substitute oxygenated blood, then "the whole concept is remarkably close to the truth."

Because Egyptian medical information was held in high esteem by other cultures, their beliefs about the circulatory system were subsequently adopted. Significant interactions between the ancient Greeks and Egyptians

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* Notable deaths from these aortic conditions include physicist Albert Einstein and actor George C. Scott, who died of abdominal aortic aneurysms. Comedians Lucille Ball and John Ritter died from aortic dissections.

were both direct (for instance, the Greek Ptolemaic dynasty ruled Egypt for 275 years) and indirect (many Egyptian literary works were translated and adapted by the Greeks). Because of this, there are numerous similarities in how these cultures came to view the heart.

Hippocrates (c. 460–c. 377 BCE), who is often called "the Father of Medicine" and who lends his name to the modern Hippocratic oath, was the leader of a medical school on the Greek island of Kos. Celebrated throughout history for his philosophical approach and clinical observations, Hippocrates did much to remove medicine from the realm of magic and superstition. Before Hippocrates, the belief was that all illnesses were a form of punishment by the gods and the only way to prevent or get rid of them was to appease the gods with praise, gifts, sacrifice, and prayers. Hippocrates, though, was heavily influenced by Egyptian medicine, which stressed concepts like cleanliness and a healthy diet. His reliance on the ancient Egyptians may also explain his belief in an air-filled system of arteries. He held, for instance, that the trachea was an artery—which explains its original name, the *arteria aspera*.

Whether or not Hippocrates was in accord with the Egyptian belief that the heart was the seat of consciousness is unclear. His works express seemingly contradictory stances, sometimes identifying the heart, sometimes the brain. One possible explanation for this is the fact that historians have found it difficult to determine which of the many works attributed to Hippocrates were actually written by him and which of them originated with his followers and colleagues.

What we know for sure is that in early ancient Greece, shortly before Hippocrates began his work, natural philosopher and medicinal theorist Alcmaeon of Croton developed a set of truly groundbreaking views on how the body functions. Sometime between 480 and 440 BCE, he hypothesized that the brain was the most important organ. Not only was

it the source of intelligence, he said, but it was integral to the functioning of sensory organs like the eyes. This stance may have made Alcmaeon the first craniocentrist—a believer that the workings of the body center around the head and what's in it. For many centuries, though, craniocentrism would remain in the shadows of cardiocentrism.

One influential cardiocentrist was the Greek philosopher Aristotle (384–322 BCE). Although he is known as "the Father of Biology," he certainly did not earn the title for holding accurate knowledge of organs like the heart, brain, and lungs. Far more likely it was because of his pioneering work in the field of taxonomy. Aristotle made detailed observations about hundreds of plants and animals, dissecting many of them and using the characteristics he observed (e.g., blood or no blood) to pioneer a system by which all living things could be classified.

In one such observation, Aristotle watched the action of the heart in a live chick embryo. He noted that it was the first organ to develop, and hypothesized that large animals like humans had a three-chambered heart, with right, left, and center cavities.* According to Aristotle, medium-sized animals had two chambers while small animals had but one.

Aristotle also believed that the heart was the most important organ in the body: the seat of intelligence, emotions, and the soul.† With no knowledge of the nervous system, Aristotle claimed that the heart served as a hub for all incoming sensory information, with signals traveling to it by way of blood vessels from organs like the eyes and ears. As for the brain, Aristotle hypothesized a far less lofty role. He believed that it acted very much like a modern radiator, whose job was to cool the heart.

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* One explanation for this may be that he did not consider the right atrium to be a separate chamber but merely a widened junction of the vena cava as it connected to the heart.

† The Athenian philosopher Plato (born around 425 BCE) believed that the soul had three distinct parts: The *logos* existed in the head and dealt with reason, while the *thymos* (also spelled *thumos*) resided in the chest and was concerned with anger. The lowest soul, *eros*, was found in the stomach and liver, where it controlled the body's baser emotions and desires.

Half a millennium after Aristotle, Claudius Galenus (129–216 CE), better known as Galen, was born in Pergamon, a city on the Aegean coast. Once part of the ancient Greek world, during Galen's time it was a part of the Roman Empire.* The son of a wealthy architect, he studied to become a physician and philosopher. It would be difficult if not impossible to overstate Galen's impact on the field of medicine, since his teachings—and the teachings of those who followed him blindly—would hold sway for roughly the next fifteen hundred years.

Influenced by Hippocrates, Galen traveled widely as a young man and was exposed to an array of medical practices in places like Alexandria, Egypt—a center for scientific and medical advancement. Like Aristotle, whose principles Galen also followed, he was fully convinced of the existence of the soul and its intimate relationship with the organs, which he would soon be observing firsthand.

While working as a physician at a Roman gladiatorial school in his hometown, Galen became fascinated with internal anatomy. Presented with a parade of gashes, slashes, and traumatic amputations, Galen found that he could curb blood loss by applying astringents, like vinegar, to the wounds. These compounds caused blood vessels to contract, thus reducing the flow of blood escaping from them. Galen also used wine-soaked bandages and spice-laden ointments to facilitate the healing process and curb infection. Though he had no clue what infections were or what caused them, the alcohol in these treatments likely helped curb bacterial growth.

Galen referred to wounds as "windows into the body," but after moving to Rome around 160 CE, he found his view clouded by the city's prohibition on human dissection. It was a taboo that had also existed in ancient Greece, except for a short but illuminating period in the early third century BCE. It was then that two physicians, Herophilus of Chalcedon

* Now in Turkey.

and his younger contemporary Erasistratus of Ceos were able to conduct vivisections on condemned criminals. Among the discoveries made by Herophilus were that the heart has valves, whose one-way function was subsequently demonstrated by Erasistratus. The younger scientist also described the heart as a pump, and both men made the anatomical and functional distinction between veins (*phlebes*) and arteries (*artēriai*), though they did not stray from the mistaken belief that arteries were filled with air.*

There can be no argument that a ban on human dissection severely hindered the advancement of anatomy and physiology in ancient Greece and Rome. With few exceptions, the prohibition continued throughout the Western world for roughly eighteen centuries after Herophilus and Erasistratus, until it was finally eliminated in fourteenth-century Italy.

In 1992, Yale University historian Heinrich von Staden addressed the question of why the ancient Greeks considered human dissection to be a taboo, concluding that there were two major factors. The first was a set of formidable cultural traditions related to the contaminating and polluting power attributed to corpses. For example, anyone coming into contact with or even looking at a corpse, including the body of a loved one, had to go through a lengthy process of purification, which ranged from bathing to applying various substances to the body (like blood or clay), to fumigation and confessions. Similar rituals were performed at the deceased's dwelling, hearth, water supply, and place of interment. Anyone, therefore, who performed a human dissection would have been acting far beyond culturally acceptable boundaries, polluted and polluting to the point of criminality.

The second factor contributing to the Greeks' human dissection taboo, von Staden wrote, was a set of negative connotations related to cutting

* Their discoveries went far beyond those related to the heart and circulatory system. Herophilus studied the brain, cranial nerves, liver, and womb. He also identified the four layers of the eye, including the initial descriptions of the cornea, choroid (a.k.a. the white portion of the eye), and the retina.

human skin. The Greeks, he said, considered skin to be "a magical symbol of wholeness and oneness." Presumably there were exceptions during times of war, when it was okay to pierce, slice, and dice one's enemies.

Hundreds of years later, and faced with similar Roman taboos, Galen was forced to make inferences about the human circulatory system by carrying out experiments on animals. Working on monkeys like macaques, as well as pigs, sheep, goats, and dogs—often in public—his renown grew. To his credit, Galen, like his predecessors, described the heart as a pump with valves, and he disproved the long-held belief that arteries carried air and not blood. He did so by opening up a dog's artery underwater. Since blood and not air could be seen escaping, it proved conclusively that Egyptian and Greek physicians had been wrong in their contention that arteries were part of the respiratory system.

Galen studied additional organ systems as well. He was able to determine the basic functions of the urinary bladder and kidney, and he tested and distinguished the functions of cranial and spinal nerves, thus providing evidence that the brain, rather than the heart, was the control center for what would become known as sensory pathways and motor pathways—the routes taken by information coming from and headed out to the body, respectively.

Mostly, though, what resulted from Galen's legacy were problems—longstanding and well-documented problems. In hindsight, some of the mess can be chalked up to Galen's inability to obtain human cadavers to dissect. For example, his description of kidneys was based on dogs, and it turns out that the position of canine kidneys, with the right kidney higher than the left, is actually reversed in humans.

Far more serious, however, were the errors rooted in Galen's strong beliefs about the *functioning* of the human body. For starters, Galen believed that venous and arterial blood were separate entities, with different origins. Venous blood, he said, was dark and thick. Produced

by the liver from ingested food, it flowed to the right side of the heart, which in turn pumped it out to supply the body with nutrients. Some of the blood, however, passed from the right side of the heart to the left side, through invisible pores in the interventricular wall separating the right and left ventricles. There, Galen claimed, it would mix with pneuma, an air-like spiritual essence obtained from the surrounding atmosphere and delivered to the left side of the heart via the trachea and the lungs. He reasoned that the resulting arterial blood would grow brighter and warmer than the venous stuff, becoming something called "vital spirit," which would be distributed to the body via the arteries. The blood reaching the brain would be imparted with "animal spirit," which would then flow out to the body via nerves, which Galen believed to be hollow. Waste materials, described as "sooty fumes," were eliminated via the trachea during the process of breathing.

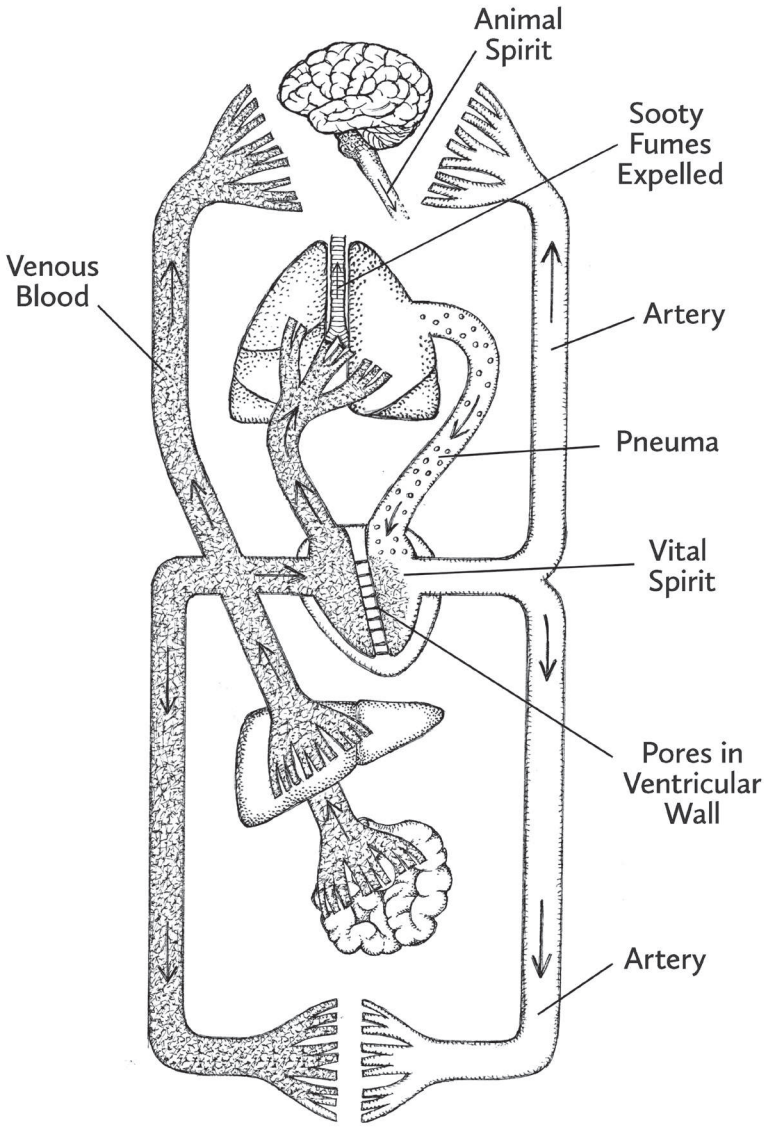
Whew!

Although his description of the circulatory system is certainly a laundry list of errors, from an anatomical perspective the most serious mistake Galen made may have been his failure to recognize the true connection between the pulmonary and systemic circuits—in other words, the path by which one could trace the movement of blood from the right side of the heart to the left side *by way of the lungs*. By citing invisible pores as the connection between the sides of the heart, Galen set circulatory anatomy on a centuries-long wrong track.

Unfortunately, Galen also subscribed to Hippocrates's six-hundred-year-old claim that the body contained four substances produced by the liver and spleen, called humors: blood, phlegm, yellow bile (or choler), and black bile.* These corresponded to nature's four elements—air, water, fire, and earth—and each reflected two of the four physical qualities—hot,

* Galen was apparently unconcerned about not actually seeing black bile. In fact, no one had. The substance does not exist.

GALEN'S CIRCULATORY SYSTEM



cold, wet, and dry. The combinations could be confusing, since they varied from reference to reference. What *was* of prime importance, though, was a need to keep these humors in balance if a person expected to have good physical and mental health, since each humor had a specific effect on the body, analogous to its qualities.

As a result of all this, physicians and so-called barber-surgeons spent centuries prescribing therapeutic purging to counter what they perceived as humoral excesses.* For example, fevers and the flushed cheeks and elevated pulse that often accompany them were thought to result from too much blood. The medical personnel of the day therefore sought to alleviate these conditions by reducing blood volume, and they bled patients early and often. The belief was that calm, cool, and cyanotic (i.e., blue) were preferable to frenetic, feverish, and flushed.

By similar reasoning, Galen believed that the overall composition of the humors resulted in the manifestation of distinct personality traits, depending on the blend. "Sanguine" folks, with blood as their leading humor, were sociable and optimistic, while someone who was "choleric" would be impatient and prone to anger. A "melancholic" person, full of black bile, was prone to sadness, and a "phlegmatic" individual might seem unemotional, calm, and apathetic. One way to gauge the historical significance of these humor-dependent characteristics is the fact that these terms that have reached the present more or less intact, although now they're mostly used as adjectives to describe temporary states of mind rather than to define rigid personality traits.

Although Galen made many errors, the real problem with his work is not the work itself—given the circumstances, many of his mistaken

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* Barber-surgeons were Middle Age medical practitioners, who, along with cutting hair, performed amputations (since they were already equipped with razors), as well as procedures believed to help keep the four humors in balance, like administering enemas and prescribing emetics (vomit inducers).

theories were understandable. What became a truly devastating development for science was that church leaders in the Middle Ages declared Galen's word to be divinely inspired and thus infallible, guaranteeing it a long legacy. Galen's writings were vast in number, with his surviving works accounting for something like three million words. After the fall of the Roman Empire, his and other Roman works fell into disfavor, and so his texts, written in ancient Greek, were not immediately translated into Latin, which remained the language of scholarship. During the early Middle Ages, though, they *were* translated into Arabic, principally by Syrian Christian scholars. Although Galen was not a Christian, he may have been a monotheist, and the translations that followed, from Arabic into Latin, likely built upon the Christian leanings of the previous translators. This quirk of fate made his writings more palatable to the medieval church, and the consequences were catastrophic.

Due to the church's infatuation with Galen and a handful of other ancient scientists whose theories were compatible with religious belief, Galen's mistake-laden views became unchallenged medical doctrine in Europe and elsewhere for well over a thousand years after his death, in approximately 216 CE. Until well into the 1500s, and in some instances beyond that, many physicians seeking truth found it in what they had read, not what they'd observed. As a result, this church-supported discouragement of new medical research led to centuries of intellectual torpor, if not hibernation.

One practice whose unfortunately long life and popularity can be at least partially attributed to Galen's influence was the previously mentioned therapeutic bleeding, which lasted until nearly the turn of the twentieth century. Bloodletting for medicinal purposes began with the Egyptians, spread to ancient Greece and Rome, and reached its peak in Europe during the 1800s. Wed to the concept of humorism, physicians and barber-surgeons wielded specially designed bloodletting instruments

to treat a range of conditions, which included plague, smallpox, and hepatitis. Women were bled to relieve menstruation, and patients were drained before amputations to remove the amount of blood thought to have been circulating in the soon-to-be-former limb. Even drowning victims were bled!

Other patients were deemed to have an insufficiency of blood and were compelled to drink the blood of freshly executed criminals. This practice may have begun in ancient Rome, when people with epilepsy drank the blood of recently slain gladiators. The research of medical historians Ferdinand Peter Moog and Axel Karenberg found that the custom may have stemmed from a general belief on the part of Roman physicians in the supposed curative effects of blood drinking. This claim would have been strengthened by the spontaneous recovery of some epilepsy patients from their seizures, recoveries that had nothing to do with blood drinking but were ascribed to the practice anyway.

Although it seems almost impossible to consider, this sort of thing continued on through the Renaissance and the Industrial Revolution, and well into the nineteenth century. As advances and innovation took hold across Europe and the United States across a range of scientific and nonscientific fields, the same could not be said for many aspects of medicine. And while the use of bloodletting instruments like fleams (picture a pocketknife) and scarificators (boxes containing multiple blades, into which fingers were inserted) was curtailed, they were replaced by a far more ancient bloodletter: the medicinal leech (*Hirudo medicinalis*). Leeches are annelid worms (like earthworms) equipped with sawlike teeth and an array of anticlotting agents in their saliva, and their infamous bloodsucking abilities were used to treat ailments ranging from fever and headaches to mental illness.

The first use of leeches for medical purposes may have begun with Ayurvedic medicine, a whole-body healing system whose roots stretch

back three thousand years ago or more in what is now India. The deity Dhanvantari, the Hindu god of Ayurveda, is often depicted (in more recent statues) holding a leech in his hand.

As for how Europeans came to use leeches, one possibility is that the practice may have moved westward along trade routes from the Middle East or Asia. But even if the ancient Egyptians and Greeks swapped medical practices passed down from Indian or Mesopotamian physicians, it is clear that medicinal leech therapy had multiple independent origins, since it was also practiced by the Aztecs and the Mayans. In each case, the idea behind the use of leeches was likely similar to the idea behind humorism: that by balancing the various forms of elemental energy within the body, one could achieve wellness.

Describing what is certainly the most warped use of leeches on record, Pierre de Brantôme, the sixteenth-century French historian, wrote that leeches were inserted into the vaginas of women before their wedding nights. The reasoning for this was that, by doing so the brides could seem like virgins:

> Now the leeches, in sucking, do engender and leave behind little blebs or blisters full of blood. Then when the gallant bridegroom cometh on his marriage night to give assault, he doth burst these same blisters and the blood discharging from them.

According to Brantôme, having hubby maul the mock maidenhead invariably led to an annelid-assisted version of postcoital bliss: "the thing is all bathed in gore, to the great satisfaction of both . . . so the honor of the citadel is saved."

Uh-huh.

Like the similarly common European practice of medicinal cannibalism, the topic of therapeutic bleeding is often swept under the

rug, perhaps due to embarrassment. In the United States, for example, few people are aware that in 1799 a team of physicians drained a total of around eighty ounces of blood from former President George Washington in an attempt to treat a throat infection. This was approximately 40 percent of his total blood volume!

The Founding Father was also blistered (a painful technique thought to draw out sickness) and purged at both ends, with enemas and emetics. Reported to have been in horrible pain and weakening rapidly, Washington fell unconscious from what would today be diagnosed as hemorrhagic shock. He died the next day. In looking over the history and the credentials of those doctors who treated President Washington, I realized that these were not the incompetent hacks that one might have initially suspected. They were, in fact, first-rate physicians, which would be expected, given Washington's stature. The problem was the medical community's continued adherence to Galen's deeply flawed directives about balancing the four humors. More than two thousand years after Hippocrates very likely cribbed them from even more ancient Egyptian, Mesopotamian, or Ayurvedic medics, these beliefs remained deeply entrenched within Western medical doctrine.

In the 1800s, the use of leeches received a major boost due to the fact that Napoléon Bonaparte's chief army surgeon, François-Joseph-Victor Broussais, swore by them. Known affectionately as Le Vampire de la Médecine, he reportedly attached thirty leeches to every new patient he saw, no matter what symptoms they presented. Once the malady was established, Broussais was known to treat patients with up to fifty leeches simultaneously, often giving them the appearance of wearing coats of glistening chain mail. Fashion-conscious ladies of the time took notice, and dresses decorated with fake leeches "à la Broussais" became all the rage. Given his popularity, Broussais was responsible for a massive uptick in medicinal leech use in France, which peaked at forty-two million

leeches imported in 1833. The demand initiated a decent-sized cottage industry, in which all that was required to generate some coin was an old horse to lead out into a shallow pond, and a basket to collect the leeches once they latched on to their sad equine host.

With the rise of antibiotics, leech therapy faded away in the early twentieth century, only to experience a resurgence beginning in the 1970s. At that time, surgeons were developing microsurgical techniques to deal with the problem of reattaching limbs. Knitting together thick-walled arteries was generally not an issue, so oxygenated blood was able to reach the reattached structures. The problem stemmed from an inability to sew together the thin-walled veins. Instead of returning to the heart, venous blood would pool and clot, and the reattached tissue would inevitably die. Surgeons discovered, however, that if they applied leeches to the area around the reattached structure, the bloodsuckers would set up a sort of auxiliary circulatory system, drawing off the waste- and CO_2-laden venous blood while still allowing arterial blood in to nourish and supply the reattached tissue. Simultaneously, anticoagulants in the leech saliva prevented clot formation. Eventually, the patient's own repair system would produce new veins, and once normal circulation became established, leech therapy, which often employed hundreds of leeches per surgery, could be halted. Things ended less well for the tiny annelid heroes, whose success was usually celebrated with an unceremonious and lethal dunking into a jar of alcohol.*

Thankfully, although the Western world was held back by centuries of adherence to the teachings of Galen, the rest of the world was able to make its own discoveries.

On the popular game show *Jeopardy*, the question to the answer, "He

* Current practitioners of alternative medicine believe that in addition to anticlotting properties, leech saliva contains a range of bioactive substances with therapeutic benefits ranging from anti-inflammatory and anesthetic properties to uses in treating edema and breaking up blood clots.

was the first to correctly track the path of blood to and from the lungs" would undoubtedly be "Who is William Harvey?" But the truth is that accurate information about the heart's pulmonary circuit did *not* begin with the seventeenth-century English physician and had actually been documented some three hundred years earlier. Given the near fanatical devotion to the teaching of Galen, some of the explorers who proposed revised routes for blood's path through the circulatory system did so at their own peril.

Ibn al-Nafis (c. 1210–1288 CE) was a Syrian-born polymath who studied medicine in Damascus and then ascended to the role of physician in chief at the Al-Mansouri Hospital in Cairo.* At the age of twenty-nine, he published his most famous work, *Commentary on Anatomy in Avicenna's Canon*. Avicenna, the Latinized name for Abu Ali al-Husayn Ibn Sina, was a Persian scholar in the first century CE, who produced an amazing body of work on a variety of topics. On the medical front, Avicenna studied Galen's writings and tweaked them for his students, making corrections based on his own research. He was also deeply influenced by Aristotle, which explains his belief that the heart, and not the brain, functioned as the body's control center. Avicenna's most famous work, *Canon of Medicine*, is a five-volume medical encyclopedia that integrates Aristotelian ideas, Persian, Greco-Roman, and Indian medicine, and Galenic anatomy and physiology. It became the standard medical text in medieval universities and was translated into Latin, Europe's academic language of choice, in the twelfth century. Avicenna's *Canon* was still in use well into the eighteenth century.

In his commentary on Avicenna's work, Ibn al-Nafis addressed a problem that had been vexing physicians and anatomists for a thousand years—namely, the invisible perforations in the interventricular wall that Galen had claimed allowed the movement of blood from the right

* His full name was Ala al-Din Abu al-Hassan Ali Ibn Abi-Hazm al-Qarshi al-Dimashqi, but he was called Ibn al-Nafis.

ventricle to the left ventricle. Ibn al-Nafis, who studied comparative anatomy and may have dissected cadavers, realized that Galen had proposed the unseen pores for one reason: he had not known that large amounts of blood were constantly flowing into the left side of the heart from the lungs. Of the cavity between the left and right ventricles, Ibn al-Nafis wrote:

> There is no passage as that part of the heart is closed and has not apparent openings as [Avicenna] believed and no non-apparent opening fit for the passage of this blood as Galen believed. The pores of the heart are obliterated and its body is thick, and there is no doubt that the blood, when thinned, passes in the *vena arteriosa* [pulmonary artery] to the lung to permeate its substance and mingle with the air . . . and then passes in the *arteria venosa* [pulmonary vein] to reach the left cavity.

With this, Ibn al-Nafis became the first to propose a nonimaginary connection between the right and left sides of the heart. Further research would not confirm his observations until four hundred years later, when Marcello Malpighi used an early microscope to identify the tiny pulmonary capillaries surrounding the lung's microscopic air bags, the alveoli. These capillaries conclusively linked the pulmonary arteries carrying deoxygenated blood to the lungs with the pulmonary veins carrying oxygenated blood back to the heart.*

Although Ibn al-Nafis was almost certainly the first to correctly determine the route of pulmonary circulation, his work unfortunately did not have a lasting influence on Western medicine. It was largely forgotten until 1924, when an Egyptian physician found a copy of his *Commentary* in a Berlin library.

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* This is the only example in the human body where a vein carries oxygenated blood and an artery carries deoxygenated blood.

Similarly, practitioners of traditional Chinese medicine (TCM) have been using their own determinations about the circulatory system and the heart, which they consider to be "the emperor of all organs," for over two thousand years. In TCM, while the basic functions of the heart are understood in a way that coincides with Western medicine, the heart remains the center of the mind and consciousness. TCM remains largely beyond the scope of this book, though we will see it again.

If the Cambridge-educated William Harvey (1578–1657) was not quite the cardiac pioneer portrayed in history books, he is certainly the most famous. He may have also been the first Western scientist to proclaim that the human body operates like a machine, with each organ having its own function or functions. Harvey used the scientific method to explain circulation as a natural phenomenon, often bucking political or religious dogma associated with the teaching of the Bible or Galen. Through experiments on the blood vessels of snakes and fish, and the superficial arteries and veins of the human arm, Harvey demonstrated that the circulatory system worked through the laws of physics, and that the movement of blood results from the beating of the heart. This was a controversial revelation in the early seventeenth century, and in some ways helped set the stage for the explosion of medical advances that occurred during the Enlightenment.* Still a man of his time (and a member of the Church of England), though, William Harvey did not dispute the accepted metaphysical role of the heart as the "spiritual member" of the body and the seat of all emotions.

This sort of dichotomy between modern theories and deeply entrenched beliefs helps explain the disconnect that often existed between theory and practice. Additionally, although advances were being made in anatomy and physiology, the same cannot be said for successfully

* The intellectual and philosophical movement known as the Enlightenment is usually considered to have lasted from the mid-1600s until the early nineteenth century.

combating disease. The continued use of leeches to "breathe veins" long after humorism fell into disfavor not only serves as an example of the glacial pace at which therapy caught up to theory, it also explains the everything-but-the-kitchen-sink approach to the treatment of conditions whose cures remained out of reach.

Harvey published his classic and incredibly popular work *Exercitatio anatomica de motu cordis et sanguinis in animalibus* (meaning "An Anatomical Study of the Movement of Heart and Blood in Animals") in 1628, but by then he may have been the third or even the fourth person to correct Galen's error. More surprising still is that William Harvey wasn't even the first *European* to accurately map the flow of blood to and from the lungs.

Michael Servetus (c. 1511–1553) was a Spanish physician who came to a similar conclusion as Ibn al-Nafis regarding Galen's invisible pores and the true nature of the link between the pulmonary and systemic circuits. He may, in fact, have cribbed his hypothesis from Ibn al-Nafis, who went uncredited. But whether the ideas were original or not, Servetus wrote the following in his seven-hundred-page book, *The Restoration of Christianity*, published in 1553:

> This communication is made not through the middle wall of the heart, as is commonly believed, but by a very ingenious arrangement the refined blood is urged forward from the right ventricle of the heart over a long course through the lungs; it is treated by the lungs, becomes reddish-yellow and is poured from the pulmonary artery into the pulmonary vein.

Unfortunately for Servetus and his work's legacy, he went far beyond giving a thumbs-down to one of Galen's divinely inspired revelations about the circulatory system. He also filled his magnum opus with

blasphemous statements, most scandalously including rejections of both infant baptism and the Holy Trinity. As a result, the Spaniard found himself in the unusual position of infuriating both the powerful Roman Catholic authorities and the newly emergent Protestant ones, all of whom quickly pinned him with the somewhat less than favorable tag of "heretic."

Servetus was arrested on April 4, 1553, but escaped three days later, whereupon he was tried and executed in absentia by the French Inquisition. They burned Servetus and his naughty books in effigy, with blank paper standing in for the actual texts.

Attempting to flee to Italy, he was captured in Geneva, and in a touching show of bipartisanship, the Protestants decided to put him on trial for his life—in person this time. Everyone, it seemed, agreed that Servetus was guilty and deserved to burn. Surprisingly, the preeminent Protestant theologian John Calvin stepped in to plead for mercy, possibly feeling guilty about the fact that Servetus had been arrested while attending a sermon that he was preaching. Regrettably for Servetus, however, Calvin's plea had nothing to do with sparing his life. Instead, Calvin requested that the condemned man be decapitated instead of being burned at the stake. In the end, Calvin was chided in a letter for his undue leniency and Michael Servetus found himself surrounded by flaming copies of his own book—real ones this time. Of his published works, it appears that only three copies have survived, reportedly hidden away for decades to avoid destruction. From a medical perspective, the elimination of *The Restoration of Christianity* from the public eye meant that Servetus's claims about pulmonary circulation were essentially forgotten.

Beginning in the twelfth century, the Roman Catholic Church had begun to loosen its ban on human dissections as long as they were performed at universities and *not* by clerics. Founded not long after, in 1222, the University of Padua in northern Italy became a preeminent

destination for scholars and physicians studying anatomy. By the mid-sixteenth century, it became especially renowned for its anatomy theater and the frequent presence of Belgian anatomist Andreas Vesalius (1514–1564). By this time, the religious, moral, and aesthetic taboos against human dissection that had paralyzed medical research for centuries had lifted, and Vesalius was able to pioneer the field, studying the body in ways that Galen never could. Notably, he produced a large set of exquisitely detailed illustrations of the human body, which he shared with his students, often in lectures about just how wrong Galen had been. In 1543, Vesalius published the remarkable *De humani corporis fabrica libri septum* ("The Seven Books on the Structure of the Human Body") in which he emphasized that direct observation was key to an understanding of human anatomy. In it, Vesalius's skepticism of Galen was often clear, even if it took a revision in his 1555 second edition to change his original quote that blood "soaks plentifully through the [interventricular] septum from the right ventricle into the left" to the following: "I do not see how even the smallest amount of blood could pass from the right ventricle to the left through the septum." He did not, however, put forth his own hypothesis on pulmonary versus systemic circuits. Additionally, Vesalius stressed that there were important differences between animals (upon which Galen based his research) and humans. Though his work contributed to breakthroughs regarding several organ systems, a key contribution was his determination that the heart functioned as a pump that circulated blood around the body. If not quite an original assertion, it was incredibly effective coming in the sixteenth century, at a time when the use of mechanical pumps had begun in earnest—generally to move water from place to place.

While Vesalius's research was sanctioned by the University of Padua, thanks to the lifting of the dissection taboo, his often-contradictory stances on centuries of established medical dogma still managed to make

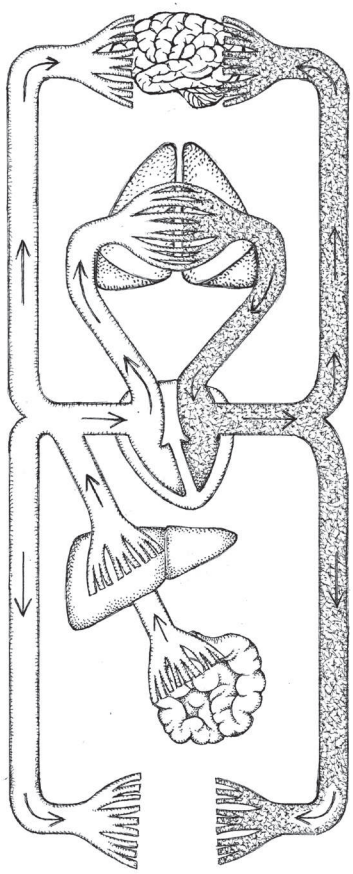
him an enemy of the Roman Catholic Church. So, too, did his Bible-opposing (and accurate) observation that men and women shared the same number of ribs. Vesalius died under mysterious circumstances while returning from a trip to Jerusalem. Some have wondered what might have compelled Vesalius to visit the Holy Land, with rumors that he had fled Spain after accidentally performing an autopsy on a living nobleman. Citing a lack of evidence, this story was dismissed by Vesalius biographer Charles O'Malley. He suggested instead that Vesalius may have been using the trip as an excuse to get away from the Spanish court, with the hope of eventually reclaiming his old anatomy chair at the University of Padua. Unfortunately, whatever the reason for his pilgrimage, he died on the island of Zakynthos (in what is today Greece), though no one is quite certain about how that happened. Modern biographers list poor conditions aboard ship, a shipwreck, or a contagious disease as possibilities.

A pupil of Vesalius's named Matteo Realdo Colombo (c. 1516–1559) later became anatomy chair at the University of Padua. In a chapter on the heart and arteries in his 1559 book *De re anatomica* ("On Things Anatomical"), he wrote what stands as a remarkably accurate pre-Harvey description of the pulmonary circulation:

> Between these ventricles there is a septum through which most everyone believes there opens a pathway for the blood from the right ventricle to the left . . . But they are in great error, for the blood is carried through the pulmonary artery to the lung and is there attenuated; then it is carried, along with air through the pulmonary vein to the left ventricle of the heart. Hitherto no one has noticed or left in writing, and it especially should be observed by all.

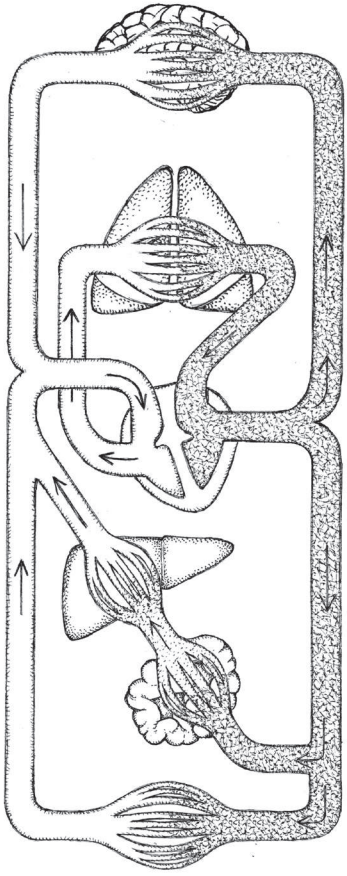
Ultimately, the Persian polymath, the Spanish physician, and the Belgian and Italian anatomists would not be remembered for their

COLOMBO'S CIRCULATORY SYSTEM



BODY

HARVEY'S CIRCULATORY SYSTEM



BODY

significant accomplishments related to the cardiovascular system. Since each of them described, with varying degrees of detail, the correct route of blood from the right side of the heart to the lungs, then back to the left side, I am left feeling that they have been treated unfairly, especially since the works of Ibn al-Nafis, Servetus, Vesalius, and Colombo predated William Harvey's 1628 publication by 389,* 75, 73, and 69 years, respectively.

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* An approximate date.

Still, though, there is no denying that Harvey's work, if it did not lay the foundations of modern cardiology, certainly helped bring physicians onto the ground floor. His reliance on scientific observations and methodology were blueprints for those who followed him, now equipped with what was essentially a modern perception of how the heart and circulatory system operated and how to study them.

Of course, there were additional floors to build, as researchers were still investigating pulse and blood pressure, and improvising instruments to investigate heart sounds. Still others were studying the exchange of gases between the circulatory and respiratory systems, and a fast-growing list of circulatory system–related defects and diseases. But even before the nature of blood and its path through the body were identified, some seventeenth-century physicians began toying with the idea that instead of simply draining the red stuff in the event of illness, it might make more sense to *add* it.

Practically the whole of the blood was replaced
by beer before life was replaced by death.
—Richard Lower, *Tractatus de corde*

One person in 1666 made the recommendation that if a man and wife
did not get along well, each should have a transfusion from the other,
and by thus mixing their blood, they would be made compatible.
— Cyrus C. Sturgis,
"The History of Blood Transfusion"

[9]

What Goes In . . .

In 1614, the German physician and chemist Andreas Libavius (c. 1540–1616) appears to have been the first person to suggest that a blood transfusion, rather than a bloodletting, might be a way to restore health. Libavius described how this could be accomplished by attaching tubes to blood vessels, but he also emphasized that the inherent difficulties of such a procedure would render any such attempt foolhardy. As it turned out, he wasn't wrong.

To modern readers, the early attempts at transfusions and intravenous (IV) injections will, at best, come off as weird. At worst, they may seem quite horrible. This was, of course, a time when the nature of the circulatory system and the blood traveling through it were unknown, and when much of what *was* known was wrong.

There have been ugly rumors, written and otherwise, that the first blood transfusion took place in 1492, with the recipient being Pope Innocent

VIII. The pontiff is mostly known today for his condemnation of witches and magicians, and with it his 1483 appointment of the infamous Tomás de Torquemada as grand inquisitor of Spain.* Several dubious accounts written in the nineteenth century† contend that in 1492, the pope was on his deathbed, having been in and out of a stupor for years. (Given the man's extreme cruelty, some may consider this to have been a solid career move.) According to these reports, with every effort to revive the pope exhausted, a Jewish physician volunteered to save the religious leader using a new technique. Italian author Pasquale Villari told it like this:

> All the blood of the prostrate old man should pass into the veins of a youth who had to yield up his to the Pope. The difficult experiment was repeated three times, the result being that three boys lost their lives, without the Pope receiving any benefit of it, probably because air had penetrated into their veins.

In 1954, Dutch medical historian Gerrit Lindeboom undertook comprehensive research and turned up no evidence that this blood transfusion had taken place. Of the story's originator, Lindeboom said, "It turns out his vivid imagination framed unhistoric hypotheses." The tale also smells a lot like "blood libel," which would make it one of many centuries-old false allegations asserting that Jews used Christian blood, usually from children, for a laundry list of nefarious purposes.

Given the fifteenth-century belief that drinking human blood had a curative effect, it is far more likely that, if anything, the dying pope was instructed to quaff the blood of these children in a potion—although there is always the possibility that this, too, could be a blood-libelous distortion.

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* His goal as leader of the Spanish Inquisition was to rid Spain of heretics—particularly Jews and Muslims who had converted to Catholicism in name only—through expulsion, torture, or executions.

† Reviewed by A. Matthew Gottlieb in 1991.

Successful and *safe* blood transfusions would remain out of reach until the turn of the twentieth century. It would take many miserable attempts, though, to stop physicians from trying to introduce a variety of substances, some of them actually blood, into the veins of their patients.

Christopher Wren (1632–1723) was an English mathematician, scholar, and architect, famous for his design of Saint Paul's Cathedral in London. He was also interested in experiments of an anatomical and physiological nature. In a 1656 letter, he wrote:

> The most considerable experiment I have made of late, is this; I injected wine and ale into the mass of blood in a living dog, by a vein, in good quantities, till I made him extremely drunk, but soon after he pissed it out . . . It will be too long to tell you the effect of opium, scammony, and other things which I have tried this way. I am in pursuit of further experiments, which I take to be of great concernment, and what will give great light to the theory and practice of physick.

The reasoning behind using wine for injection comes once again from the ubiquitous Roman physician Claudius Galenus, who believed that it contributed to the formation of blood by the liver. The practice showed up in Christopher Marlowe's play *Tamburlaine the Great*, written around 1587:

> Filling their empty veins with airy wine
> That being concocted turns to crimson Blood.*

The transfusion of alcohol into patients continued into the 1660s, but by then some in the medical community began exploring how they might

* According to scholar, poet, and English professor J. S. Cunningham, "concocted" = digested.

transfuse actual blood into humans. In keeping with the long string of feuds between England and France, physicians from the two countries began ignoring each other's transfusion-related work in order to claim priority. Sorting through all of this, two near certainties emerge: In 1665, a British physician and surgeon named Richard Lower (1632–1691) made the first direct blood transfusions, using pairs of dogs and transfusing from the carotid artery of one dog into the jugular vein of the other; in each pair, the recipient dog had been previously bled, nearly to death, and was then rejuvenated by blood transfused from the second dog. And in 1667, the French physician Jean-Baptiste Denys (also spelled Denis) was the first to transfuse blood into human, though the donors of that blood were not human.*

Impressed by Lower's work two years earlier, Denys (c. 1635–1704) built a system constructed out of metal tubing and goose quills and began transfusing the blood of sheep and calves into his patients. One of his first was Antoine Mauroy, who received the bovine option. Mauroy was said to be "a manic-depressive type suffering from a psychosis."† The rationale for the seemingly strange choice of donors appears to be a belief that the "mildness" of the calf blood would cure whatever was causing Mauroy to beat his wife, run around naked, and set houses on fire.

The procedure began with Mauroy being tied to a chair and bled, presumably to rid his body of bad blood while making room for the good stuff. Following this, he received about six ounces of calf blood through a metal tube, which Denys inserted into a vein in his arm. Mauroy complained about some burning in his arm but otherwise exhibited no serious side effects. After nodding off for a bit, the patient awoke and

* Cyrus Sturgis, a doctor who presented a paper on the history of blood transfusion at the annual meeting of the Medical Library Association in 1941, claims that donor was a calf, though a sheep is mentioned in other references.

† Denys's first patient appears to have been an unnamed fifteen-year-old, who received a transfusion of sheep blood earlier in 1667.

appeared calm—which many of the onlookers who had watched the procedure much preferred to Mauroy's usual behavior.

Unfortunately, a second transfusion, which was done the following day at the suggestion of Mauroy's wife, was somewhat less successful. This time, upon receiving the transfusion, the patient began sweating profusely and, between bouts of throwing up his recent lunch (reportedly bits of bacon and fat), he complained of severe pain in his lower back, saying also that his arm and armpit were burning. Soon after, he began exhibiting chills, fever, erratic pulse, and severe nose bleeds. Appearing extremely fatigued, he soon fell asleep, only to wake up the next morning looking rather calm (for him) and sleepy. Expressing a desire to urinate, Mauroy reportedly produced "a great glass full of urine, of a colour as black as if it has been mixed with the soot of chimnies."

With the benefit of twenty-first-century hindsight, it is clear that Antoine Mauroy was suffering from his body's multipronged response to incompatible blood. The back pain and black urine were a result of his kidneys dealing with the shock of filtering massive numbers of transfused red blood cells that had been literally torn apart by the immune system in a process known as hemolysis.

In accordance with the medical wisdom of the seventeenth century, Mauroy was then bled, the Galenic equivalent of "Take two aspirin and call me in the morning." Eventually, though, through what was certainly more luck than medical treatment, he began to recover. Of course, Denys took this to mean that his transfusion therapy was a success, and he immediately began treating additional patients.

Meanwhile in England, Richard Lower organized a demonstration of his own for the Royal Society of London. He hired a man named Arthur Coga, who was described by Parliament member and diarist Samuel Pepys as "cracked a little in the head," and paid him twenty shillings "to have some blood of a sheep let into his body." Lower made incisions in the

carotid artery of the sheep and an unspecified vein in Coga's arm, then inserted a silver pipe into each vessel, with a length of quills connecting them. According to Lower, nine or ten ounces of sheep blood entered the subject, and soon after, Coga "found himself very well, and hath given in his own Narrative under his own hand, enlarging more on the benefits, he thinks he hath received by it."

Only a few months later, the enthusiasm for blood transfusion was shattered on both sides of the English Channel when the French patient Antoine Mauroy died. According to his wife, the man had resumed his psychotic behavior and thus required another transfusion—but it was later discovered that his conduct had led her to employ a treatment of her own design. This came in the form of a dietary supplement of arsenic, which she added to her husband's meals. Strangely, Madame Mauroy failed to mention this to Denys when the couple approached him requesting a third transfusion. The physician refused to treat the man, noting his patient's less than healthy appearance, but that did not stop Mauroy's wife from suing him and having him arrested for manslaughter when Mauroy dropped dead several days later. Though Denys was found not guilty, the uproar surrounding the case, along with reports of additional patient deaths, all but slammed the door on the practice of human blood transfusions.

In 1668, France banned the procedure, with a proclamation known as the Edict of Châtelet, and England soon followed suit. A pair of transfusion-related deaths in Italy led to a denouncement of the practice by magistrates in Rome. And so all went quiet on the transfusion front, for nearly 150 years.

In 1818, horrified by women bleeding to death after childbirth, English obstetrician James Blundell (1790–1878) began the first successful human-to-human blood transfusions. He did so by using a syringe filled with approximately four ounces of blood drawn from the husband of

the patient, and then injecting the blood into a superficial vein in the woman's arm. Reportedly, half of the transfusions he performed had positive results. Unfortunately, given the problems Blundell faced, which included nonsterilized instruments and no knowledge of blood typing, his results often failed, and the well-intentioned practice was soon abandoned.

Although blood transfusions were still frowned upon for most of the nineteenth century, mostly because they frequently had poor outcomes, some rather surprising substances were regularly injected into the blood vessels of both animal and human subjects. Intravenous injection of milk began during a Canadian cholera epidemic in 1854. The physicians who thought this one up were under the mistaken belief that white blood cells were actually red blood cells in the process of transformation. Citing an earlier study, they said they were confident that the "white corpuscles" of milk, which were actually minute globules of oil and fat, would eventually be converted into red blood cells.

In reality, most red blood cells are produced from stem cells in the red bone marrow found in long bones like the femur and the humerus. Approximately two million red blood cells are produced every second, while a similar number of cells at the end of their approximately 120-day life span are recycled by the spleen.

Milk transfusions were performed as late as the 1880s by British surgeon Austin Meldon. According to a short paper he published in the *British Medical Journal* in 1881, Meldon injected milk into twenty patients for illnesses that included tuberculosis, cholera, typhoid fever, and pernicious anemia. He explained that the "very unpleasant symptoms" and even deaths that sometimes followed the procedure could be explained by the milk having gone sour. To remedy this, Meldon recommended that physicians use goat milk, explaining that "it is much more easy to bring that animal in close proximity to the patient, thus avoiding any necessary delay between milking and the injection."

Admittedly, this sounds ridiculous today, but it's easy to see why people might have been willing to accept milk transfusions as a panacea at a time when, for example, a famous and still-in-business pharmaceutical company recommended using heroin to treat children with colds, and cocaine appeared in Sears, Roebuck and Company catalogues. Without clear evidence for what was and wasn't valid medicine, almost anything could be pitched as the next successful cure-all. As for goat milk transfusions, according to Meldon, by following a few common-sense practices, his fellow physicians could prevent "that depression which so frequently follows the operation." One can imagine that these practices included straining out the goat hair before an injection and not letting the donor eat the hospital bedding.

"I look upon it as a much better and safer operation than transfusion of blood," Meldon wrote.

The practice of injecting milk into patients was abandoned around the turn of the century, when so-called normal saline was finally adopted for intravenous use. This is the solution most commonly used in modern IVs, and it consists of nine grams of sodium chloride (NaCl) dissolved in sterile water, creating a 0.9 percent saline solution, which approximates several key properties of blood plasma. Its first usage was during an 1832 cholera pandemic, when British physician Thomas Latta followed through on a hypothesis recently set forth in the *Lancet,* the top medical journal of its day. The author of the article, a newly minted Irish physician named William Brooke O'Shaughnessy reasoned that because cholera victims were dying from dehydration (losing major amounts of body fluid and salt through diarrhea), it would make sense to replenish the body's lost liquid with a solution approximating the salinity of blood. Latta's rehydration therapy was remarkably successful, but it did not gain enough momentum to supplant the standard treatments of the time, namely bleeding, leeches, emetics, and enemas—all of which resulted in *increased* loss of body fluids.

By the early 1880s, a better understanding of human blood chemistry led British physiologist Sydney Ringer to improve upon the earlier recipe for saline, adding potassium to the sodium chloride solution. Lactated Ringer's solution bears the inventor's name, and it is still widely used today.

In 1901, Karl Landsteiner (1868–1943), an Austrian pathologist, revolutionized the ground rules for blood transfusion after discovering the ABO blood group.* In brief, erythrocytes (like other cells) have specific surface proteins called antigens embedded in their cell membranes. These antigens come in two different varieties: A and B. If the surface proteins on a blood donor's red blood cells don't match those of the recipient, the recipient's immune system will attack the donor blood. The result is the previously mentioned hemolysis—literally "blood cell cutting." In addition to putting stresses on the kidney-driven urinary system, incompatible transfusions can lead to a dangerous form of erythrocyte clumping, called agglutination, which can clog small blood vessels and lead to serious medical problems, like strokes and loss of organ function. This, in turn, accounts for the kidney pain experienced by recipients of incompatible transfusions, including the *extreme* repercussions experienced by the seventeenth-century recipients of blood donated by the barnyard set.

Today, problems related to blood clotting and the storage of donor blood have been solved, and we know about the Rh blood group system and the Rhesus (Rh) factor, named for the Rhesus monkeys in which they were first discovered. Most people have the Rh antigen on their red blood cells (making them Rh-positive), while others don't (making them Rh-negative). Problems used to arise if an Rh– mother gave birth to multiple Rh+ children. Having gradually built up Rh+ antibodies during

* Adriano Sturli and Alfred von Decastello, who worked in Landsteiner's lab, discovered a fourth blood type, AB blood, a year later. In 1930, Landsteiner won the Nobel Prize in Physiology or Medicine.

her first pregnancy, the mother's immune system would be fully prepared to "attack" the blood of the second Rh+ fetus. Thankfully, modern prenatal screening and treatment prevent such occurrences today.

Additionally, blood is now crossmatched and screened for pathogens and toxic substances before being transfused, thus ensuring that transfusions are as compatible and safe as possible during a myriad of treatments related to surgery, injury, blood disorders, and disease.

Things have come a long way since the grim days of barnyard blood transfusions and the concept of the four humors. But just as centuries of physicians puzzled over the path, function, and replacement of blood, they also struggled to understand and treat the maladies of the heart. The half-century-long decline, and eventual death, of Charles Darwin will serve as a backdrop for this portion of our journey.

You know that running bug people talk about?
Well, I've been well and truly bitten.
—Sadiq Khan

Love bug, leave my heart alone.
—Richard Morris and Sylvia Moy

[10]

The Barber's Bite and the Strangled Heart

Though he was not its originator, Charles Darwin will forever be associated with the phrase "survival of the fittest."* But in 1836, as the twenty-seven-year-old naturalist stepped off the HMS *Beagle* at the end of his five-year voyage, he was not a fit man. For the remaining forty-six years of his life, Darwin would suffer from a laundry list of medical woes, which included heart palpitations, chest pain, dizziness, fatigue, eczema, and muscle weakness. Additionally, he experienced poor vision, tinnitus, sleeplessness, nausea, vomiting, boils, and chronic flatulence.

In 1842, Darwin moved his rapidly growing family from what he referred to as "smoky dirty London" to a quiet country home some

* The term "survival of the fittest" was actually coined by philosopher/biologist Herbert Spencer, who used it in his own book, *The Principles of Biology*, published in 1864, after reading *On the Origin of Species*.

fourteen miles southeast of the city.* Not only did Down House provide him with more space (he and his first cousin/wife, Emma, would have a total of ten children), it also signaled the beginning of his near-complete withdrawal from the public eye. Darwin wrote about this period in his autobiography:

> We went a little into society, and received a few friends here; but my health almost invariably suffered from the excitement, violent shivering and vomiting attacks being thus brought on. I have therefore been compelled for many years to give up all dinner-parties; and this has been somewhat of a deprivation to me, as such parties always put me into high spirits. From the same cause I have been able to invite here very few scientific acquaintances.

By avoiding the "excitement" brought on by stress, and even such pleasurable events as a performance of George Frideric Handel's *Messiah*, Darwin was only intermittently successful at lessening the severity and frequency of his symptoms, which were followed by periods of fatigue he unfortunately referred to as being "knocked up." But while the cause of his decades-long illness remains open to debate, many historians have suggested that Charles Darwin was a hypochondriac—someone who not only fears illness but is mistakenly convinced that he or she is unwell. Obsessively preoccupied with his own health, he appears to have tried every available therapy, including some that would now be considered full-on quackery. These treatments included electrical stimulation of the abdomen with shock belts (a.k.a. galvanization) and "Dr. Gully's Water Cure," a form of hydrotherapy in which the patient was heated with a

* Darwin's doctors urged him to move to the country to escape London's air, "a destructive malady . . . justly termed *Cachexia Londinensis*, which preys upon the vitals, and stamps its hues upon the countenance of almost every permanent resident in this great city."

lamp until dripping with sweat before undergoing a vigorous rubdown with cold, wet towels.

This particular treatment had been developed by University of Edinburgh medical graduate James Manby Gully. It was based on the popular belief of the day that diseases were caused by faulty blood supply to organs like the stomach and heart. In brief, Gully contended that by applying cold water to the body, the circulatory system would direct diseases *away* from those important organs and *toward* less vital regions, like the skin, where they could be eliminated. The water cure became a favorite of Darwin's, and may in fact have been helpful—although only because the weirdness was coupled with a light exercise regime and a sensible diet. Darwin once wrote of the treatment, "At no time must I take any sugar, butter, spices, tea, bacon, or anything good."

Gully was also an unyielding opponent of the use of drugs to combat disease, resorting instead to medical clairvoyant readings and homeopathy. The latter is a form of alternative medicine created in the 1790s by German physician Samuel Hahnemann and operating on the doctrine of "like cures like" (*similia similibus curantur*). Basically, the idea is that natural substances that can produce symptoms of a particular disease in healthy people can, in tiny amounts, cure people who have that disease. To which I say, go figure.

Darwin was also administered, and in some cases *self*-administered, an array of compounds, which included ammonia, arsenic, bitter ale, bismuth (the active ingredient in Pepto Bismol), calomel (a mercury-containing laxative and horticultural fungicide), codeine (an opioid pain reliever), "Condy's Ozonized Water" (an oxidizing agent used to purify water), hydrocyanic acid (the highly poisonous prussic acid), "oxyde of iron" (a.k.a. rust), laudanum (tincture of opium), mineral acids (minerals unknown), alkaline antacids, and morphine. Shockingly, none of the

treatments did very much to improve Darwin's condition, and there have even been whispers that some of this crap may have actually worsened his health.

Ultimately, though, despite decades of chronic anxiety (particularly a fear of heart disease and impending death), physical ailments, and personal tragedies, including the deaths of three of his ten children, Charles Darwin wrote nineteen books, including his landmark studies on the mechanism of biological evolution. Given the game-changing nature of *On the Origin of Species*, arguably the most influential academic book ever written, some have questioned why Darwin spent the last decade of his life writing about the sex lives of plants, fertilization in orchids, the movement and habits of climbing plants, and the formation of vegetable mold through the action of worms. But considering Darwin's near-obsessive desire to avoid stress that might sicken him further, it makes sense that these studies, though innovative and scientifically important, would have been part of a conscious effort to avoid hot-button topics. It was his immersion in scientific work (and not cold water) that became Darwin's primary defense against events of a distressing nature.*

In December 1881, Charles Darwin was seized by a severe attack of precordial pain, defined as pain originating from nerves in the region of the chest immediately in front of the heart. His doctors described his heart condition as "precarious" with "symptoms of myocardial degeneration."

Darwin's letters reflected the realization that he was suffering from serious heart disease. He wrote to his longtime friend botanist Joseph Dalton Hooker: "Idleness is downright misery to me . . . I cannot forget

* After *Origin*'s publication in 1859, Darwin left the defense of the book to others, most notably biologist Thomas H. Huxley. Known as "Darwin's bulldog," Huxley vowed to fight "with claws & beak" for what Darwin referred to as his "damnable heresies."

my discomfort for an hour . . . So I must look forward to Down graveyard as the sweetest place on earth."

Over the next four months, Darwin experienced several such incidents of chest pain, accompanied by nausea and faintness. He was diagnosed with "angina pectoris"—from a Latin term to describe suffocating or strangling pain in the chest. We now know that angina is itself commonly a symptom of coronary artery disease, which occurs when the coronary arteries supplying the heart itself are obstructed by atherosclerotic plaques. Angina can also result when coronary arteries undergo vascular spasm, a sudden and brief constriction resulting from drug or tobacco use, exposure to cold, or even emotional stress.

But whatever the cause, the reduced blood flow leads to oxygen and nutrient starvation in the heart muscle downstream from the vessel blockage—a condition known as ischemia. This, in turn, stimulates pain receptors in the heart, serving up a warning of worse things to come if the plaques or a clot manage to completely block the blood flow to the vessel. The result, then, is a myocardial infarction, better known as a heart attack.

Angina itself can sometimes mimic a heart attack, with the pain perceived as originating from the jaw, neck, back, shoulder, or left arm. Although there are several proposed mechanisms for this "referred pain," most researchers now believe that the neural pathways carrying information from the heart's pain receptors to the brain run quite close to, and may even merge with, similar pathways coming from the other regions, like the jaw or neck. This fools the brain and its owner into thinking that the pain is coming from a location unrelated to the heart.

Incidents of angina usually occur during extremes of exercise or emotion, when the heart rate quickens but the cardiac muscle's suddenly increased requirements for oxygen and nutrients cannot be met. In its

stable form, angina subsides several minutes after the physical activity is curtailed or the stress is removed.

Though cardiology was by no means an established field in Darwin's time, by the early 1880s doctors believed that the causes of angina pectoris were rooted in: (1) the heart's status as an organic structure subject to disease and decay, and (2) its connection to emotion and psychological elements—as they were perceived (correctly or incorrectly) at the time. As such, Darwin's doctors covered their bases, prescribing rest and stress-free living.

As for how Darwin actually dealt with his deteriorating pump, among the contents of what we can only imagine must have been a large medicine cabinet were the narcotic morphine, for the pain, and the antispasmodic amyl nitrite.

If amyl nitrite (not to be confused with amyl nitr*a*te, an additive in diesel fuel) sounds familiar, one reason may be that it remains in use today as a treatment for heart disease and angina. The other reason is that it is a commonly used recreational drug. Amyl nitrite is usually inhaled, and it works by vasodilation: that is, expanding the diameter of blood vessels. In doing so, it increases blood flow and reverses vascular spasm. Interestingly, the vasodilatory effect is also accompanied by a brief euphoric state, and so the contents of amyl nitrite capsules (called "poppers") are sometimes snorted recreationally, their psychotropic effects prolonged when combined with drugs like cocaine. Another effect of amyl nitrite is relaxation of involuntary smooth muscle in the anal sphincters—an officially recognized buzzkill for some folks.

Amyl nitrite's status as the primary medication for angina began to change in 1879, when English physician William Murrell published a paper about another compound—one that was already famous, and sometimes infamous, for its spectacular *non*medical effects. Murrell

claimed that a drop or two of nitroglycerin in a 1 percent solution was far more efficient than amyl nitrite in the treatment of angina pectoris. Also known as glyceryl trinitrate, nitroglycerin was thought to work much the same way as amyl nitrite, i.e., by dilating coronary blood arteries and increasing flow to the oxygen-starved heart. In fact, its primary mechanism of action is to reduce the volume of blood filling the heart—though this was not determined until well after its initial therapeutic use. With less blood to pump, the heart does not have to work as hard and so requires less oxygen. Though they may not have understood this particular mechanism of action, Murrell and his peers were right about the vessel-widening properties of nitroglycerin, since the body converts it into a potent vasodilator, nitric oxide.

The Italian chemist Ascanio Sobrero first synthesized nitroglycerin around 1846 but it was Sweden's Alfred Nobel who became famous for his work with the compound. Nitroglycerin was also widely used as an explosive, and Nobel began searching for a way to make the compound safer to handle after his younger brother was killed in an explosion at the family's armaments factory. Nobel added stabilizers and absorbents, ultimately producing a substance he called dynamite.

Scientists renamed the medicinal version trinitrin to avoid scaring bomb-phobic pharmacists and their customers. Before his death in 1896, Alfred Nobel, whose considerable fortune was closely tied to his patent for dynamite, called it an "irony of fate" that he had been prescribed trinitrin to treat his own heart condition.

Like amyl nitrite, nitroglycerin is still in use today. Currently administered through transdermal patches and IV infusion, it is most commonly taken sublingually in tablet form. At the first sign of angina, a pill is placed either under the tongue or between the cheek and gum. With an abundance of capillaries located close to a perpetually wet surface, both regions allow for rapid drug diffusion into the circulatory system. This is especially

important for compounds that, if taken orally, might be broken down and rendered less effective or even ineffective during passage through the digestive tract, or turned into inactive metabolites by the liver. Another example of a drug usually given sublingually is the antihypertensive nifedipine. Sublingual administration is also often used for patients in hospice care who may be unable to swallow painkillers like morphine, and for those suffering from gastric ulcers or nausea.

On Tuesday, April 18, 1882, Charles Darwin stayed up later than usual, chatting with his thirty-four-year-old daughter, Elizabeth. Just before midnight, he experienced a bout of agonizing pain, alleviated only somewhat when his wife and daughter administered amyl nitrite with some brandy. He spent much of the following day nauseous and in excruciating pain before eventually losing consciousness at 3:25 p.m. Darwin's doctors determined that his final symptoms were "Angina Pectoris Syncope"—unstable angina with a loss of consciousness.* At just before 4 p.m. on April 19, 1882, Charles Darwin died at the age of seventy-three from heart failure.

Given Darwin's fame, dozens of researchers over the course of the past century and a half have attempted to determine the condition or conditions that may have contributed to the great man's ultimate demise. The list of ailments they drew up include agoraphobia (an anxiety disorder); a bacterial infection called brucellosis; chronic arsenic poisoning (arsenicosis); chronic anxiety syndrome; "chronic neurasthenia of a severe grade"†; Crohn's disease (an inflammatory bowel disorder); cyclic vomiting syndrome; depression; extreme hypochondria; gastric ulcers; gout; lactose intolerance; an inner ear

* "Unstable angina" is defined as angina that occurs at rest, and becomes more severe and more frequent.

† Neurasthenia was an ill-defined Victorian fad disease of unknown etiology, characterized by physical and mental exhaustion.

disorder called Ménière's disease; panic disorder; mitochondrial encephalomyopathy; lactic acidosis and stroke-like episodes; a maternally inherited neuromuscular disorder; a psychosomatic skin disorder; and repressed homosexuality.

In 1959, during the centennial anniversary of the publication of Darwin's most famous work, Saul Adler, an Israeli scientist who specialized in tropical medicine, concluded that Darwin's health woes were almost certainly *not* psychological in origin. Indeed, he believed they had begun decades earlier and thousands of miles from Down House—on the very journey that made him famous.

In 1908, the Brazilian physician Carlos Chagas was invited by officials from the Central Railroad of Brazil to visit a village called Lassance. The rough-and-tumble town, known for its droughts and poor soil, is located along the banks of the São Francisco River in the state of Minas Gerais. It was the terminus of a new railway line, and so it was packed with railroad workers, most living in rugged, unsanitary conditions. Chagas had been summoned because many of the workers were falling ill and dying from what was believed to be malaria.

Though much has been written about malaria, the term "tropical scourge" cannot convey the horrible devastation brought on by this most lethal of all mosquito-transmitted diseases. During the French effort to build the Panama Canal several years earlier, the malaria/yellow-fever tag team killed an estimated twenty-two thousand workers.*

Malaria is spread when an uninfected female *Anopheles* mosquito bites an infected person and acquires the protozoan parasite *Plasmodium* from their blood. The mosquito then transmits the parasite to the next person

* According to the World Health Organization (WHO), malaria killed 405,000 people in 2018, a devastating number, and 67 percent were children under five years of age. Around 93 percent of all malaria-related deaths in 2018 occurred in Africa.

it bites. Once inside the human body, the parasite enters the circulatory system and travels to the liver, where it replicates and can lie dormant for up to a year. Once the protozoan exits the liver and infects red blood cells, it undergoes additional reproduction, with the blood stage of the parasite responsible for symptoms that include high fever, shivering, chills, headache, nausea, vomiting, and body aches.

Chagas, who specialized in the disease, set up a simple lab, but he soon realized that he wasn't dealing with malaria at all. Instead, the malady he was observing seemed far more reminiscent of African sleeping sickness, a deadly disease transmitted by the tsetse fly. The stricken Brazilian workers Chagas saw exhibited an array of acute symptoms, which ranged from fever, headache, pallor, and difficulty breathing to abdominal and muscle pain. And many arrived at his makeshift lab with swollen purple eyelids. Although most patients seemed to recover quickly from the illness, approximately 30 percent of them went on to develop a far more serious set of chronic symptoms. These included severe digestive tract issues, like an enlarged esophagus and colon, neurological problems, like stroke, and cardiac-related issues that included irregular heartbeat, cardiomyopathy (a disease of the heart muscle), and congestive heart failure, a generalized term for a chronic condition in which the myocardium doesn't pump enough blood to meet the requirements of the body.

Chagas determined that the culprit was *Triatoma infestans*, a bloodsucking insect known in Portuguese as *o barbeiro*—the barber—presumably for its habit of nicking victims on the face. Like mosquitoes, *Triatoma* and its relatives don't have chewing mouthparts, and so technically they do not bite. Instead, they employ a pair of hypodermic needle–like stylets to pierce the skin and an underlying blood vessel. Saliva containing an anticlotting agent (a.k.a. an anticoagulant) is then injected into the blood. Finally, the insect snorks up a blood meal as if through a straw.

"Knowing the domiciliary habits of the insect," Chagas wrote, "and its abundance in all the human habitations of the region, we immediately stayed on, interested in finding out the exact biology of *o barbeiro*, and the transmission of some parasite to man."

The physician soon discovered his parasite: a protozoan that spent part of its life cycle in the hindgut of the insect. Initially, Chagas believed that *o barbeiro*'s "bite" transmitted the pathogen to humans, but the route of infection turned out to be something a bit more unsavory. To clear additional space in its digestive tract and to eliminate excess fluid weight filtered from its meal, *Triatoma* defecates while gorging on blood.

The common vampire bat (*Desmodus rotundus*), another obligate blood feeder and messy eater, exhibits a similar weight-reducing strategy. As these bats feed, their high-powered kidneys allow them to quickly eliminate the excess liquid from their blood meals by urinating, even while their victims are being drained. Because vampire bats need to consume a truly enormous amount of blood each night—up to 50 percent of their body weight—carrying any excess weight would make it difficult for the bats to make their unique flight-initiating jumps.

Back at the insect poop pile, the parasite in *Triatoma*'s feces enters its human host when it is rubbed into the puncture wound or a nearby mucous membrane, typically one associated with the eyes and mouth. The characteristic swelling of the victim's eyelids observed by Chagas occurs after *o barbeiro*'s fecal material is accidentally rubbed into an eye. Alternately, animals and people can be infected orally, through consumption of food or drink contaminated by infected *Triatoma* feces. The infection can also be passed from mothers to their babies at birth.

Chagas named the protozoan *Trypanosoma cruzi*, in honor of his mentor Oswaldo Cruz, who made important contributions to discovery of trypanosome-transmitted diseases. Subsequent studies have shown that *T. cruzi* enters the blood through capillaries in the previously mentioned mucous membranes, eventually invading the lining (endothelium) of

blood vessels supplying the heart. From there, the invader gains access to cardiac muscle cells.

In approximately 20 percent of those infected by *T. cruzi*, this microbial blitzkrieg leads to irreversible structural and functional damage to the heart and associated vasculature.* Making matters even worse is the fact that unlike other trypanosomes, *T. cruzi* is an intracellular parasite, which means that it enters into normal cells and multiplies there, instead of remaining in the blood, where it could be more easily treated with medications like antibiotics. Recent studies have shown that although *T. cruzi* appears to be absent from the blood of chronic victims, the parasite often persists deep within the heart musculature. There, decades after the initial infection, destruction of the myocardium becomes the major cause of mortality for what we now call Chagas disease, with detection of the parasite possible only postmortem.

Chagas and the researchers who followed him also determined that the protozoan's creepy-crawly insect host belonged to a neotropical family called Reduviidae, which includes more than one hundred species. Some reduviids exist as ambush predators, while others feed on the blood of nesting rodents and sleeping mammals. A few nonreduviid species, including the notorious bedbug, have also become adapted to living with humans, attacking victims as they sleep. But while bedbugs are not yet known to transmit disease, the barber bug, *Triatoma infestans*, and its Central American cousin, *Rhodnius prolixus*, deposit their trypanosome-laden feces onto a multinational list of victims. Housing with thatched roofs and adobe walls is prime habitat for the bugs, and so most of the people they infect are those living in poverty.† Oral transmission through feces-contaminated food and drink is also a serious problem.

In Peru, the bugs are known as *chirimacha*; in Venezuela, as *chipo*; and in

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* A similar invasion by *T. cruzi* can take place in the liver, lungs, spleen, brain, or bone marrow.

† *Rhodnius prolixus*, the second-most important vector for Chagas disease, is also found in northern South America.

Central America, as *chinche picuda*. In the Argentinian Andes that Charles Darwin visited in 1835, the bloodsucker was (and is) known as *vinchuca*, although Darwin mistakenly referred to it as "Benchuca" in his notes.

This brings us back to the 1959 study by Saul Adler. The eminent Israeli parasitologist suggested that Chagas disease was responsible for Darwin's chronic ill health and eventual death. "His symptoms can be fitted into the framework of Chagas disease at least as well as into any psychogenic theory for their origin," Adler wrote.*

The key to Adler's hypothesis was the fact that Darwin himself had described being set upon (and presumably pooped on) by Benchuca, a.k.a. *vinchuca*, a.k.a. *Triatoma infestans*, while visiting Argentina in 1835:

> At night I experienced an attack, & it deserves no less a name, of the Benchuca, the great black bug of the Pampas. It is most disgusting to feel soft wingless insects, about an inch long, cawling [sic] over ones body; before sucking they are quite thin, but afterwards round & bloated with blood, & in this state they are easily squashed. They are also found in the Northern part of Chili & in Peru: one which I caught at Iquiqui was very empty; being placed on the table & though surrounded by people, if a finger was presented, its sucker was withdrawn, & the bold insect began to draw blood. It was curious to watch the change in the size of the insects body in less than ten minutes. There was no pain felt. —This one meal kept the insect fat for four months; In a fortnight, however, it was ready, if allowed, to suck more blood.

The initial response to Adler's hypothesis was mixed. Two journal articles, one by Nobel Prize–winning biologist Peter Medawar in 1967, suggested that Darwin "had both Chagas infection and a neurosis."

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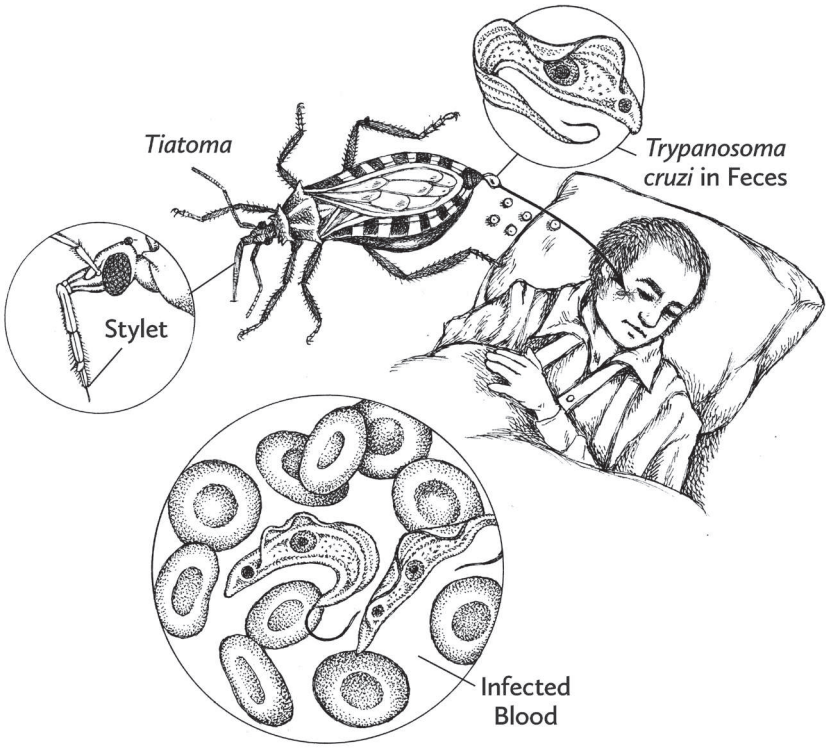
* Psychogenic illnesses are those thought to arise from mental or emotional stressors.



Others, however, weren't convinced. In 1977, Ralph Colp Jr. published a book on Darwin's illness in which he claimed that Darwin's health problems were purely stress-related. He followed up with a second volume in 2008 in which he refuted the Chagas disease hypothesis, writing, "Adler's theory of Chagas disease met with a series of receptions: acceptance, rejection, again acceptance, and then controversy."

Other scientists rejecting the Chagas hypothesis noted that Darwin had reported "palpitations and pain about the heart" even before the *Beagle* set sail, an indication of previously existing heart disease. Those poo-pooing (sorry) the possibility that Darwin had Chagas disease also mentioned the fact that there was no record of him having "the fever that characteristically accompanies the initial [Chagas] infection" (i.e., the acute phase of the disease that almost always presents before the

dormancy period). Similarly, there were no reports in Admiralty records of the voyage indicating that other crew members had come down with Chagas disease. The latter isn't terribly surprising, though, since the disease was not characterized until 1909.

In 2011, Darwin's health and death became a topic of speculation at the Historical Clinicopathological Conference, held at the University of Maryland School of Medicine, where previous examinations into the demise of long dead patients included discussions of Alexander the Great, Christopher Columbus, Edgar Allan Poe, and Ludwig van Beethoven. The attendees had an extensive list of Darwin-related diagnoses to discuss, but before they did, gastroenterologist Sidney Cohen, one of the conference organizers, made sure to temper the media's expectations with this statement: "This is purely a symptom-based assessment, an analysis of this journey of invalidism that [Darwin] suffered throughout his life."

Ultimately, Cohen and his colleagues concluded that "Chagas [disease] would describe the heart disease, cardiac failure or "degeneration of the heart"—the term used in Darwin's time to mean heart disease—that he suffered from later in life and that eventually caused his death." They also observed that the onset of Darwin's chronic illness, which he described in his writings as beginning in 1840, occurred after a latent period of several years past the 1836 return of the *Beagle*. This latency would be expected after an initial exposure to *T. cruzi*.

Had that exposure occurred, the protozoan would have first invaded Darwin's circulatory system, then colonized his stomach, small intestine, and gallbladder, where damage to associated nerves would have resulted in gastrointestinal distress characterized by excessive vomiting, flatulence, and belching—which, indeed, Darwin had.* Finally, another complication from Chagas disease, chronic heart failure, would have occurred, killing the most famous naturalist of all time.

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* Cohen also suggested that, absent Chagas disease, cyclic vomiting syndrome and gastric ulcers could explain Darwin's long-term gastrointestinal distress.

In an attempt to resolve once and for all the mystery of Darwin's demise, there have been requests to test his remains for the presence of *T. cruzi* DNA using modern polymerase chain reaction (PCR) techniques. This procedure has been used on samples from nine-thousand-year-old mummies from Chile and Peru, proving that Chagas disease was already well established in human populations in South America by then. One man's research project is, however, another man's desecration, and the request was turned down by the curator of Westminster Abbey, where Charles Darwin is buried.

As a result, the best that scientists can do is speculate. Though Chagas disease is consistent with Darwin's symptom patterns, we cannot be certain if his ailments and death were the result of the disease, the disease in combination with other ailments, or something else entirely. "Darwin's lifelong history does not fit neatly into a single disorder . . . I make the argument that Darwin had multiple illnesses in his lifetime," Cohen concluded.

Whether or not Chagas disease contributed to Darwin's ill health and eventual death, the naturalist would doubtless have been interested in the fact that the geographical territory of the bitey bug in question is expanding. As the climate warms, the range of *Triatoma infestans* is spreading north. Additionally, some species of reduviids not previously known to feed on humans are now making the switch—likely due to human encroachment into natural areas. Perhaps predictably, an explosion in the number of Chagas disease victims has followed. According to the World Health Organization (WHO), between six and seven million people are currently infected, mostly in Latin America, and the Centers for Disease Control and Prevention (CDC) estimates that more than three hundred thousand people in the United States have the disease.

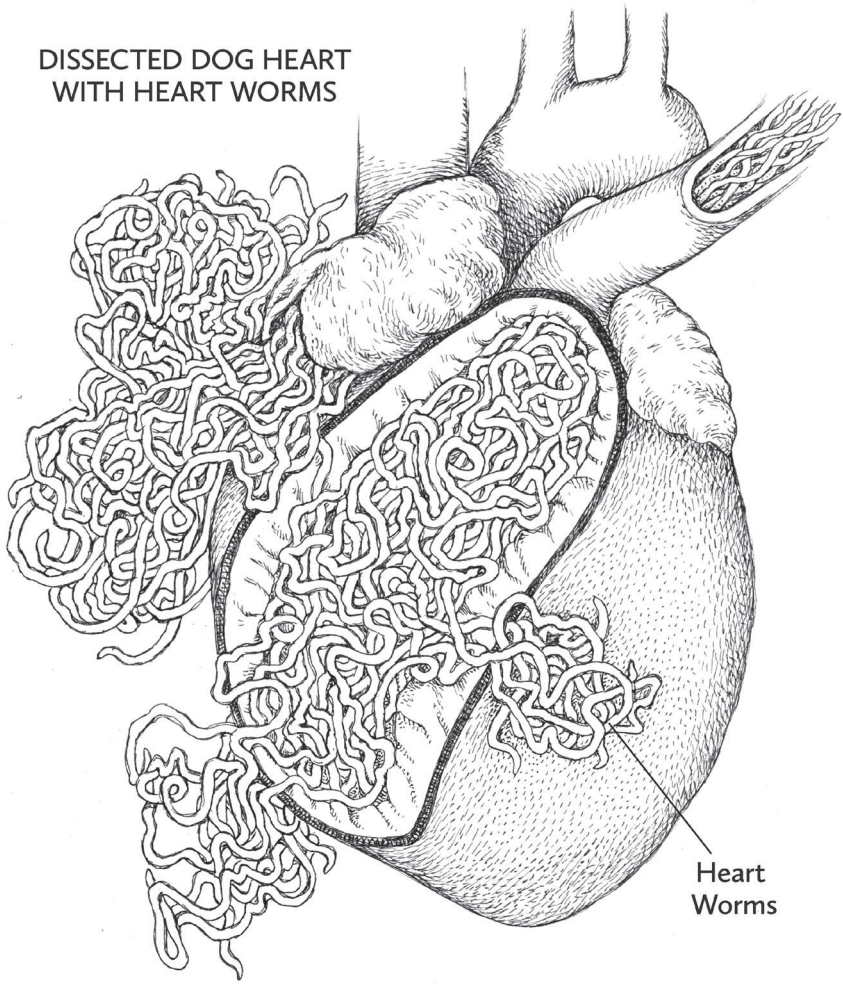
According to Loyola University New Orleans professor Patricia Dorn, a Chagas disease expert, if there is a silver lining in all of this doom and gloom it's that the number of new infections in Latin America is actually

dropping. This, she explained to me, is primarily due to the effectiveness of pesticide spraying programs. Additionally, Dorn said, although up to 50 percent of the North American *Triatoma* specimens tested were carrying the *T. cruzi* parasite, the bites of these species are relatively ineffective at transmitting Chagas disease. She explained that this was because, unlike their southern relatives, the North American insects do not defecate while feeding. Because of these fortunate table manners, Dorn estimates that only one in every two thousand bites transmits the disease to a victim. As a result, the vast majority of people carrying the disease in the United States were *not* infected in the States. Instead, they were bitten in Latin America and brought the infection back home with them.

It's not all good news, however. Even when they do not transmit *T. cruzi*, *Triatoma* bites are a primary cause of anaphylaxis, a serious and potentially life-threatening allergic reaction familiar to those with severe asthma or peanut allergies. Dorn also told me that a recent paradigm shift toward an antiparasitic treatment for chronic Chagas disease remains controversial, since it relies on the assumption that the *T. cruzi* parasite remains present in all chronic sufferers, rather than placing the blame (as previously thought) on the patient's overactive immune response.

Finally, although transmission of *T. cruzi* to humans is still rare in the United States, American dogs are showing postmortem signs of the disease, quite possibly because they eat the *T. cruzi*–infected insects and/or come into contact with their feces. Texas A&M's veterinary school associate professor Sarah Hamer led a study on government work dogs along the Texas-Mexico border, and found that 7.4 percent of the study animals tested positive for Chagas disease. In a similar study on shelter dogs across seven diverse ecoregions of Texas, Hamer and her colleagues found that "a conservative statewide average of 8.8%" of the dogs tested positive for the infection.

Arguably, the most infamous of blood-borne canine diseases is heartworm. Caused by the parasitic roundworm *Dirofilaria immitis*, it can also affect cats, coyotes, foxes, ferrets, bears, sea lions, and even



humans. The only method of transmission is through the bite of an infected mosquito. If allowed to progress, masses of threadlike worms up to twelve inches in length will fill the right side of the heart and the great veins supplying it, giving them the appearance of being stuffed with angel-hair pasta. For dog owners, prevention (through monthly pills or biyearly shots) is far cheaper and easier than treatment, in which drugs are administered to kill the worms. After treatment, the dead parasites immediately begin to break down, necessitating that treated dogs avoid exercise for several months, lest pieces of the heartworms become lodged in the pulmonary vessels, causing death.

The story of reduviid bugs, the *T. cruzi* parasites they harbor, and Chagas disease in the twenty-first century is one that is still unfolding. What is known, however, is that the insects that may have contributed to the lifelong sickness and eventual death of "the Father of Evolution" are themselves evolving—adapting to habitat destruction by preying upon the very species that brought it about. Thus far, we have been spared widespread outbreaks of Chagas disease, but future changes in insect behavior, combined with climate change and the encroachment of humans (many of them living in conditions of poverty), could have disastrous consequences. And whether or not Charles Darwin suffered from Chagas disease, it is a near certainty that he would have found the barber bug's evolution as fascinating as it is frightening.

PART 3

From Bad to Better

Then heard he through her frame the busy life-works ply,
But the sound was not of life; and he knew that she must die.
—Ebenezer Jones

[11]

Hear Here: From Stick to Stethoscope

In 1816, on a cool September morning in Paris, thirty-five-year-old physician René-Theophile-Hyacinthe Laënnec was walking past the Louvre palace when he saw two children playing with a long piece of wood. One child held an ear to the end of the stick while the other scratched the opposite end with a pin. Laënnec watched them for a few moments, their play providing him with a brief distraction from the harsh realities of his profession. For these were the days when consumption ran rampant in his beloved city, killing countless thousands of Parisians, including Laënnec's mother, brother, and two of his mentors.

Named for the observation that victims appeared to be slowly consumed by disease from within, the term "consumption" was originally used for several respiratory diseases, including lung cancer and bronchitis. The particular killer lurking in Paris, and the one that would become most associated with the term, had been marking the bones of its victims with characteristic knobby lesions* since the ancient Egyptians (where it showed up in the mummies), Greeks (who called it *phthisis*), and Romans (who referred to the wasting disease as *tabes*).

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* "Lesions" are defined as tissue damage caused by a disease or trauma.

Like the ancient physicians, Laënnec, his colleagues, and their fellow Parisians, had no clue what they were dealing with. The cause of consumption was thought to be a combination of bad air ("miasmas") and heredity. What they did know was that consumption killed slowly, draining victims of their energy and their color, and producing significant weight loss.

In a phenomenon that would later be echoed by the mid-1990s style known as "heroin chic,"* the symptoms of consumption became highly romanticized in the days during which Laënnec practiced medicine. In Europe and its current and former colonies, pale skin and waifish waists (the latter enhanced by stiff corsets) became the beauty standard for early nineteenth-century women. Artists, writers, and poets almost glorified the deadly disease. American essayist Ralph Waldo Emerson wrote that his consumptive fiancée was "too lovely to live long," while English poet and landscape gardener William Shenstone said, "Poetry and consumption are the most flattering of diseases." But unlike the doomed hourglass-figured heroines of *La Bohème* and *La Traviata*, people suffering from consumption were likely feeling anything but romantic. The illness tore through and shredded the great cities of Europe. Thousands of victims were laid to waste after draining bouts of night sweats, chills, and violent, uncontrollable coughing.

One symptom of consumption was the presence of lesions called tubercles (from the Latin for "little hill") on the lungs and lymph nodes. In 1839, the German physician Johann Lukas Schönlein may have been the first to use the modern moniker for the disease, tuberculosis (TB), though it would be nearly a half century before consumption would become widely known by that far less romantic-sounding name. The rebrand followed Schönlein's fellow physician and countryman Robert Koch's 1882 discovery that the tubercles were caused by a bacterium, which he named *Mycobacterium tuberculosis*.

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* Thin and pale-skinned, with dark under-eye circles, model Kate Moss became a sort of poster child for this, thankfully, brief pop-culture phenomenon.

Following this new knowledge came a dramatic revision in woman's fashion. Long, trailing skirts were abandoned, as they were thought to sweep bacteria into the home, and corset sales plummeted as well, since it was believed that in reducing the flow of blood, the undergarment would exacerbate the effects of TB. Men's styles were also affected, with beards and muttonchop sideburns falling out of favor, as they were thought to harbor hordes of microbes.

In the late 1800s, what had begun as instructions for sufferers of TB to find sunshine, fresh air, and altitude evolved into the massive sanatorium movement, with facilities opening across mountainous regions of Europe, like the Alps. In 1885, the first US sanatorium opened in upstate New York's Saranac Lake, followed by a facility in Denver.

It wasn't until 1943, though, that microbiologist Selman Waksman discovered a true cure for TB. He isolated the substance streptomycin from another bacterium and determined that it killed *M. tuberculosis*. The first human patient received the antibiotic in late 1949 and was cured of the disease. More new drugs followed, and by the early 1990s it seemed as if TB might be completely eradicated. Unfortunately, that was not to be. As for why, there was plenty of blame to go around: funding was pulled for worldwide TB drug distribution, many infected people did not stick with their treatment regimens, and cheaply produced antibiotics did not contain what they claimed to contain. As a result, mutated forms of TB began appearing on the scene, and these strains were resistant to antibiotics that had been effective until then. Multidrug-resistant tuberculosis (MDR-TB) has now clawed its way back to plague status across much of the world, with 1.4 million deaths from TB reported in 2019 by WHO.*

Though not spread by skirts or sideburns, as feared by people in the

* According to WHO, two-thirds of the approximately ten million cases of TB worldwide in 2019 originated in eight countries. In order of incidence they are: India, Indonesia, China, the Philippines, Pakistan, Nigeria, Bangladesh, and South Africa.

late 1800s, tuberculosis is in fact *highly* contagious. It travels through the air via coughing, sneezing, or spitting. Once internalized, the bacterium attacks the lungs primarily, but can also affect the kidneys, spine, brain, and even the heart, where it can cause inflammation, a thickening of the outer pericardium, and fluid buildup in the pericardial space. The heart infection known as tuberculous endocarditis (TBE) was first diagnosed in 1892. It can be especially deadly because even today it is typically diagnosed late, and often accidentally, during procedures like heart valve replacement or open-heart surgery. Sometimes it is discovered only during autopsy.

For physicians making determinations about TB in 1816, there were two principal modes of diagnosis. Both involved listening to the sounds made by the body, a practice known as auscultation (from the Latin verb *auscultare*, "to listen"). The first method was known as percussion, during which the physician would tap on the patient's chest (or abdomen) with a middle finger or a small hammer and listen as the sound resonated back to their presumably trained ear. The method was developed by physician Leopold Auenbrugger, the son of an Austrian innkeeper. He had seen his father tapping on wine barrels to determine the volume of wine they held, and he adapted the technique to determine whether a patient's chest was full of secretions. If so, like a full wine barrel, the tapping would produce a sound that Auenbrugger described as low-pitched and dull. For his patients, the sound almost invariably meant that they were suffering from consumption. Auenbrugger had honed his ability to differentiate between these tones while working at a Spanish military hospital in the 1750s. He checked his finding by performing autopsies to determine if there was TB-related fluid buildup in the chest cavity surrounding the heart and lungs.

The second sound-related technique available to early nineteenth-century doctors was called "immediate auscultation." In effect, this meant pressing an ear directly to the patient's chest in order to listen for lung and

heart sounds. This came along with a wide-ranging set of issues. Many patients did not bathe, while others were infested with lice and other tiny vermin. Still others were too obese for chest sounds to be heard clearly, and the very idea of a male doctor pressing his head to a female's breast presented its own problems.

After encountering a particularly embarrassing situation with a plump female patient, Laënnec remembered his earlier encounter with the two children at play:

> I recalled a well known acoustic phenomenon: if you place your ear against one end of a wood beam the scratch of a pin at the other end is distinctly audible. It occurred to me that this physical property might serve a useful purpose in the case I was dealing with. I then tightly rolled a sheet of paper, one end of which I placed over the precordium (chest) and my ear to the other. I was surprised and elated to be able to hear the beating of her heart with far greater clearness than I ever had with direct application of my ear. I immediately saw that this might become an indispensable method for studying, not only the beating of the heart, but all movements able of producing sound in the chest cavity.

Laënnec had invented the stethoscope (from the Greek *stēthos*, for "chest," and *skopein*, meaning "to explore") and he spend the remainder of his life experimenting with a design. He settled on one that was nearly indistinguishable from the ear trumpets used by the hard of hearing. Laënnec also learned to differentiate the chest sounds heard through the stethoscope made by patients suffering from pleurisy, emphysema, pneumonia, and, of course, tuberculosis. The invention gave physicians another measurement, like pulse rate, that could be compared to a generalized "normal" reading, adding an important diagnostic tool to their black leather bags.

Stethoscopes also caused quite a stir among the Parisians who could afford them, or boast that their physicians used them. According to nineteenth-century specialist Kirstie Blair, along with this surge in popularity came "a growing fascination in medicine and in popular culture with the operation of the heart, pulses, and circulation."

Not long after getting married in 1824, Laënnec began to suffer a series of symptoms that included weakness, coughing, and shortness of breath. Leaving Paris for the improved climate of Brittany, he experienced some slight improvement, but soon his condition worsened. Perhaps unwilling to accept what he already knew, Laënnec gave his stethoscope to a nephew, asking him to auscultate his chest and to describe the sounds he heard. The resulting diagnosis was horrific. He was suffering from

"consumption," the disease he himself had helped to elucidate with his invention. René Laënnec died of tuberculosis on August 13, 1826. He was forty-five years old.

Today, tuberculosis remains a serious health problem, especially in developing countries where socioeconomic conditions and poor healthcare infrastructure make it difficult to obtain the monthslong antibiotic treatment required to cure multidrug-resistant TB.

The stethoscope, meanwhile, has undergone tremendous innovation since its invention, but the basic concept remains the same. The two-eared (binaural) version was invented in 1851 by Irish physician Arthur Leared and went into production the following year. It remains a physician's go-to instrument for listening to a patient's heart and lungs. It is also used to check on the condition of blood vessels, like the carotid artery, where the sound of blood squeezing past a blockage has been well characterized.

And though the stethoscope no longer has quite the same high-tech appeal that it did in nineteenth-century Paris, in a 2012 study, it beat out surgical scrubs, the reflex hammer, the otoscope (the thing they stick into your ear), and the pen, as the medical equipment associated with the highest perception of trustworthiness of the doctor seen with it.

Dr. Laënnec would have been proud.

Surgery of the heart has probably reached the limits set by nature to all surgery; no new method, and no new discovery, can overcome the natural difficulties that attend a wound of the heart.
—Stephen Paget (in 1896)

[12]

Don't Try This at Home . . . Unless Accompanied by a Very Special Nurse

A little more than a century after René Laënnec's discovery of the stethoscope, another breakthrough would provide crucial inroads into multiple aspects of modern cardiology. This new technique would become an integral tool in the placement of cardiac pacemakers and the replacement of heart valves, allowing physicians to reopen closed coronary arteries and deliver drugs directly into the heart—all without the risk and trauma of cracking open a patient's rib cage, or blindly puncturing the heart wall with a syringe. What's more, the story behind it would turn out to be as strange as anything a novelist could dream up.

Though Werner Forssmann was born into a family well entrenched in Berlin's upper middle class, things became far more difficult for him when his father was killed in action in 1916 during World War I. With his mother forced to spend long hours at an office job, twelve-year-old Werner was encouraged by his grandmother and his physician uncle to continue his education. Bright and scientifically inquisitive, he took their advice, graduating from one of Germany's best secondary schools

before entering medical school at the Friedrich-Wilhelm University in Berlin in 1922.

While studying to become a surgeon, Forssmann became intrigued with the concept of examining and treating the heart atraumatically—that is, without cutting into it. He realized that procedures like intracardiac injections, which were the only method to get medication directly into the heart at the time, were as dangerous as they were important. Blindly puncturing the walls of a beating heart could, for example, damage coronary vessels and lead to bleeding into the pericardial cavity. Forssmann reasoned that if a noninvasive technique yielding similar effects could be developed, it would become an important tool for cardiologists.

Forssmann graduated from medical school in 1928, and was a year into a surgical residency at a hospital near Berlin when he recalled seeing an old print of a researcher passing a tube down the jugular vein of a horse and into the right side of the horse's heart. This had been done in order to measure the pressure of the blood being pumped to the lungs. Forssmann tried in vain to convince his superiors that something similar could be done in humans, using the antecubital vein, a superficial vein of the upper arm, located near the crease of the elbow. Since the vessel also carries blood in a fairly direct route back to the heart, Forssmann reasoned that it could be used to gain access to the organ without surgery. Through the antecubital vein, doctors might be able to inject dyes that could be viewed with a fluoroscope, a form of x-ray machine that provided real-time images of the interior of an object.*

* Although the danger of burns from fluoroscope-related exposure to ionizing radiation had been known since Wilhelm Röntgen's experiments in 1895, fluoroscopy was used for some seriously trivial reasons, none more so than the Foot-O-Scope. Installed in shoe stores beginning in the 1930s, customers would insert their feet into the boxy-looking contraption as a way to fit them with properly sized shoes. Amazingly, many of the estimated ten thousand units sold in the United States were still in use until the 1970s.

Forssmann's supervisors disagreed, and though they forbade him from attempting the procedure, the newly minted physician decided to carry on anyway. For a tube with a suitably small diameter, he settled on a urethral catheter, which also had the proper length. The problem Forssmann now faced would be getting his hands on the catheters and other surgical instruments he required, since they were kept in a locked closet to which he had no key. Undeterred, his solution was to chat up the operating room nurse, who *did* have a key. According to Forssmann, he "started to prowl around nurse Gerda Ditzen like a sweet-toothed cat around the cream jug." The young surgeon's pitch was apparently so effective that Ditzen not only gave up the keys to the closet, but she eventually volunteered to be his experimental subject.

On the appointed night, and well after the surgical theater had closed, the stealthy pair made their move, using Ditzen's keys to access a small operating room. The nurse expressed a desire to sit in a chair during the procedure, but Forssmann convinced her that it would be best if he strapped her down to a surgical table instead. She agreed, and Forssmann proceeded to prepare her left arm—or at least that is what she believed. Halfway through the preparations, Forssmann slipped away for several minutes, which must have greatly puzzled the strapped-down nurse. Unbeknownst to Ditzen, Forssmann had been busy locally anesthetizing his own arm, making an incision near the bend of his elbow, and slipping the well-oiled catheter into *his* antecubital vein. Only when he returned to her side did Nurse Ditzen realize that she had been duped.

After some well-earned grumbling, the nurse agreed to continue assisting Forssmann, which must have come as something of a relief to him since he had already fed the catheter in to a distance of twelve inches. He untied his partner in crime, and the pair set off for the x-ray room, where Ditzen was able to convince the x-ray nurse on duty to take a fluoroscopic image of Forssmann's shoulder and chest. Forssman then had

to fend off a concerned fellow-physician friend, who had rushed into the x-ray room, threatening to yank out the catheter. Forssmann managed to do so, but to his disappointment, when he examined an initial radiograph he realized that the catheter tip had not yet reached his heart.

Undeterred, he advanced the tube to the twenty-four-inch mark, reportedly feeling no pain, only a sensation of warmth as he guided the catheter along its path. As the tip reached the base of his neck, Forssmann inadvertently stimulated the nearby vagus nerve and began coughing. After recovering, he stood behind the fluoroscope while Nurse Ditzen held up a mirror so that he could watch his own progress on the fluoroscopy machine. Then he pushed on, literally, until the end of the catheter finally entered the right auricle, an ear-shaped external extension of the right atrium. The radiography technician snapped several pictures, which provided Forssmann with the fluoroscopic evidence he needed, and which would subsequently be published in a scientific paper.

Although Forssmann took some serious flak from his supervisors, he was allowed to continue on in his position as a surgical resident, eventually transferring to the Berliner Charité Hospital, one of the largest university hospitals in Europe. But in November 1929, things fell apart quickly after the media descended on the esteemed facility and began writing about what Forssmann had done. Instead of congratulating the young physician, the medical community widely reacted with contempt. Bizarrely, the chair of surgery at another hospital charged Forssmann with plagiarism, claiming (with no substantiating evidence) that *he* had performed the first cardiac catheterization in 1912.

Meanwhile, derided by his colleagues for what they saw as a publicity stunt, Forssmann was dismissed on the grounds that he had not received permission to carry out the catheterization. Rehired in 1931 because of his surgical skills, he performed a total of nine catheterizations on himself over the course of a year before he was given the boot yet again. Taking a

position at the municipal hospital in Mainz, Forssmann met and married Elsbet Engel, a resident working there in internal medicine. Soon, though, they were *both* let go, since married couples were forbidden to work together.

Perhaps taking the hint, Forssmann left the field of cardiology, becoming a urologist and opening up a practice with his wife (equipped, one must assume, with a full complement of catheters) near Dresden. He served as a medical officer for the German army during World War II but was captured in 1945 and served in an American POW camp for a short time until the end of the war. He returned home to find Dresden reduced to ashes but his family, miraculously, alive.

For the next three years, Forssmann was forbidden to practice medicine because of his affiliation with the Nazi Party, which he had joined in 1932, and so he worked as a lumberjack while his general practitioner wife became their growing family's principle means of support. In 1950, he was able to resume his urology practice, this time in the impressively named spa town of Bad Kreuznach.

As an outsider in the now fast-developing field of cardiology, Forssmann watched as cardiac catheterization labs opened in the United States and London, where his pioneering efforts were lauded. In Germany, however, he was turned down for a professorship at the University of Mainz because he had failed to complete his PhD dissertation.

"It was very painful," Forssmann said about his exile, many years later. "I felt that I had planted an apple orchard and other men who had gathered the harvest stood at the wall, laughing at me."

Despite his *serious* moral failings before and during the war, Forssmann was awarded a Nobel Prize in Physiology or Medicine in 1956 for his work on cardiac catheterization, which, after all, turned out to be a groundbreaking procedure. Upon learning that he'd won the award, he told a reporter, "I feel like a village parson, who has just learned that he has been made bishop."

Soon after, "Bishop" Forssmann was offered a position heading up a German cardiovascular institute. He turned the job down, explaining that it had been over twenty years since he had last experimented on himself, and that he lacked knowledge about recent advancements related to the cardiovascular system. Undeniably true, however, is the fact that many of these advancements had resulted from his own pioneering efforts in the field of cardiology.

Doctors now perform catheterizations for many reasons, and they do so by threading catheters through veins in the arm, groin, or neck to approach the heart or any of the four coronary arteries supplying it. One important use of catheters is balloon angioplasty. Picture inflating a balloon in a narrowed or blocked coronary blood vessel in order to widen it. After this, the catheter is used to place an arterial stent, a springlike device that holds back the walls of the newly widened vessels, preventing them from narrowing again. Cardiac catheters are also used to take pressure measurements in specific heart chambers, to snip off tiny bits of cardiac tissue for biopsies, to look for valve problems, and to repair or replace those valves if they're found to be defective.

After suffering from two myocardial infarctions, Werner Forssmann died in 1979, but not before he wrote an autobiography, the aptly titled *Experiments on Myself*. In it, he spent little time writing about the swastika-wearing elephant in the room—his Nazi Party affiliation. According to a journal article on the topic, he may have joined the party out of an early belief that National Socialism was better than the alternative, communism, but his attitude eventually changed to one that was more critical of Nazi ideology, a political trajectory typical of many German doctors during the era.

According to the support letters that Forssmann gathered in order to earn the "denazification certificates" that would allow him to work again, his mentors and associates described him as neither a militarist nor an activist, but as someone who detested the violence that was carried out

by the party he had joined. There is evidence to suggest that he refused the opportunity to carry out unethical experiments and that he continued to offer Jews medical care after it had been disallowed. Ultimately, he was designated as a Category 4 Nazi (i.e., "a follower") by the French Occupation Administration and fined 15 percent of his salary for three years.

In the end, readers are left with the story of a groundbreaking discovery—the unique aspects of which are tainted by the abominable political affiliation of its discoverer.

Somewhere, far down, there was an itch in his heart,
but he made it a point not to scratch it.
He was afraid of what might come leaking out.
—Markus Zusak, *The Book Thief*

[13]

"Hearts and Minds" . . . Sort Of

The idea of a connection between the mind and the heart (as well as the blood running through it) remains firmly entrenched in our language, songs, and poetry. The words of William Shakespeare, John Lennon and Paul McCartney, Emily Dickinson, Tom Petty, and Stevie Nicks are bursting with cold hearts, broken hearts, and hearts given away in vain, while other tickers are lonely, get dragged around, or get chained up. Of course, there are also hearts that are bursting with joy or have messages coming straight from them. As for blood, take a minute or two and see how many blood-related idioms you can come up with for anger or lust. I'll wait.

Okay, that's enough (and sorry if that little exercise made your blood boil).

All of this is likely due, in large part, to roughly fifteen hundred years of adherence to the teachings and terminology of the Roman physician Galen and his influential followers, who believed that the heart was the seat of the soul as well as emotion. Additionally, some of these concepts, like "cold-blooded" and "hot-blooded," were themselves handed down from even more ancient philosophers like Hippocrates and Aristotle, who associated the heart with emotions, the soul, intelligence, and memory.

Traditional Chinese medicine, which has many present-day adherents, also has strong associations between the mind and heart. TCM has always held that the heart is primary among the organs.* In addition to its role as a pump, its practitioners believe it to be involved in emotional and mental processes, serving as the residing place of the mind and spirit, consciousness, and intelligence. TCM also holds that heart dysfunction leads to psychological and physiological problems, ranging from palpitations and restlessness to pallor, shortness of breath, and memory loss. It is noteworthy that all of these things are also acknowledged as symptoms of heart disease by Western medicine—albeit with alternative explanations for their causes.

Likewise, the holistic healing system of Ayurvedic medicine emphasizes the role of the heart as vital to the concept of mind/body/spirit. It maintains that while Western medicine, which focuses on symptoms and diseases, is often a lifesaver, a healthy life also depends on keeping the bodily energies (*vata*, *pitta*, and *kapha*) in balance. Ayurvedic medicine proposes to maintain this balance through a combination of diet, herbs, meditation, and other relaxation techniques like yoga.

Although advances in the fields of medicine, psychology, and psychiatry, as well as modern research into behavioral physiology and neurophysiology, have conclusively proven that the heart is *not* the seat of the mind, it took centuries for that concept to firmly take hold in the West. The first hints of movement away from cardiocentrism came as early as the seventeenth century—but these claims were often based on poor or nonexistent science, and as a result, they were met with nothing that might be confused with acceptance. Perhaps the most influential of the early noncardiocentrists was the philosopher and mathematician René Descartes (1596–1650). Descartes was famous for his contributions

* A 2019 study published in the journal *Geriatrics* estimated that 14 percent of the population of mainland China over the age of fifty utilized a TCM practitioner.

to geometry and algebra, but he also had a keen interest in anatomy and physiology. In 1640, he claimed that the true "seat of the soul, and the place in which all our thoughts are formed" was . . . no, not the brain, but close—a tiny nubbin of endocrine system inside the brain known as the pineal gland.

Located between the two cerebral hemispheres, the pineal gland gets its name from its roughly pine-cone shape. It was the last of the endocrine (i.e., hormone-releasing) glands to be discovered, and it is now known to be involved in regulating circadian rhythms, like our internal twenty-four-hour clock, and some reproductive hormones. Unfortunately, Descartes's concept of the pineal gland, which he described as suspended within one of the brain's chamber-like ventricles and surrounded by "animal spirits," was nearly as faulty as his explanation of its function. Descartes reckoned that, "Since [the pineal gland] is the only solid part in the whole brain which is single, it must necessarily be the seat of common sense, i.e., of thought, and consequently of the soul; for one cannot be separated from the other." Descartes also reasoned that since the brain had both left and right sides, that fact somehow precluded it from being involved in mental activities.*

Things began to turn around for Team Craniocentrism with the work of English physician Thomas Willis (1621–1675), who became a pioneer in the modern understanding of the brain and neurophysiology. Willis took part in autopsies during which he studied the anatomy of the brain and its intricate supply of blood vessels, especially a circular convergence of arteries at the base of the brain which came to be known as the circle of Willis. A professor of natural philosophy at Oxford, he was expected to teach his students about the soul, but, informed by his research, he

* Even further anatomically from the facts was the Flemish physician Jan Baptista van Helmont (1580–1644), who also believed that soul did not reside in the heart. Instead, he claimed, it could be found within the folds (or rugae) of the stomach.

used the brain as a starting point rather than falling back on the standard cardiocentric explanations. In addition to his work on human bodies, Willis conducted experiments on animals, determining that different regions of the brain were specific to different functions. Willis also used his anatomical knowledge and medical observations to provide early insight into the craniocentric origin of intellectual disabilities and psychological disorders, including narcolepsy and myasthenia gravis (a neuromuscular disease that causes weakness in skeletal muscles). He also described some disabilities affecting the brain as being caused by so-called disorders of brain chemistry. He even coined the term "neurology."

While all of this is incredibly impressive, readers should remember that the mid-seventeenth century was a *very* different time for scientist types. Although Willis was certainly a game changer in the field of neurobiology, his writings are rife with rationales that were clearly meant to placate the Church of England. Additionally, his treatment for emotional disorders left some room for improvement, since it included beating patients with a stick.

But quibbling aside, the ball had been set rolling, and by the 1670s, the brain, which for millennia had been believed to be little more than a radiator to cool the heart, would begin to replace that organ as the seat of the mind, soul, intellect, consciousness, and emotion—at least in the West. Coinciding with this shift was a growing knowledge about nerves and the involuntary workings of the autonomic nervous system, which meant a new understanding of the connections between the heart, body, and mind. As we'll soon see, this transition also ushered an understanding of how emotional factors like stress, poverty, personal tragedy, and unhappiness can lead to heart disease. And eventually, the cessation of brain activity, not the stilling of the heart, became the determinant of life's end.

Through it all, poets, songwriters, and other storytellers ignored the adoption of craniocentrism by the scientific community to varying degrees—and given the alternatives a shift would've created (Janis Joplin's "Piece of My Brain" and Joseph Conrad's *Brain of Darkness* come to mind), this was quite likely a wise move. Actually, though, even as modern science has conclusively eliminated a link between the heart and emotion/cognition, many Westerners still turn to that imagery not only in their metaphors and music, but in their own quasireligious beliefs.

Some people believe that the heart contains the emotional characteristics of its owner, and that a transplanted heart can transfer these personality traits from donor to recipient. Most famous, perhaps, was the experience described by the late Claire Sylvia, who in 1988 became Massachusetts's first heart-lung transplant recipient. She later documented her experience in a best-selling memoir. In it, the previously health-conscious dancer describes her recovery from transplant surgery, during which she began experiencing serious changes in her habits, attitude, and tastes in both fashion and food. The latter was exemplified by a newly acquired taste for beer and a sudden craving for junk food, especially chicken nuggets of the KFC variety. As it turns out, she informed her readers, these were the very objects found in the jacket of her eighteen-year-old organ donor after he was killed in a motorcycle accident.

In her own book, cultural historian Fay Bound Alberti floats several possible explanations that could either dispute or support the phenomena experienced by Claire Sylvia and others. One is wishful thinking: the organ recipient may feel reassured to imagine that some part of the donor's personality lives on within them. It is also possible that the recipient may find the feeling of possessing someone else's heart traumatizing and may undergo genuine psychological alteration as a result. Alberti mentions the possibility that there is in fact some form of "systemic memory," in

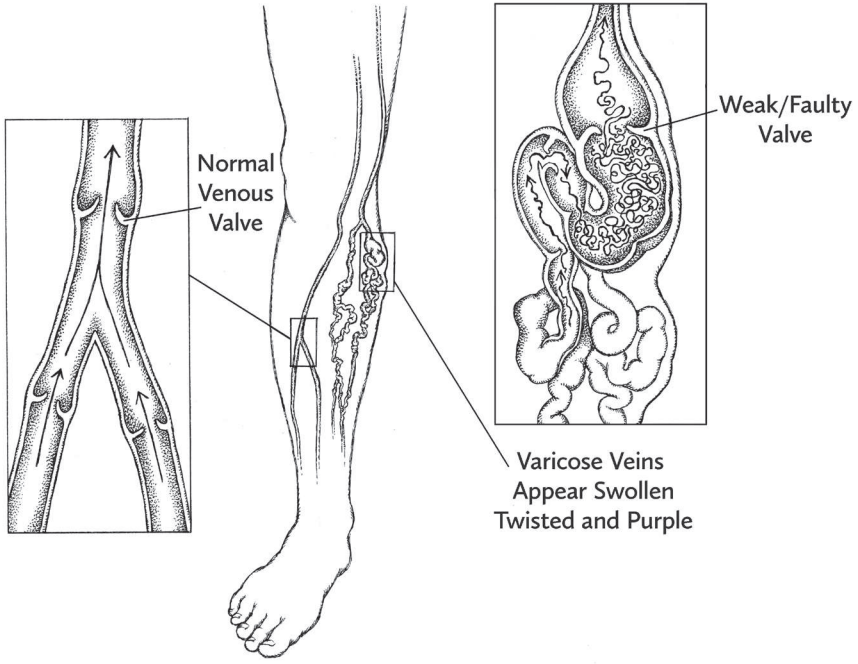
which the cells of the body are somehow imprinted with the experiences of the individual.

This last line of reasoning is unsupported by mainstream science, but it is often embraced by those who practice a previously mentioned type of alternative medicine called homeopathy. Homeopathic medicine holds that water retains the memory of the material dissolved in it, and that "like cures like"—in other words, that health benefits can be derived from ingesting pills, tinctures, or superdiluted solutions containing trace, or even undetectable, amounts of the substance that caused the malady in the first place.

As an example of the practice, one popular British homeopathy website recently suggested a new treatment for varicose veins, a circulatory problem in which weak or damaged venous valves allow blood to pool in the vessels, thereby twisting and distorting them. The condition is common in the feet and legs, where low-pressure blood must overcome gravity to return blood to the heart. Conventional treatments for varicose veins range from pressure socks (akin to the tight skin covering giraffe legs) to assorted therapies designed to close off affected veins and promote the growth of new vasculature in the area.

Meanwhile, the suggested homeopathic treatment is ingesting *Pulsatilla*, a genus of herbaceous perennials known as pasqueflower. Blooming in early spring, the plant's bell-shaped flowers are beautiful. Less beautiful is the fact that *Pulsatilla* is also *highly* toxic if consumed. In addition to inducing hypotension (blood pressure of less than 90/60 mm Hg) and reducing heart rate, *Pulsatilla* can cause diarrhea, vomiting, convulsions, and coma. Reportedly, the plant was used by indigenous Blackfoot people to induce abortions.

The British homeopathic website also notes that should *Pulsatilla* be unavailable, something called "Calc carb" is a good substitute, stating



that "People who do well with Pulsatilla often tend to be mild-mannered, avoiding arguments if they can . . . Whereas Pulsatilla tends to suit people who are generally warm-blooded and prefer to have fresh air in their homes, those requiring Calc carb are definitely chilly, with markedly sweaty feet. They hate damp conditions or damp weather but, like those needing Pulsatilla, tend to be mild in manner, perhaps verging more to the shy side or slightly nervous."

Personally, I would suggest that calc carb be referred to instead as "O ShAT" (oyster shells annihilated thoroughly) to reflect its true identity, as the main ingredient is bones, shells, and eggs. It is also used as a gastric antacid (e.g., Tums) and is found in household cleaners. If this is starting to sound familiar, that's because calc carb is often referred to as calcium carbonate ($CaCO_3$), or chalk.

Finally, although the phrase "There's a sucker born every minute"

is closely associated with showman and huckster extraordinaire P. T. Barnum, there is actually no evidence that he ever said it. Though its origin is uncertain, the phrase was said to have become popular among gamblers and confidence men starting sometime between the late 1860s and early 1870s. For some reason, I thought this information was worth including here.

"I think you are wrong to want a heart.
It makes people unhappy."
—L. Frank Baum, *The Wonderful Wizard of Oz*

[14]

What Becomes of the Brokenhearted?

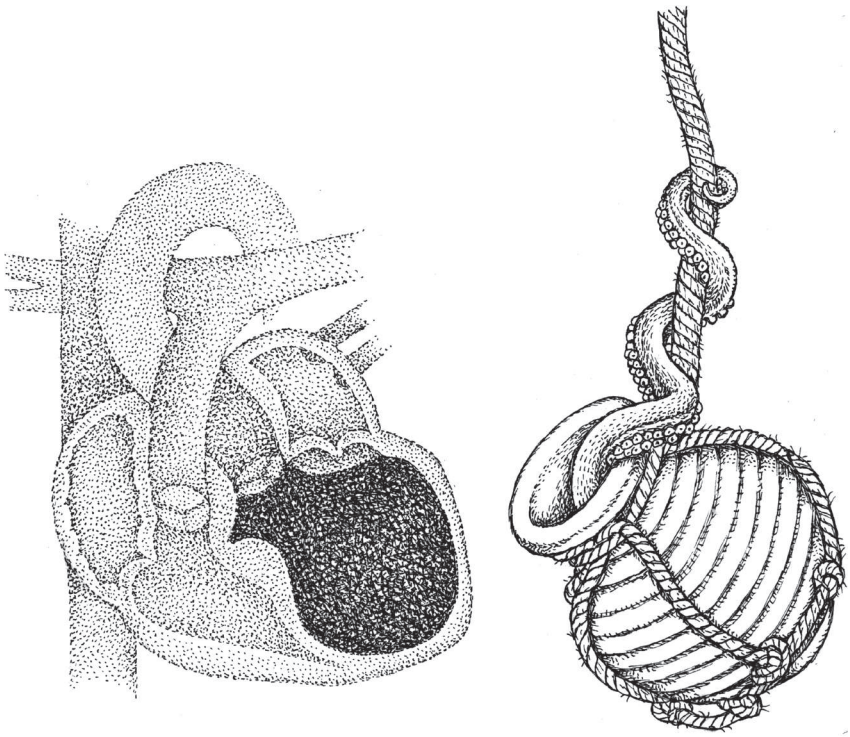
While most beliefs about the heart's emotional and spiritual importance exist outside the realm of modern scientific proof, recent research into one particular form of coronary disease has found an indication that hearts and minds are connected after all—if not in the way ancient or alternative medicine suggest.

In 1990 cardiac researchers in Japan studied a group of thirty patients, each of whom had entered the hospital complaining of chest pains and shortness of breath. When tested initially, they all showed symptoms resembling those of a heart attack: dysfunction of the left ventricle, as well as abnormal electrocardiograms (ECGs), graphical representations of the electrical activity of the heart. Upon examination, however, the doctors found no signs of narrowing in the coronary arteries, a symptom typically found in patients suffering from an infarct (i.e., tissue death due to insufficient blood flow). In fact, the majority of the patients showed no signs of heart disease at all. Even odder were the results of another test performed to evaluate the condition of the left ventricle. After inserting cardiac catheters to inject dye into the ventricle (thank you, Werner Forssmann!), the physicians took x-rays as the patients' hearts

went through their cycles of filling and emptying. When examining the resulting ventriculograms, the researchers were struck by the fact that as the left ventricle finished contracting, it took on a weird shape: narrow at the top and ballooning out at the bottom. It reminded the Japanese researchers of the octopus traps, or *tako-tsubo* ("octopus" plus "pot"), that were used by local fishermen. Then, in yet another departure from the typical outcomes of a myocardial infarction, the majority of the patients in question saw their heart conditions resolve during the following three to six months. Apparently, whatever damage had occurred was completely reversible, which made this condition unique among diseases of the cardiac muscle, a.k.a. cardiomyopathies.

Since the initial studies of what has become known as Takotsubo syndrome, researchers have made considerable strides in their understanding of who experiences this strange malady and what triggers it. Interestingly, 90 percent of those who suffer from Takotsubo syndrome are postmenopausal women, and most of them have recently experienced acute physical or emotional stress, some of it as severe as surviving a recent suicide attempt. Many others had suffered grief over the death of a loved one. The relationship between bereavement and Takotsubo syndrome has led to an alternative name for the condition: broken heart syndrome.

The workings of Takotsubo syndrome actually make a great deal of sense. During highly emotional or stressful situations, the body's nervous system (specifically the sympathetic division of the autonomic nervous system, which regulates unconscious body systems) floods the circulatory system with stress hormones—the fight-or-flight response. These chemical messengers prepare the body to deal with real or perceived threats by managing physiological functions like heart rate, blood pressure, and breathing rate. In normal situations, this sympathetic response gets shut down when the threat passes or when emotions subside. But in patients with Takotsubo syndrome, researchers theorize that there is decreased



communication between the brain regions that process emotions and the autonomic nervous system. This causes the sympathetic nervous system to overrespond by continuing its outpouring of stress hormones—the overabundance of which leads to potentially serious cardiovascular problems. These can include spasming of the coronary arteries and their microscopic branches, a phenomenon that could explain the left ventricular dysfunction and chest pains observed in Takotsubo patients.

There are, however, unanswered questions regarding the condition. For example, it remains unclear why the left ventricle takes on its peculiar octopus-trap shape. It's also unknown whether the brain's overproduction of stress hormones is *caused* by the emotional trauma the patient suffered or whether the brain dysfunction responsible for the overstimulation of the sympathetic nervous system was already present, thus making that person more susceptible to Takotsubo syndrome.

Uncertainties aside, the condition serves as a dramatic example of the intimate connection between the heart and the brain—evidence that emotions like grief can lead to physical changes in the heart—in this case, changes of a temporary nature. But this heart/brain connection is actually a two-way street, since it is also clear that a damaged heart can lead to emotional dysfunction.

I spoke to cardiologist and University of Wisconsin professor emeritus Patrick McBride, a leading expert on cardiovascular risk factors. I was interested in learning why stress and depression negatively affect the heart and how the situation might be countered. He emphasized that due to the number of confounding factors, the link is extremely difficult to research. For example, when somebody's spouse dies, it is quite common for the survivor to end up in the hospital with a heart attack. But while the pattern is clear, the reasons for it are less so.

McBride reviewed the body's fight-or-flight response with me, the same system which kicks in during Takotsubo syndrome. While its cocktail of adrenaline, cortisol, and other stress-related chemicals is useful in managing physical threats, it can be counterproductive when it comes to emotions. When someone is under chronic stress, as they might be if a loved one had passed away after a long illness, those hormones may circulate so frequently that they can irritate the heart and blood vessels, damaging their inner lining, or endothelium. While this single layer of cells was until recently thought to be relatively inert, it actually has an endocrine function. Over the past two decades, researchers have shown that the endothelium releases its own set of hormones into the blood.

"Second to second and minute to minute, the endothelium is responding to our chemical environment," McBride told me. "If muscles need more oxygen, the chemicals released by the endothelium dilate

the blood vessels that supply them, while contracting the blood vessels elsewhere."

When the endothelium becomes inflamed, the damaged cells also release chemicals like histamine, bradykinin, and cytokines (a broad category of small proteins also released by cells of the immune system). One result is that the blood vessels become more porous, and they leak plasma into the tissues surrounding them. This leads to the characteristic swelling, redness, and pain that we associate with inflammation. Meanwhile, the chemicals that have been released signal the body's repair team to show up and get to work.

This process is helpful when inflammation is acute, but not so much when the condition becomes chronic. McBride compared the constant presence of inflammatory chemicals to rubbing your skin until it becomes raw. What's more, as the lining of blood vessels becomes more porous during prolonged inflammation, chemicals in the blood can become modified, making them behave differently. One such change occurs when LDL cholesterol undergoes the process of oxidation, becoming Ox-LDL, a substance known to be involved in the formation of atherosclerotic plaques. MacBride likened Ox-LDL to bacon grease left in a pan.

Things can get even worse if the person in question already *has* atherosclerotic plaques, since chronic inflammation can cause the vessel's inner lining to crack open. As the body's repair crew rushes in to plug the damage, a blood clot forms. Usually clotting is a good thing—an intricate cascade of so-called hemostatic chemical reactions whose fibrous final product (the clot) can effectively halt blood loss from a ruptured vessel. Here, though, the feces hits the fan if a piece of the clot breaks off and flows downstream, where it can get stuck in an increasingly small vessel like a coronary artery or an artery supplying part of the brain. This can lead to a heart attack or a stroke, respectively.

Now, somewhat more well versed on the relationship between stress and the heart, I decided to change course with McBride, seeking to explore the methods currently being used to counteract the heart-unhealthy effects of stress.

Surprisingly, McBride led off with spirituality.

"It's very clear to me that people with spiritual lives do better—and that's research-driven." When people aren't afraid of their own mortality, he explained, they have better outcomes.

His claim, however, is controversial, since for every study pointing to the benefits of religious activity as it relates to health, there are critics who claim that even the best of these studies were faulty, because they lacked controls or did not consider covariables like age, sex, ethnicity, education, behavior (like smoking and alcohol consumption), and socioeconomic and health status, before reaching their conclusions.*

The fact remains, however, that patients who receive social support or are in strong relationships are more likely to have better outcomes. "People who are lonely or widowed have worse outcomes," McBride said.

Over the past four decades, McBride and his cardiac rehab colleagues have been working to address the high rate of depression that follows heart attacks. The reason for their efforts is that, like other types of acute stress, depression aggravates circulatory tissues. In combination with the heart disease that led to the event, this can have deadly consequences. McBride told me that currently, one in every two to three recovering patients is likely to suffer from the mood disorder. To address this problem, as part of their protocol McBride's team screens every patient that has had a heart-related event for depression, regardless of whether the event was the placing of a stent, bypass surgery, or a heart attack. As a result, the medical team at the University of Wisconsin's Preventive

* The shortcomings of these studies were reviewed in 1999 in Richard P. Sloan, Emilia Bagiella, and Tia Powell's article "Religion, Spirituality, and Medicine" in the *Lancet*.

Cardiology Clinic has had psychologists and therapists on staff since the 1980s and has been championing a mindfulness program since 1994.

Mindfulness is a therapeutic technique with its roots in Buddhist meditation. When practicing mindfulness, one attempts to focus one's awareness of thoughts, feelings, and bodily sensations on the present moment, rather than rehashing the past or worrying about the future. The technique also emphasizes acceptance of thoughts and feelings without judging them, helping practitioners understand that there is no "right way" or "wrong way" to feel at any given moment. Since the late 1970s, mindfulness has become a popular stress-management program, and it is commonly employed in prisons, hospitals, and recently, in schools, where anxiety among children has become a serious concern.

McBride told me that initially the professionals running his cardio rehab program referred to these mindfulness classes as "stress management" or "stress reduction."

"All the guys would show up," he said.

But then the staff started calling it "mindfulness meditation" and bringing in elements of yoga and tai chi. "And men would never show up. It was just too Eastern for these Western dudes."

I laughed. "How'd you fix that?"

"We went back to calling it 'stress management,' and the men showed up in droves."

McBride and his colleagues use mindfulness techniques to combat the "very real fear factor" that patients go through after surviving a cardiac event. That fear has always been present, but in recent years the internet has augmented it, allowing people to quickly access a vast amount of information. Some of this online info, regarding things like healthy diets and the need for exercise, is quite useful. But, as with all self-diagnosis, the danger exists that a patient might wander onto a website promoting untested dietary supplements or simplifying medical topics to the point

of inaccuracy. The blanket claim that cholesterol harms your body serves as an example of the latter. Of course, these types of problems can be a counterproductive focus for patients recovering from cardiac-related issues like heart attacks or coronary bypass surgery. This emphasizes the need for rehab programs that provide information and instruction derived from peer-reviewed sources, like reputable medical journals. Note: Most hospitals currently have cardiac rehab programs, but these programs vary in scope—not an unimportant fact to consider when compiling information on the pros and cons of hospital options.

One constant found in many cardiac rehab programs (including the one run by McBride) is that that bringing partners, close relatives, or friends into the mix is an important part of the process. Among other things, cardiac rehab classes teach the partners and peers not to tiptoe around the person, wondering "When are they going to have the big one?"—a fear that the patient will invariably pick up on. The partner-focused classes also address related health problems, like erectile dysfunction, common in patients after a cardiac event, and provide resources about what to do should there be another heart attack, including teaching the partner CPR.

Ultimately, whether one believes in the power of meditation and yoga or just wants to make things easier for both partners during a difficult time, cardiac rehabilitation programs have been associated with a significant reduction in ten-year mortality after coronary bypass surgery, and a marked reduction of readmission and death after myocardial infarction.

The problem, though, according to McBride, is that while those who participate in cardiac rehab have better outcomes, only about one in four patients will enroll. A number of barriers to participation have been proposed. These include lack of health insurance, depression, a perception that the rehab program is inconvenient or unnecessary, and the travel time involved and transportation needed to get to and from the program.

After studying these barriers, researchers at the Mayo Clinic concluded that while factors like age (the older the patient, the less likely they'll participate) and sex (females are less likely to enroll) could not be modified, there were practices that *could* increase participation. These include in-hospital primary care by a cardiologist, referral to a cardiac rehab program while the patient is still in the hospital, in-hospital education about the importance of these programs, and a discussion with patients about transportation-related issues and how to overcome potential problems.

As off-putting as rehab programs might initially seem to the patient, they have undeniable benefits, especially, McBride emphasized, group programs. If a patient sees a peer running on a treadmill and knows that that person had their own bypass surgery only eight weeks ago, it might really hit home that now they're exercising and doing well. "They'll go, 'Hey, I just had bypass surgery. How did you get to the place where you are now?'"

"Social support of other patients becomes really important," McBride said. "They'll open up to other patients."

McBride also suggested that Chinese traditional medicine can be effective in preventing and treating cardiovascular disease, referring to it as part of a broader category of integrative medicine (IM). Roughly defined, IM seeks to understand the unique set of circumstances (physical, mental, spiritual, social, and environmental) affecting each individual's health. It then addresses them with a multidisciplinary approach tailored to the individual. McBride's group has been using IM as part of its cardiac rehabilitation for the past twenty-five or so years, ever since several physicians joined the group who were already combining Eastern and Western medical approaches.

In addition to ways to counteract stress, McBride's lab researches other methods of improving cardiac outcomes. The team has been testing

the effects of an array of compounds on arterial function—specifically, whether or not unhealthy arteries would dilate when they were exposed to test chemicals. Among the compounds they have tested are vitamins A, C, D, and E, as well as substances like ginseng, resveratrol (a chemical produced by several plants in response to an attack by pathogens), grapes, red wine, and garlic.

"And what were the results?" I asked.

"Well, I can tell you that those vitamins didn't work at all."

"So, what *did* work?"

"Red wine did. Dark beer did. But the dietary supplements did not."

The most effective compounds that McBride's team have tested have been statins, which are a class of chemicals, which includes drugs like Lipitor, that lower blood cholesterol levels. There are two sources of blood cholesterol, diet and the liver, and statins work to block the enzyme responsible for the latter. "They remarkably reduce inflammation, improve endothelial function, and reduce atherosclerotic plaques," McBride told me.

Having been taking statins myself for the past fifteen years, I found it comforting to hear him mention them in nearly the same breath as dark beer and red wine—two medications I have always strongly supported.

McBride also mentioned flavonoids, referring to the antioxidant compounds found in foods like berries, apples, citrus fruit, legumes, and even tea. Antioxidants are compounds that scavenge or prevent the formation of unstable molecules called free radicals, which are involved in tissue damage. Other antioxidants include vitamins C and E and carotenoids—though McBride stressed that he did not believe that they work in dietary supplement form, where one is never quite sure what is in the pill, and thus cannot substitute it for a healthy diet containing these compounds.

He also stressed the anti-inflammatory effects of the Mediterranean diet, with its emphasis on lots of vegetables, olive oil, and garlic, along with reduced intake of saturated fats and increased monounsaturated fats.*

One more important takeaway from my conversation with McBride was an overall sense of the importance of moderation to a heart-healthy life.

"An Ironman [triathlon] is not the right amount of exercise, and doing nothing is not the right amount of exercise," he told me. "Taking a daily walk is the right amount of exercise. People say, 'Red wine is good for you, so I'll drink a whole bottle.' No, the right amount is three ounces."

Part of America's general cardiac unwellness is due to our dietary habits, which have been leaving moderation behind. In a trend that began in the late 1970s, portion sizes (especially in fast-food and chain restaurants) in the United States have increased at a rate mirrored by increases in obesity. According to Harvard Women's Health Watch, "a typical movie-theatre soda, once about 7 ounces, can now be 'supersized' to 32 or 42 ounces," while a 2- to 3-ounce bagel now weighs in at 4 to 7 ounces.

Our meat consumption has been on the rise as well, and global demand for meat has quadrupled over the past fifty years. One notable and related study examined death rates from "circulatory disease" during World War II, focusing particularly on Nazi-occupied Norway: It turns out that despite the increase in stress, between 1942 and 1945 around 20 percent fewer people died of cardiac events. The reason? With their livestock confiscated by the Germans and little or no access to meat, eggs, or dairy products, the native population was forced to survive on a

* McBride also hailed the benefits of the DASH eating plan, which stands for "dietary approaches to stop hypertension."

low-fat diet of vegetables, grains, and fruit. As a consequence, incidents of heart disease dropped.

I came away from my research into the topic with a list of recommendations for a heart-healthy lifestyle in the face of an often-stressful world. The list includes exercising, eating a diet with more fish and less fat, reaching or maintaining an appropriate body weight, getting enough sleep (seven hours per night seems to be the magic number), not smoking, drinking only a moderate amount of alcohol, using stress-reduction techniques, and getting regular medical checkups.

After running down the list I'd compiled as my interview drew to a close, I asked McBride if there was anything else he'd like to add.

"Moderation in all things," he replied. "I think that would be a beautiful message."

Hearts will never be practical until
they are made unbreakable.
—The Wizard of Oz, MGM, 1939

[15]

What's Snakes Got to Do, Got to Do with It?

In nature, hearts and circulatory systems have evolved into efficient forms of internal transportation whose primary functions allow organisms to exchange vital materials like nutrients and gases with the external environment. We humans, however, have outpaced the evolution of our cardiovascular system, testing the limits of its ability to adapt to junk food, toxins, pollutants, smoking, and stress.

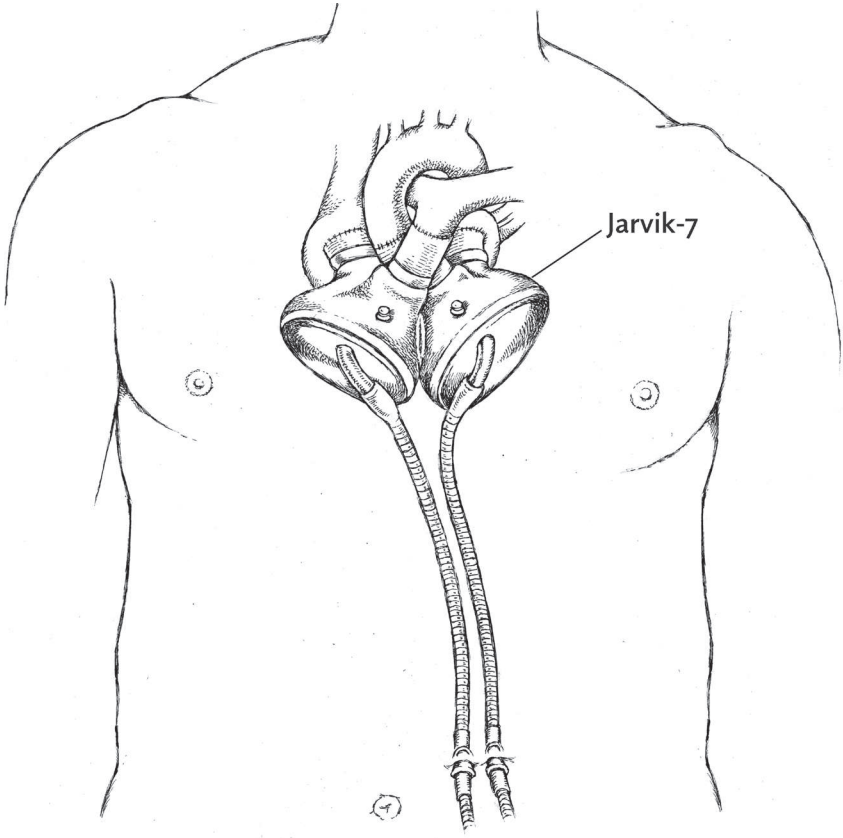
Medical research has responded to the challenge. In recent decades, for example, we've seen the rise of low-fat diets and high-tech medical procedures like coronary bypass surgery, during which clogged coronary arteries are replaced with veins from a patient's arm or leg. Far more complex are mechanical hearts. In 1982, American cardiothoracic surgeon William DeVries successfully implanted the first total artificial heart (TAH), the Jarvik-7, into a sixty-one-year-old retired dentist named Barney Clark. Clark survived for 112 days, enduring a series of serious medical conditions, which included respiratory failure requiring a tracheotomy, as well as "fevers, stroke, seizures, delirium, renal failure, and bleeding related to anticoagulation [an inability to form blood clots]."

He eventually succumbed to colitis. The story's initially positive publicity was soon blunted by Clark's downward spiral, and the subsequent negative press did much to turn the goal of mechanical hearts from permanent destination to bridge therapy for patients awaiting transplants.

On the subject of heart transplants, Christiaan Barnard (1922–2001) performed the first successful one on December 3, 1967. During a five-hour operation, fifty-three-year-old Louis Washkansky received the heart of Denise Darvall, a twenty-five-year-old car accident victim. The organ functioned quite well, but, unfortunately, the immunosuppressant medications that prevented rejection of the heart also left Washkansky vulnerable to infection. He died of double pneumonia eighteen days later.

It is now estimated that something like five thousand heart transplants are performed worldwide each year, most in the United States. But even so, millions of lives are lost each year to heart disease, and thousands more die while sitting on long waiting lists for heart, liver, and kidney transplants. We've already looked at the past history of xenotransplants and current efforts to genetically design a strain of organ-donating pigs. But it also appears that nature can provide us new methods to treat faulty hearts that are animal-based but also animal-friendly. And a growing number of researchers are now turning back to nature and its amazing evolutionary modifications in their search for answers.

One particularly noteworthy adaptation found in the animal kingdom is the ability of certain hearts to repair themselves when they become damaged—a feature human hearts, tragically, lack. When someone suffers a heart attack, it's usually due at least in part to the obstruction of one or more of the coronary arteries, which cuts off blood both to the heart and to whatever region the vessel previously supplied. Deprived of oxygen, the cardiac muscle tissue located downstream of the blockage dies. If the patient survives, the dead muscle tissue is replaced by scar tissue, which isn't contractile and which prevents new cardiac muscle cells



from forming. As a result, sections of this intricate pump are no longer functional, and the heart's beautifully coordinated workings are disrupted. Survivors are often left susceptible to future problems, including, but not limited to, additional heart attacks and, ultimately, heart failure.

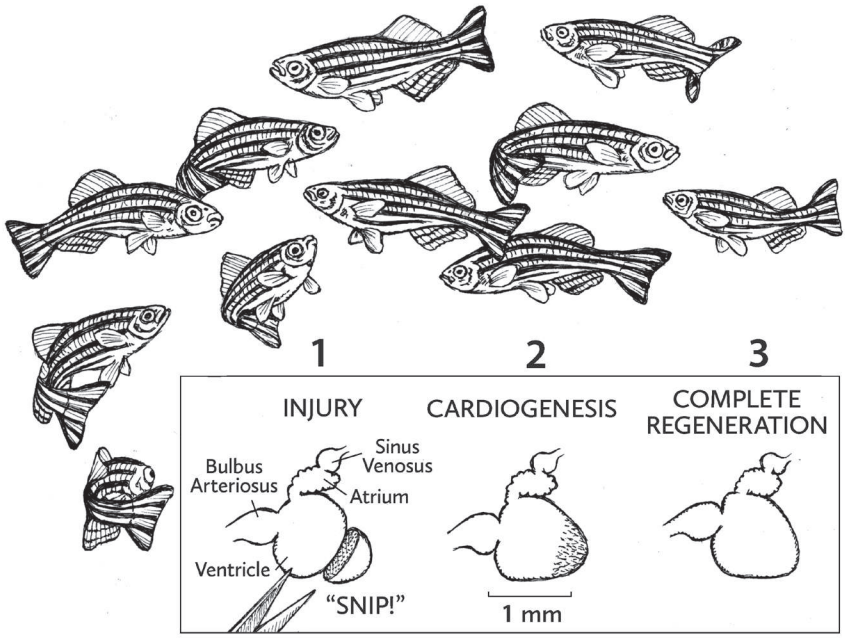
But what if physicians could replace lost or dysfunctional cardiac tissue? Such a treatment would be transformative, especially given the fact that approximately half a million Americans are diagnosed with heart failure each year, and these patients have a one-year mortality rate of nearly 30 percent. Since the phenomenon of cardiac regeneration does not occur in humans (or any mammals, for that matter), researchers have turned to the most ancient of vertebrates for an answer, the fish:

specifically, the zebrafish (*Danio rerio*), a common denizen of tropical freshwater aquaria.

Although research on these egg-laying South Asian minnow relatives began in the 1960s, their popularity, especially as models for studying human diseases, surged after 2013. That's when the results of a decade-long quest to sequence their genome became available to researchers. A fully sequenced genome can be thought of as the complete set of genetic instructions required for the development, growth, and maintenance of an organism.

Researchers were surprised to learn that zebrafish share more than 70 percent of their genes with humans, and that more than *80 percent* of genes associated with human diseases have a zebrafish counterpart. They also possess equivalents to nearly every human organ and produce hundreds of transparent, externally developing embryos. This combination of traits enables researchers to model the human condition in a fast-growing, easy-to-maintain, easy-to-see-through species. Gene mutations can be introduced into zebrafish test strains to explore the developmental genetics of human diseases like muscular dystrophy or to model cardiac abnormalities, thus allowing drug researchers to test potential therapeutic compounds.

Most exciting, though, was the discovery that zebrafish hearts are able to fully regenerate after the amputation of up to 20 percent of their single ventricle. Admittedly, this type of wound has become somewhat less common in humans, with our recent pivot away from pillaging and gladiatorial combat, but the discovery has had huge reverberations for heart research. Scientists noted that in zebrafish experiencing such an amputation, a clot quickly forms to prevent catastrophic blood loss. The truly unique part, though, is that within thirty to sixty days of the injury, the clot is replaced by fully functional muscle cells.



In a mature mammalian heart, cardiac muscle cells (a.k.a. cardiomyocytes) stop reproducing—and thus, stop producing new cells. Conversely, the zebrafish heart is not only able to produce new functional muscle cells, but it does so without the input of stem cells. There will be much more on stem cells, but for now we can think of them as a class of embryonic or adult cells with the capacity to develop into different types of cells, depending on how they are stimulated.

In adult zebrafish, new cardiac muscle cells originate from previously existing myocytes. When a specific region of the heart is damaged, undamaged myocytes in the area reenter the reproductive phase of their life cycle and begin to crank out new functional cardiomyocytes—muscle cells that are ready for action. These new myocytes migrate into the previously damaged area and replace the scar tissue that had initially formed in response to the wound. The zebrafish heart has, meanwhile, built a connective-tissue framework at warp speed, with blood vessels

rapidly regrowing into the damaged area and bringing with them collagen-secreting cells called fibroblasts. The collagen frame laid down by the fibroblasts is referred to by researchers as a "regenerative scaffold," and it serves as a structural base of support for the new heart muscle being formed.

Given the positives of being able to regrow functional heart muscle, the obvious question is: Why can't mammalian hearts do it? From an evolutionary perspective, the most likely reason is that this inability is actually beneficial—or at least it was for our ancient ancestors. Since cardiomyocytes stop dividing shortly after birth, they are not as susceptible to cancer-causing genetic mutations. As a result, cancer of the heart is extremely rare.* Since all mammals share this trait, it is clearly an ancient mammalian adaptation—or more likely, an even older adaptation that developed in early vertebrates, since there's only a single species besides the zebrafish, a type of North American newt (*Notopthalamus viridescens*), known to have cardiac regenerative ability.

The inability of our cardiomyocytes to divide also makes perfect evolutionary sense if you consider that our distant ancestors were not burdened by crappy fast-food diets, obesity, smoking, and other recently developed heart-straining bad behavior. As such, this adaptation serves as a great example of how our organs evolved in a time that was very different from our own. As for why zebrafish buck this particular vertebrate rule—it is likely the result of a beneficial mutation, since it pays to be able to

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* In brief, cells go through something akin to the life span of an organism. They're formed, then they grow and reproduce. As they move through maturity, they don't reproduce as much (if at all), and they often look very different than when they were younger. Then they work for a while, get worn out, and die. Think of cancer cells as cells that get locked in the reproductive stage. Because that's all cancer cells do: They reproduce—over and over and over again, never becoming functionally mature cells. Instead, they spread to other regions of the body (often via the circulatory or lymphatic systems). When they get there, they reproduce and reproduce and reproduce some more, ultimately screwing up the function of wherever it is they happened to have landed.

repair your own heart if you happen to be a tiny minnow-like fish (or a similarly pint-sized red-spotted newt) and thus a popular menu item for a host of bitey predator types.

But no matter how this trait evolved, the inability of the human heart to repair itself currently presents us with a serious problem, and science has presented us with the opportunity to confront it. Researchers are examining several approaches. These include identifying chemicals that would do one of the following: stimulate mature cardiomyocytes to divide; transform cells like fibroblasts into cardiomyocytes; or compel cardiac stem cells to differentiate into cardiomyocytes. Each of these is a seriously complex endeavor, especially considering that they each require modifying the behavior of cardiac blood vessels as well. After all, any potentially rejuvenated muscle tissue will need a fully functional blood supply to carry in the tissue repair team, nutrients, and oxygen.

Although removing large sections of the zebrafish heart elicits a significant regenerative response, researchers still need to develop zebrafish models demonstrating a similar response to more common human heart maladies. Because of this, scientists are now attempting to produce zebrafish models of human cardiac valve disorders, congenital heart defects, and lipid-related issues like high cholesterol.

The learning curve is steep, but researchers hope that what they have learned about the zebrafish hearts, as well as the hearts of other nonmammals, may one day usher in a new era in therapeutic heart regeneration.

Given that humans are even closer genetically to reptiles than they are to fish, it makes perfect sense that reptiles are also proving extremely valuable to the medical community. The Burmese python (*Python bivittatus*)

is yet another example of how nonhuman hearts are helping scientists develop therapies for some very human diseases.

The snake in question, easily identified by the distinctive arrowhead markings atop its head, is native to the grassy marshes, forests, and caves of Southeast Asia. The Burmese python is usually ranked as the second- or third-largest species of snake in the world, and the female can attain lengths upwards of twenty feet, with a girth approximating that of a telephone pole. A python of that size would likely weigh in at around three hundred pounds.* Males are slightly smaller, maxing out at around fifteen feet.

I actually had one of these beautiful reptiles as a teen, although mine was only about four feet in length. Still, the presence of a snake in my home excited my friends and me to no end, especially at feeding time. But not everyone felt that way about *il serpente*, this including my mom and at least six of my beloved eight Aunt Roses.† I also vividly recall that, after being informed about Alice, the guys doing construction on our house on Long Island shunned my room like it was a plague ward. I, on the other hand, was fascinated by the constrictor's calm demeanor, how it shed periodically, and its ability to unhinge its jaws before swallowing a weekly parade of larger-than-python-head-sized mice. The medical community's interest in the snake, though, is related to something I never knew during my childhood. Nobody did. It was the observation, made in 2005 by researchers at the University of California, Irvine, that within

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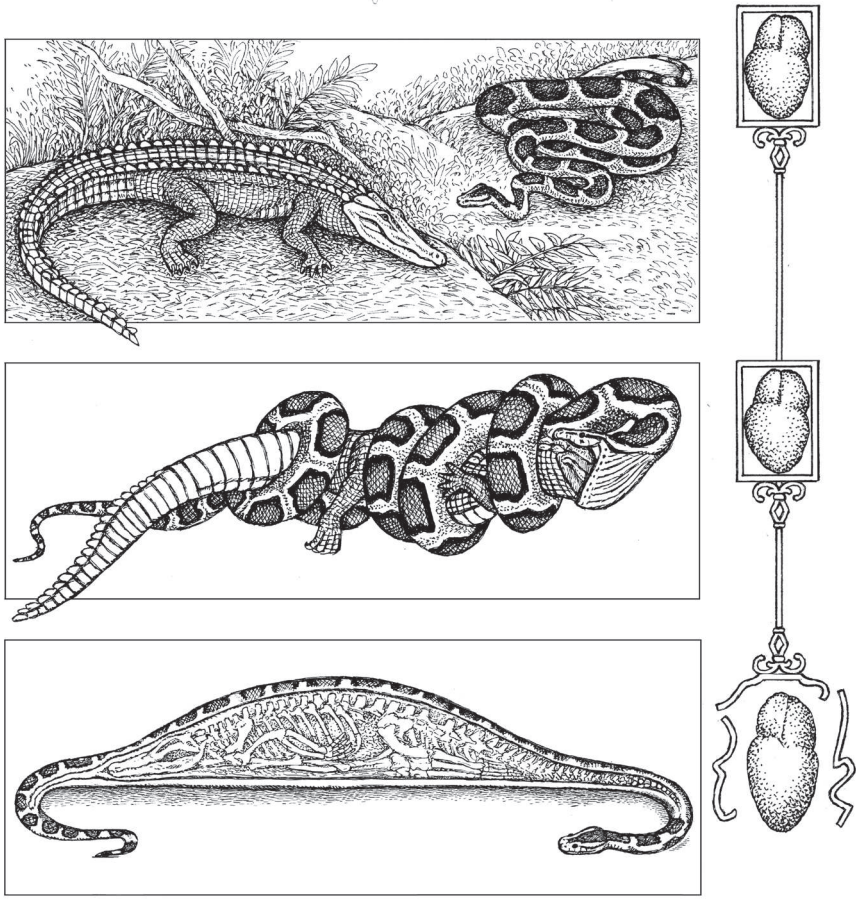
* The green anaconda (*Eunectes murinus*), native to South America, is generally believed to be the second *longest* snake in the world but the largest in terms of body mass. The largest specimen ever measured was twenty-eight feet in length and was estimated to weigh over five hundred pounds. For sheer length, the reticulated python (*Python reticulatus*) sits atop most lists, with one specimen measured at thirty-three feet.

† Readers of my previous books may recall that I had something like eight Aunt Roses while growing up, and that to differentiate them I set up a sort of field guide based on characteristics like height and facial mole placement.



three days of consuming a meal, the heart of a Burmese python increases in size by 40 percent.

I spoke to University of Colorado Boulder researcher Leslie Leinwand, who has been studying this phenomenon in Burmese pythons for over a decade. She explained that the unusual adaptation is a byproduct of the python's odd meal schedule. In its native environment, a python can go for a year without eating any food, suffering very little in the way of negative effects—despite the fact that any mammal would perish should

it try this feat. "And so these animals have adapted to do extreme things," Leinwand told me. "One of these is eating gigantic meals when they get the opportunity."

Like boa constrictors and anacondas, pythons are constrictors. They hunt by ambushing their prey, which can often outweigh them by up to 50 percent. The little guy I owned as a kid ate rodents, but in the wild, Burmese pythons prey on pigs, deer, and even small humans. The snakes subdue the victims with a nonlethal bite before quickly entrapping them within the thick coils of their muscular bodies. Contraction of these muscles causes the prey's chest cavity to compress, preventing it from expanding and thus filling the lungs during inspiration. Death by asphyxiation follows. Soon after, the snake uncoils, and unhinges its jaws (a truly interesting sight to behold). Then, beginning at the head, the constrictor "walks" its way down the victim's body, eventually swallowing its meal whole.

This type of feeding puts the snake in a fair amount of danger from predators. Imagine for a moment consuming something the size of a Great Dane in one bite and then waddling off to wait for digestion to run its course. On second thought, maybe you shouldn't imagine that. The bottom line is that it makes sense that constrictors evolved the ability to feed less frequently.

But pythons have also developed a phenomenal shortcut that enables them to get back on the move as fast as possible. Not only are they able to digest prey up to half of their own body weight in a period of only four to six days, but they are able to harness that digestion into tissue growth. With the exception of the Burmese python's brain, which is confined within the skull, "nearly every organ in the body undergoes an extremely rapid growth in size and mass," Leinwand told me.

This change is not merely due to an accumulation of fluid; it consists of actual tissue growth, usually taking place within twenty-four hours

after consuming a meal. "Something that would never happen in a mammal," Leinwand added. I thought about mentioning one particular post-Thanksgiving weigh-in that I'd experienced, but thought better of it.

Leinwand's initial research interest had been in physiological human heart growth—namely, the growth that takes place in athletes' hearts. Most people think of heart enlargement in humans as purely a symptom of disease, and it's true that it can result from conditions like untreated high blood pressure or coronary artery disease. This type of heart growth is called pathological hypertrophy. "Hypertrophy" refers to growth in the *size* of specific cells—in this instance, the cardiac muscle cells. And "pathological" relates to an injury or disease state. To be clear, not all hypertrophy is bad, since, for example, it is a common result of weight training.*

"In some of these [disease-related] cases," Leinwand explained, "the muscle gets really, really big, but that happens at the expense of the heart chambers. So you end up with extremely thick heart walls but relatively small chambers. That's different than what happens in a highly conditioned athlete. They end up enlarging both the muscle *and* the chambers proportionately—larger amounts of muscle but also larger chambers for the blood to flow into and out of." This was the type of growth she was seeing in pythons.

Leinwand told me that the idea had come to her that if her team was able to understand how a python heart could grow so quickly, they might be able to reverse or prevent heart disease in humans, specifically by offering a lifesaving option for those whose hearts had become too unhealthy to benefit from exercise. (In hearts that *can* withstand exercise, the benefits include better circulation, increased oxygen supply to tissues, lower blood pressure, and a decrease in blood triglyceride levels.)

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* Hypertrophy is different from hyperplasia, a form of growth in which cells remain the same size but increase in number. An example of hyperplastic growth would be the increase in body size that occurs throughout childhood.

Unfortunately, though, the logistics of the python-related experiments quickly turned into a nightmare. Sometime in the 1990s, people in southern Florida began releasing their unwanted pet pythons into the Everglades. One of the most species-diverse habitats in the United States, the Everglades are also a perfect environment for the tropical temperature–loving pythons, allowing them to survive the entire year with neither the threat of cold weather nor a seasonal lack of food. Worst of all, the menu available to the invasive serpents in the Everglades is an extensive one, which includes endangered species like bobcats, as well as other midsized mammals like raccoons, opossums, and foxes.* The scaly invaders also became the dominant predator of marsh rabbits.

Within three decades, the population of pythons in Florida had risen to somewhere between half a million and a million. It was an ecological nightmare that in 2012 led the US Department of the Interior to ban the sale of Burmese pythons, while another federal ban the same year prohibited the transportation of pythons across state lines. These bans have been a step in the right direction for the Everglades, although they have done little to curtail the rapidly growing snake population embedded there. But the crisis made it almost impossible for Leinwand and her colleagues to obtain specimens for their studies.

Still, Leinwand told me, after almost three years of struggling with the python-transportation roadblock, the scientists were able to maneuver around "a web of bureaucracy" to secure the specimens required.

They began their investigation of the python heart by focusing on those specimens that had recently eaten. Among their earliest discoveries was that when they drew blood from snakes that had recently consumed a large meal, it was white—"so filled with fat that it was basically opaque,"

* A 2012 paper in the *Proceedings of the National Academy of Sciences* reported that sightings of raccoons and opossums in the Everglades decreased by almost 99 percent between 2003 and 2011, while bobcat sightings dropped almost 88 percent. Pythons were identified as the culprits.

Leinwand told me. In humans, that would be bad news, since the fat would likely accumulate in their organs and lead to heart disease, in which fatty plaques form within the walls of the narrow heart-supplying coronary arteries.

"So, when we saw the snake blood looking like milk," she said, "I wondered why they didn't exhibit any symptoms of heart disease, since their hearts must be filled with fat."

But further examination revealed that the postmeal python hearts weren't filled with fat at all. In fact, there was actually *less* fat in their hearts than in snakes that had been fasted. Eventually, the research team figured out why.

"For you and me," Leinwand said, "or even a healthy rodent, fat is fuel, and it gets burned. When you begin to get heart disease, you stop burning fat and it accumulates in the heart."

But in pythons, something else occurs. A python's response to consuming a megameal is that its heart turns into a fat-burning machine. Simultaneously, the heart grows larger—but not in the pathological way, which given the animal's peculiar feeding habits would be maladaptive. Leinwand wondered what it was about the snake's physiology that enabled its heart to develop like that of an athlete rather than a couch potato.

The researchers determined that the trigger substance for the dramatic increase in heart size was the fat in the blood—more specifically, three fatty acids that occur naturally in food. These are myristic acid, palmitic acid, and palmitoleic acid. Humans take them as dietary supplements, like fish oil (though cardiologist Patrick McBride would likely make a face at this).

Leinwand and her team proved the role of the fatty acids by injecting the trio of substances into fasted snakes. In each case, their hearts increased in size, just as if they had recently eaten a meal. The same three

substances also worked in mice, whose hearts responded by growing as large as the hearts of mice that had been exercising for weeks *without* the fatty-acid supplement. And, remarkably, in mice and fasted snakes alike, that growth maintained normal anatomical proportions, rather than mimicking the heart enlargement caused by disease. You'll recall that in pathological heart enlargement, myocardial growth is *not* reflected by an increase in the volumes of the atria and the ventricles. Finally, and hopefully, there has been no evidence that the fatty-acid cocktail employed by the researchers triggers any disease pathways.

Although the initial results were startling, it is clear that there remains a considerable amount of work to be done. The next phase of Leinwand's studies will test the fatty acid against larger animal models of heart disease. The hope is that each of these steps will bring them closer to their real goal.

"Ultimately," Leinwand told me, "my colleagues and I hope to use what we've learned not as a substitute for heart-healthy exercise but, for example, in cases where patients suffering from heart disease are unable to exercise, and where a therapeutic alternative could offer those patients a healthier heart and a longer life."

And having already established a biomedical company, Leslie Leinwand hopes that one day she'll turn snake oil sales into a positive career choice. It was a point made clear in 2017, when she won the American Heart Association's Distinguished Scientist Award for outstanding contributions to the field of heart health.

Someone has to stand up and say,
"The answer isn't another pill.
The answer is spinach."
—Bill Maher

[16]

Grow Your Own

To explore a very different approach to cardiac regeneration I visited Harald Ott, a researcher at the Harvard Stem Cell Institute. Ott and his colleagues are involved in an ambitious project: to grow human hearts, and potentially other organs, from stem cells.

When most of the roughly two hundred types of cells found in the human body reproduce, the outcome is an identical cell. Muscle cells produce more muscle cells, fat cells (adipocytes) produce more fat cells, and so on. Stem cells are different, though, because given the right conditions, they can be stimulated to produce different cell types. Most stem cells still have their limits. Stem cells in the blood, for example, can produce only other blood cells. But embryonic stem cells are special, because they can be stimulated to produce any type of cell (so they're described as "pluripotent"). They can be harvested from a few places—like the umbilical cord or from embryos, with the latter making their collection and use extremely controversial. Their pluripotency, however, has made them incredibly valuable for researchers involved in stem cell

therapy, which seeks to address diseased or malfunctioning organs not by transplant but by growing those organs from stem cells.

"So why is it necessary to engineer human hearts?" I asked Ott, who is at the forefront of a very unique aspect of stem cell research.

He explained that the field of medicine had gotten really good at dealing with acute problems like traumatic injuries and diseases like pneumonia. As a result, more people are surviving those acute events, and many of them are living to a ripe old age—an age when their organs begin to break down.

"Some of the tissues like the liver or bones after fracture have built-in regeneration systems," Ott told me. "But many organs [like the heart] don't have the capability to regenerate themselves."

Initially, this might not be a huge issue, since some of these organs, like the lungs, have a reserve of extra cells. But that reserve can run out.

"End organ failure is a global epidemic affecting millions of people," he said. "So rather than dying from car accidents, pneumonia, and other issues, millions of people are getting older and older, and accumulating massive injuries that lead to deteriorating function."

As a result, there has recently been a serious shift in gears within the medical research community. Whereas for much of the twentieth century the goal was to repair damaged tissues and organs, considerable effort is now focused on engineering organs like the heart, kidney, and pancreas, in order to replace the patients' original but failing equipment.

Ott was first drawn to stem cell research because of the work of cardiologist Doris Taylor at the University of Minnesota in the mid-to-late 2000s. Her studies initially centered around rebuilding cardiac function by transplanting stem cells into the hearts of test rabbits that had suffered acute myocardial infarction. During Ott's time in Taylor's lab, they determined that simply injecting cells into a faulty

heart wasn't effective enough, and that they would need to regenerate three-dimensional structures, not just repair them. Since then, Taylor has continued her work, eventually moving on to become the director of regenerative medicine at the Texas Heart Institute. Ott, meanwhile, took a fellowship in cardiothoracic surgery at Massachusetts General Hospital and a position as an instructor of surgery at Harvard Medical School.

Ott explained that his current experiments build off tissue-engineering research from the 1990s. In those studies, researchers showed that functional three-dimensional tissue could be generated by building cells onto a scaffolding of an extracellular matrix composed primarily of collagen.* The extracellular matrix of a tissue is secreted by its cells and gives tissues like bone and cartilage their form and their distinct physical characteristics. The characteristics of a matrix composed of collagen are that it can be stretched without breaking (i.e., it has tensile strength), that it does not elicit an immune response (i.e., it has low antigenicity), and that it readily allows other cells (like myocytes) to grow on it.

"I'm not an engineer by training," Ott told me. "So when I started working at this, instead of creating a scaffold from scratch I used organs from cadavers."

Ott and his colleagues put cadaver hearts through a process called decellularization, in which special detergents are used to dissolve away all of the cells. What they were left with was a flexible heart-shaped structure composed solely of a collagen-based extracellular matrix.

I examined one of his early decellularized heart specimens, which had

* If this sounds vaguely familiar, it's because the rapid regeneration of the zebrafish heart takes place upon a scaffold of collagenous connective tissue as well, in that case laid down by fibrocytes after a traumatic injury.

come from a pig. It was opaque and stark white in color, composed of solid components like collagen, elastin, and fibronectin—a cell adhesion molecule that binds cells to these substances (kind of like glue). Basically, though, it looked just like a pig heart. I found it fascinating that the complex structure before me had been produced by cells that no longer existed. What they had left behind was a heart whose architecture had been precisely preserved, thus making it perfect framework upon which Ott and his colleagues could build a new heart.

Because all of the cells had been removed, leaving behind only structural proteins, the scaffold would not be subject to the same immune response as a transplant heart. When the body recognizes cells as allogenic—that is, not of the self, and therefore immunologically incompatible—the immune system attacks those cells. This is the primary reason for the rejection of so-called allotransplants, those transplants that come from incompatible donors. Upon what was essentially a blank template, though, a research team could theoretically build a compatible organ with little fear of rejection.

A key question that remained, however, was: How would Ott and his team repopulate his heart-shaped framework with new cells that wouldn't be attacked? He explained that his research had gotten a huge boost from the 2012 Nobel Prize–winning discovery by John Gurdon and Shinya Yamanaka that mature cells could be genetically reprogrammed into stem cells. They did this by introducing four genes responsible for keeping stem cells immature into the mature cells. Even better news was that the resulting cells weren't just any stem cells—they were stem cells of the pluripotent variety. You'll recall that depending on how these stem cells are stimulated, they have the ability to differentiate into any of the approximately two hundred cell types that exist in the human body. As for where these mature pretreatment cells would come from, the easier

the access, the better, and so it was exciting when researchers found that fibroblasts fit the bill.

Although they coinhabit the myocardium with cardiac muscle cells, fibroblasts are also the most common type of cell found in connective tissue, which includes the skin's dermal layer. Among other things, and as mentioned during the zebrafish discussion, they are responsible for producing structural proteins like collagen and elastin fibers and the extracellular matrix, the noncellular material that surrounds cells. Ott explained that the ease of accessibility to fibroblasts in the skin makes them far less trouble to obtain than cells from a cardiac biopsy.

Once the fibroblasts have successfully been turned into stem cells and then into cardiac muscle cells, they can then be seeded back onto the cell scaffolding. This, so far, has been Ott's sticking point. His team has been able to grow small patches of heart, and to get those cells to contract when stimulated. But they have not yet been able to create an entire pumping human heart.

Other labs working on the issue aren't attempting to build new hearts, but are exploring the use of similarly reprogrammed sections of contractile cells. Led by Sian Harding, a professor at Imperial College London, researchers in the United Kingdom and Germany were able to grow patches composed of human myocytes, which were then stitched on to the hearts of living rabbits, where they became fully functional cardiac muscle tissue. With human trials set to begin soon, it is hoped that this technique will enable cardiologists to replace the noncontractile scar tissue that results after a heart attack.

But patches of myocardial cells do not a heart make, and one major challenge that Ott and his colleagues face is getting his reprogrammed cells to form three-dimensional structures, like the coronary blood vessels that would be required to supply his newly built hearts. The cells

themselves need to create these structures, serving not just as building blocks but as participants in the manufacturing process. Maddeningly, the blueprints for that behavior already exist within the cell, coded into the genetic portfolio—but so far, they are not accessible to scientists, who are still on the search for a way to switch the behavior on.

Until Ott and his colleagues can "flip this switch," they will improvise. Unable to create blood vessels purely from scratch, they decided to start at the same place they're starting with heart tissue: with scaffolding—in this case a section of decellularized blood vessel. Like the rest of the heart, the coronary blood vessels that supply it leave behind a framework of connective tissue once their cellular components have been dissolved away.

"We tell the cell, 'You're an immature blood vessel cell, and by the way here's a pipe. Can you just line that pipe for me?' And then the cells will do that," Ott said. "That's what's really unique about our scaffolding—in these decellularized organs, we actually have intact piping."

Creating three-dimensional structures to replace their faulty human counterparts remains a serious challenge. But using a previously existing scaffold, in this case the connective-tissue framework from a formerly functional blood vessel, isn't the only avenue of research being explored to address the problem.

Biomedical engineer Glenn Gaudette from Worcester Polytechnic Institute is also working on therapeutic heart regeneration, but he found himself using a rather different type of framework after one of his grad students returned from lunch with something amazing he had discovered in the cafeteria.

I met with Gaudette in his lab to discuss what happened next.

He began by explaining that anyone doing repair work on a damaged

heart, or any damaged organ for that matter, knows the importance of blood vessels—many of them of the microdiameter variety.

"Heart muscle dies when it doesn't get enough blood flow," Gaudette told me.

This was, as Ott had previously pointed out to me, of particular concern in heart regeneration studies and was proving to be a sticking point in Gaudette's own research. While his team has been able to get heart cells to grow on the scaffolding of blood vessels around a decellularized heart, they have not been able to fully reproduce its structural and functional complexity.

"And that's why we came up with this," Gaudette said, offering me something small and green to peruse.

I held the object carefully, marveling at its veins and how it looked remarkably like a spinach leaf that he might have purchased at a grocery store. Gaudette assured me that it was, and that he had.

"Those veins transport water," he said. "Our veins transport blood. From an engineering standpoint, they both transport fluids. So my grad student at the time, Josh Gershlak, said, 'If we get rid of all the spinach, would we still have those vessels left behind?' And that's where the whole experiment started."

As Ott does with his donor hearts, Gaudette and Gershlak (now a postdoc) subject their spinach leaves to a chemical bath that strips them of their cells but keeps the extracellular framework. Similarly, this allows the vessels to retain their original structure and prevents that structure from being rejected by the eventual recipient's immune system.

Gaudette gave me a tour of his lab, during which I saw how the specimens are prepared. The spinach leaves he employs are hung individually in small bottles, each located about four feet below a gravity-fed supply of special detergent. As the detergent drips downward, it

passes into a series of thin rubber tubes, each terminating in a large-gauge hypodermic needle, which is inserted into the tip of a leaf stem.

This gravity drip system provides a constant flow of detergent into the leaf. As the detergent encounters the plant's cells, it opens tiny holes in them and allows their contents to drain, so that when the detergent departs out the leaf tip, it carries with it the cellular contents. After a five-day perfusion period, what remains is a colorless, structurally perfect model of a leaf, albeit one with no plant cells remaining. The model is composed of the sturdy structural polysaccharide named cellulose.

If that substance rings a bell it's probably because plant cell walls are composed of cellulose, also known as the dietary fiber that passes undigested through our intestines, Roto-Rooter-style. In fact, no vertebrates can digest cellulose by themselves, although some do enlist the aid of endosymbiotic bacteria. Vast numbers of these microorganisms exist in digestive system organs, like the cecum of a horse or the rumen of a cow. The symbiosis aspect relates to the fact that the bacteria get a nice, warm place to live, while their four-footed cosymbionts get the benefit of the cellulase (the enzyme that breaks down cellulose).

Released into the digestive tract, the enzyme comes into contact with the herbivore's cellulose-rich diet, breaking the polysaccharide down into easily digestible compounds like simple sugars. This adaptation allows the herbivore's digestive system to extract nutrients and energy from previously undigestible stuff like grass. Among the invertebrates, even those infamous for their plant- and wood-munching prowess, many can't digest cellulose without help either. Some groups of termites, for example, require endosymbiotic bacteria in order to digest wood, and baby termites will starve to death if they don't obtain their own starter colony of flagella-waving gut microbes.

They do so by consuming a bit of feces from a parent or nestmate. Other termite species are flagellate-free, having evolved the ability to produce their own cellulase without the need to host fifty billion or so microbial gut-guests.

For Glenn Gaudette's purposes, though, the important thing is that cellulose is not only structurally sound, but it is close to being biologically inert, with the human body showing little or no immune response to the stuff. As such, it's a near-perfect biocompatible material, and has already been approved for use in certain medical devices. These include sheets composed of cellulose fibrils, spun by bacteria and applied to wounds, and implantable capsules for drug delivery.

Cellulose is a component of more than one attempt to engineer structures like the heart from scratch. Instead of using spinach leaves, researchers at Tel Aviv University are taking the 3D bioprinting approach. Their efforts, though early, seek to use a biopsy from a patient as the "ink" for their 3D printer. In April 2019, with much fanfare and media coverage, Tal Dvir and his team announced that they had indeed printed a small heart (about the size of a rabbit's heart). The obstacles confronting these scientists are many. Among them is the fact that while the cells of the printed structure can contract, the heart itself cannot yet pump. Additionally, Dvir's team will need to address the question of how to print the tiny blood vessels of the heart.

There is still much research to be done, and there are many obstacles to overcome. But the outlook for cellulose is exciting. Gaudette's lab has been able to get human heart cells to grow on the spinach scaffolding, and experiments are now underway to dissolve the cellulose after it has served its purpose. The hope is that one day, vessels formed on a structure of cellulose will be able to be stimulated to become surrogate blood vessels composed solely of human cells.

And while it's impossible to predict how much of this research will ever find practical applications, it is intriguing that scientists like Gaudette are looking toward the plant kingdom for a new and extremely novel way to benefit humans.

Given the complexity of regenerating a heart, or other organs like kidneys and lungs, I wondered why something so drastic was necessary. Why not search instead for better repair techniques or focus on disease prevention?

The answers relate to the fact that there are approximately 40,000 organ transplants performed in the United States each year (about 10 percent of them are heart transplants), and, as of September 2020, there were approximately 109,000 candidates on the US national waiting list. These patients are beyond disease prevention, and in many cases have organs so damaged that repair cannot offer a long-term solution. It's been estimated that every day about twenty people die while waiting.

Harald Ott explains it like this. "If the radiator in your car is broken, they don't *fix* your radiator anymore—they just swap it out for another one."

With this in mind, the ultimate goal of regenerative medicine is to come up with a replacement for those hearts (as well as kidneys, livers, lungs, and intestines) that isn't dependent on an often terminally long waiting list or the prospect of having transplant recipients spend the rest of their lives on immunosuppressant drugs. Other researchers continue to look for those replacements in the animal kingdom—for instance, genetically altering pigs to provide organs comparable to human organs, without the threat of tissue rejection.

I asked Ott to speculate on where he thinks organ regeneration therapies are heading: "Let's say it's twenty years from now and all of

this research has worked out *really* well. Somebody has a damaged heart. What happens next?"

"They walk into a clinic, a skin biopsy is taken, and you grow them a heart," Ott said. "Once the patient reaches a point where their heart is just not doing well enough anymore, you just swap it out."

"And other organs as well?"

"And other organs as well," he repeated. "That's what I hope for."

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Creatures like the icefish and the snow-burrowing tube-nosed bats would have been as fascinating to me as a child as they are today. Back in the 1960s, though, my exposure to such things came mostly through shows like The Undersea World of Jacques Cousteau and Mutual of Omaha's Wild Kingdom ("Jim, these icefishes have big hearts that help insure their survival in tough conditions. And you can insure your own family's survival with coverage from Mutual of Omaha").

But even if this type of information wasn't quite as exciting to others (my parents and assorted puzzled relatives, for example), I'm certain that having watched my childhood reaction to learning about the existence of giant calamari, they got a sense of the exhilaration that might drive an adult to climb into a rotting blue whale carcass, go diving in the Arctic to observe icefish, or, in my case, to spend twenty years chasing down and studying vampire bats.

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They definitely knew.

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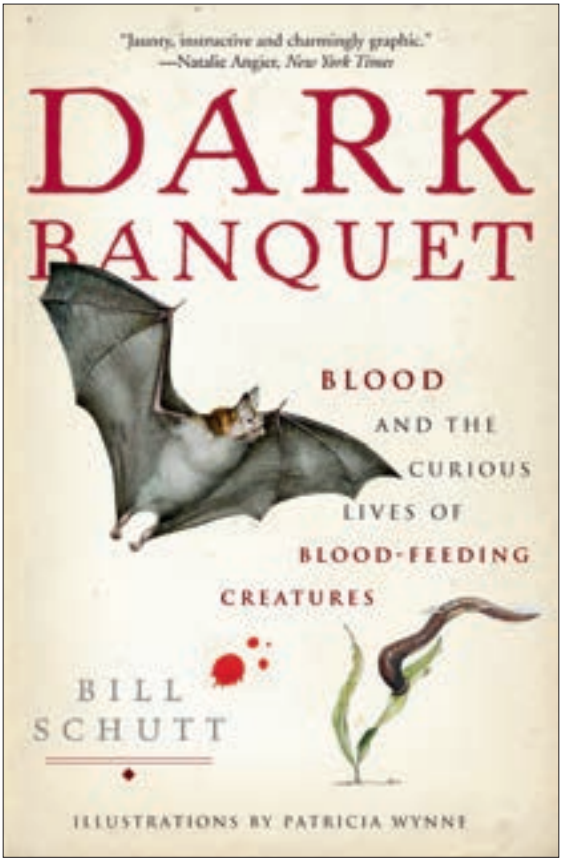

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