THE SERENGETI RULES

THE QUEST TO DISCOVER HOW LIFE WORKS AND WHY IT MATTERS

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FIGURE 1 The Naabi Entrance Gate, Serengeti National Park.

Photo courtesy of Patrick Carroll.

INTRODUCTION
MIRACLES AND WONDER

The corrugated gravel road known officially as Tanzania Route B144 provides a bone-jarring, teeth-rattling, bladder-testing connection between two of the great wonders of Africa.

At its eastern end stand the massive green slopes of Ngorogoro Crater, a giant, more than ten-mile-wide caldera formed by the collapse of one of the many extinct volcanoes of the Great Rift Valley, and home to more than 25,000 large mammals. To the west lie the vast plains of the Serengeti, our destination on this cloudless, postcard-perfect day.

The route in between is a stark contrast to the lush Ngorogoro highlands. There is no visible source of water; the Maasai herdsmen and boys we pass in their bright red shuka graze their livestock on whatever brown stubble they can find. But as we bounce our way through the first simply marked gate to Serengeti National Park, the landscape changes.

The Maasai vanish, and the nearly barren tracts they use are replaced by straw-colored grasslands, and instead of cattle and goats, sleek black-striped Thomson gazelles look up to see who or what is kicking up dust all over their breakfast.

The anticipation in our Land Cruiser rises. Where there are gazelles, there may be other creatures lurking in the tall grass. We pop open the top of the vehicle, stand up, and with the African rhythms of Paul Simon's *Graceland* playing in my head, I start to scan back and forth. This is my first visit to what the Maasai call "Serengit" for "endless plains." Joining me on my pilgrimage to this legendary wildlife sanctuary is my family:

pilgrims with families and we are going to Graceland . . .

At first, I am a bit concerned. Where is all the wildlife? Yes, it is the dry season, but things look *really dry*. Can this place live up to its reputation?

The continuous grass plain is broken only occasionally by small rocky hills, or *kopjes.* From their granite boulders, animals (or tourists) can scan around for miles. There are also gray or red termite mounds projecting up to a few feet over the tops of the grass. One's eye is naturally drawn to these shapes.

"What is that over there?" asks a voice in the vehicle.

A couple of us grab our binoculars and zero in on a lone mound a couple of hundred yards away.

"Lion!"

A golden lioness is standing on top, staring out over the surrounding grass.

OK, so they are here, I murmur to myself. *But this is the famous Serengeti?*

It is going to be really hard to spot things in this tall dry grass. I am the only biologist in my clan, I can't expect anyone else to want to do this for days on end.

As we drive on, some streaks of green grass appear, with a few iconic flat-topped acacia trees sprinkled about. A creek bed meanders through the green patches, and it has plenty of water. We go over a small rise, round a bend, and skid to a stop—zebra and wildebeest block the road and fill the entire view.

It is a sea of stripes. Perhaps 2,000 or more animals have gathered near a large waterhole, raising a ruckus. The zebras' calls are something between a bark and a laugh: "kwa-ha, kwa-ha," while the wildebeest seem to just mutter "huh?" These herds are stragglers from the greatest animal migration on the planet, when as many 1 million wildebeest, 200,000 zebras, and tens of thousands of other animals follow the rains north to greener grazing grounds.

Coming next to the waterhole from over the small rise on our left—the Dawn Patrol—a parade of elephants with several youngsters scurrying to keep up. The herds part to make way.

From that point on, the Serengeti offers an unending canvas containing mammals of many sizes, shapes, and colors: small gray warthogs with tails standing straight up like our radio antenna; not two or three but at least nine species of antelope—the tiny dik-dik, the massive eland, impala, topi, waterbuck, hartebeest, Thomson's and the larger Grant's gazelles, and the ubiquitous wildebeest; black-backed jackals; towering Masai giraffe; and yes, all three big cats on this first day, including several more lions, a leopard dozing in a tree, and a cheetah posing just feet from the road.

Although I have seen many pictures and movies, nothing prepared me for, nor spoiled the thrill of, encountering this stunning scenery for the first time.

A strange, but very pleasant feeling sweeps over me as I gaze across a wide green valley, with multitudes of creatures and acacia stretching as far as I can see, and the sun beginning to set behind the silhouettes of the surrounding foothills. Although it is the first time I have ever been to Tanzania, I feel at *home*.

And indeed, this is home. For across the Rift Valley of East Africa lay buried the bones of my and your ancestors, and those of our ancestors' ancestors. Sandwiched between Ngorogoro Crater and the Serengeti lies Olduvai Gorge, a thirty-mile-long twisting maze of badlands. It was in its eroding hillsides (just three miles off of the current B144) that, after decades of searching, Mary and Louis Leakey (and their sons) unearthed not one, not two, but *three* different species of hominids that had lived in East Africa 1.5 to 1.8 million years ago. Thirty miles to the south at Laetoli, Mary and her team later discovered 3.6-million-year-old footprints made by our small-brained but upright-walking ancestor *Australopithecus afarensis*.

Those hard-earned hominid bones were precious needles in a haystack of other animal fossils that tell us that, although the specific actors have changed, the drama we can still see today—of fleet herds of grazing animals trying to stay out of the reach of a number of wily predators—has been playing for thousands of millennia. Hoards of ancient stone tools found around Olduvai and butchery marks on those bones also tell us how our ancestors were not merely spectators but very much a part of the action.

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Human life has changed immensely over the millennia, but never so much or so quickly as in the past century. For almost the entire 200,000-year existence of our species, *Homo sapiens*, biology controlled us. We gathered fruits, nuts, and plants; hunted and fished for the animals that were available; and like the wildebeest or zebra, we moved on when resources ran low. Even after the advent of farming and civilization, and the development of cities, we were still very vulnerable to the whims of the weather, and to famine and epidemics.

But in just the past hundred years or so, we have turned the tables and taken control of biology. Smallpox, a virus that killed as many as 300 *million* people in the first part of the twentieth century (far more than in all wars combined) has not merely been tamed but has been eradicated from the planet. Tuberculosis, caused by a bacterium that infected 70–90 percent of all urban residents in the nineteenth century and killed perhaps one in seven Americans, has nearly vanished from the developed world. More than two dozen other vaccines now prevent diseases that once infected, crippled, or killed millions, including polio, measles, and pertussis. Deadly diseases that did not exist in the nineteenth century, such as HIV/AIDS, have been stopped in their tracks by designer drugs.

Food production has been as radically transformed as medicine. While a Roman farmer would have recognized the implements on an American farm in 1900—the plow, hoe, harrow, and rake—he would not be able to fathom the revolution that subsequently transpired. In the course of just one hundred years, an average yield of corn more than quadrupled from about 32 to 145 bushels per acre. Similar gains occurred for wheat, rice, peanuts, potatoes, and other crops. Driven by biology, with the advent of new crop varieties, new livestock breeds, insecticides, herbicides, antibiotics, hormones, fertilizers, and mechanization, the same amount of farmland now feeds a population that is four times larger, but that is accomplished by less than 2 percent of the national labor force compared to more than 40 percent a century ago.

The combined effects of the past century's advances in medicine and agriculture on human biology are enormous: the human population exploded from fewer than 2 billion to more than 7 billion people today. While it took 200,000 years for the human population to reach 1 billion (in 1804), we are now adding another billion people every twelve to fourteen years. And, whereas American men and women born in 1900 had a life expectancy of about forty-six and forty-eight years, respectively, those born in 2000 have expectancies of about seventy-four and eighty years. Compared to rates of change in nature, those greater than 50 percent increases in such a short timespan are astounding.

As Paul Simon put it so catchily, these are the days of miracles.

RULES AND REGULATIONS

Our mastery, our control over plants, animals, and the human body, comes from a still-exploding understanding about the control of life at the molecular level. And the most critical thing we have learned about human life at the molecular level is that *everything is regulated*. What I mean by that sweeping statement is:

- every kind of molecule in the body—from enzymes and hormones to lipids, salts, and other chemicals—is maintained in a specific range; in the blood, for example, some molecules are 10 billion times more abundant than other substances.
- every cell type in the body—red cells, white cells, skin cells, gut cells, and more than 200 other kinds of cell—is produced and maintained in certain numbers; and
- every process in the body—from cell multiplication to sugar metabolism, ovulation to sleep—is governed by a specific substance or set of substances.

Diseases, it turns out, are mostly abnormalities of regulation, where too little or too much of something is made. For example, when the pancreas produces too little insulin, the result is diabetes, or when the bloodstream contains too much "bad" cholesterol, the result can be atherosclerosis and heart attacks. And when cells escape the controls that normally limit their multiplication and number, cancer may form.

To intervene in a disease, we need to know the "rules" of regulation. The task for molecular biologists (a general term I will use for anyone studying life at the molecular level) is to figure out—to borrow some sports terms—the players (molecules) involved in regulating a process and the rules that govern their play. Over the past fifty years or so, we have been learning the rules that govern the body's levels of many different hormones, blood sugar, cholesterol, neurochemicals, stomach acid, histamine, blood pressure, immunity to pathogens, the multiplication of various cell types, and much more. The Nobel Prizes in Physiology or Medicine have been dominated by the many discoverers of the players and rules of regulation.

Pharmacy shelves are now stocked with the practical fruit of this knowledge. Armed with a molecular understanding of regulation, a plethora of medicines has been developed to restore levels of critical molecules or cell types back to normal, healthy ranges. Indeed, the majority of the top fifty pharmaceutical products in the world (which altogether accounted for $187 billion in sales in 2013) owe their existence directly to the revolution in molecular biology.

The tribe of molecular biologists, my tribe, is justifiably proud of their collective contributions to the quantity and quality of human life. And dramatic advances in deciphering information from human genomes are ushering in a new wave of medical breakthroughs by enabling the design of more specific and potent drugs. The revolution in understanding the rules that regulate our biology will continue. One aim of this book is to look back at how that revolution unfolded and to gaze ahead to where it is now heading.

But the molecular realm is not the only domain of life with rules, nor the only branch of biology to have undergone a transformation over the past half-century. Biology's quest is to understand the rules that regulate life on every scale. A parallel, but less conspicuous, revolution has been unfolding as a different tribe of biologists has discovered rules that govern nature on much larger scales. And these rules may have as much or more to do with our future welfare than all the molecular rules we may ever discover.

THE SERENGETI RULES

This second revolution began to flower when a few biologists began asking some simple, seemingly naïve questions: Why is the planet green? Why don't the animals eat all the food? And what happens when certain animals are removed from a place? These questions led to the discovery that, just as there are molecular rules that regulate the numbers of different kinds of molecules and cells in the body, there are ecological rules that regulate the numbers and kinds of animals and plants in a given place.

I will call these ecological rules the "Serengeti Rules," because that is one place where they have been well documented through valiant, long-term studies, and because they determine, for example, how many lions or elephants live on an African savannah. They also help us understand, for example, what happens when lions disappear from their ranges.

But these rules apply much more widely than to the Serengeti, as they have been observed at work around the world and shown to operate in oceans and lakes, as well as on land. (I could just as easily call these the "Lake Erie Rules," but that just seems to lack a sense of majesty). These rules are both surprising and profound: surprising because they explain connections among creatures that are not obvious; profound because these rules determine nature's ability to produce the animals, plants, trees, and clean air and water on which we depend.

However, in contrast to the considerable care and expense we undertake in applying the molecular rules of human biology to medicine, we have done a very poor job in considering and applying these Serengeti Rules in human affairs. Before any drug is approved for human use, it must go through a series of rigorous clinical tests of its efficacy and safety. In addition to measuring a drug's ability to treat a medical condition, these studies monitor whether a drug may cause problematic side effects by interfering with other substances in the body or the regulation of other processes. The criteria for approval pose a high barrier; about 85 percent of candidate medicines fail clinical testing. That high rejection rate reflects, in part, a low tolerance on the part of doctors, patients, companies, and regulatory agencies for side effects that often accompany drugs.

But for most of the twentieth century and across much of the planet, humans have hunted, fished, farmed, forested, and burned whatever and settled wherever we pleased, with no or very little understanding or consideration of the side effects of altering the populations of various species or disturbing their habitats. As our population boomed to 7 billion, the side effects of our success are making disturbing headlines.

For example, the number of lions in the world has plummeted from about 450,000 just fifty years ago to 30,000 today. The King of the Beasts that once roamed all of Africa as well as the Indian subcontinent has disappeared from twenty-six countries. Tanzania now holds 40 percent of all of Africa's lions, with one of their largest remaining strongholds in the Serengeti.

There are similar stories in the oceans. Sharks have prowled the seas for more than 400 million years, but in just the past fifty years, populations of many species around the world have plunged by 90–99 percent. Now, 26 percent of all sharks, including the great hammerhead and whale shark, are at risk of extinction.

Some might say, "So what? We win, they lose. That is how nature works." But that it is not how nature works. Just as human health suffers when the level of some critical component is too low or too high, we now understand from the Serengeti Rules how and why entire ecosystems can get "sick" when the populations of certain members are too low or too high.

There is mounting evidence that global ecosystems are sick, or at least very tired. One measure that ecologists have developed is the total ecological footprint of human activity from growing crops for food and materials, grazing animals, harvesting timber, fishing, infrastructure for housing and power, and burning fuels. Those figures can then be compared with the total production capacity of the planet. The result is one of the most simple but telling graphs I have encountered in the scientific literature (see Figure 2).

Fifty years ago, when the human population was about 3 billion, we were using about 70 percent of the Earth's annual capacity each year. That broke 100 percent by 1980 and stands at about 150 percent now, meaning that we need one and one-half Earths to regenerate

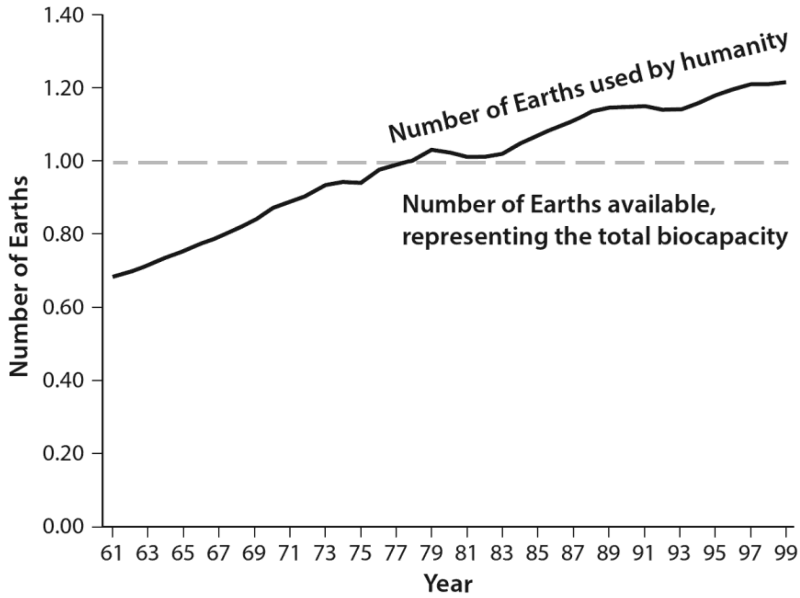

FIGURE 2 The trend in humanity's ecological demands relative to the Earth's production capacity. We are now overshooting what the planet can regenerate by about 50 percent.

Figure from Wackernagel, M., N. B. Schulz, D. Deumling, A. C. Linares et al. (2002) "Tracking the Ecological Overshoot of the Human Economy." *Proceedings of the National Academy of Sciences USA* 99: 9266–9271. © 2002 National Academy of Sciences.

what we use in a year. As the authors of this now annual study note, we have a total of just one Earth available.

We have taken control of biology, but not of ourselves.

RULES TO LIVE BY

As biased it sounds, coming from a biologist, the impact of biology over the past century demonstrates that among all the natural sciences, biology is central to human affairs. There can be no doubt that in facing the challenges of providing food, medicine, water, energy, shelter, and livelihoods to a growing population, biology has a central role to play for the foreseeable future.

Every ecologically knowledgeable biologist I know is deeply concerned about the declining health of the planet and its ability to continue to provide what we need, let alone to support other creatures. Wouldn't it be terribly ironic if, while we race toward and discover more cures to all sorts of molecular and microscopic threats to human life, we continue to just sail on blissfully or willfully ignorant of the state of our common home and the greater threat from disregarding how life works on the larger scale? No doubt most passengers on the Titanic were also more concerned about the dinner menu than the speed and latitude at which they were steaming.

So, for our own sake, let's know all the rules, not just those that pertain to our bodies. Only through wider understanding and application of these ecological rules will we control and have a chance to reverse the side effects we are causing across the globe.

But my goals in this book are to offer much more than some rules, however practical and urgent they are. These rules are the hard-earned rewards of the long and still ongoing quest to understand how life works. One of my aims here is to bring that quest to life, as well as the pleasures that come from discovery. My premise is that science is far more enjoyable, understandable, and memorable when we follow scientists all over the world and into the lab, and share their struggles and triumphs. This book is composed entirely of the stories of people who tackled great mysteries and challenges, and accomplished extraordinary things.

As for what they discovered, there is more to gain here than just better operators' manuals for bodies or ecosystems. One of the beliefs that many people have about biology (no doubt the fault of biologists and biology exams) is that understanding life requires command of enormous numbers of facts. Life appears to present, as one biologist put it, "a near infinitude of particulars which have to be sorted out case by case." Another of my aims here is to show that is not the case.

When we ponder the workings of the human body or the scene I encountered on the Serengeti, the details would seem overwhelming, the parts too numerous, and their interactions too complex. The power of the small number of general rules that I will describe is their ability to reduce complex phenomena to a simpler logic of life.

That logic explains, for example, how our cells or bodies "know" to increase or decrease the production of some substance. The same logic explains why a population of elephants on the savanna is increasing or decreasing. So, even though the specific molecular and ecological rules differ, the overall logic is remarkably similar. I believe that understanding this logic greatly enhances one's appreciation for how life works at different levels: from molecules to humans, elephants to ecosystems.

What I hope everyone will find here, then, is fresh insight and inspiration: insight into the wonders of life at different scales; inspiration from the stories of exceptional people who tackled great mysteries and had these brilliant insights, and a few whose extraordinary efforts have changed our world for the better.

***

After five days in the Serengeti, we have seen all of the species of large mammals except one. As we drive back out through the straw-colored grasslands, as if on cue, a novel silhouette appears on the horizon with a prominent telltale horn—a black rhino. With just thirty-one rhinos remaining in the entire Serengeti, it is a rare and thrilling sight. But knowing that there was once more than 1,000 of the animals here, it is also a sober reminder of the challenges ahead. Although, thanks to knowing the molecular rules of human erections, we now have at least five different inexpensive pills that can do the job, rhino horns are still being poached for use as very expensive aphrodisiacs in the Orient.

These are the days of miracle and wonder,
And don't cry baby, don't cry
Don't cry

PART I

EVERYTHING IS REGULATED

CHAPTER 1

THE WISDOM OF THE BODY

> The living being is stable. It must be so in order not to be destroyed, dissolved, or disintegrated by the colossal forces, often adverse, which surround it.
>
> —CHARLES RICHET, NOBEL LAUREATE (1913)

The snapping of tree limbs jolted me out of a deep sleep. Peering through the front screen of our large tent, perched on a wooded bluff over the Tarangire River in northern Tanzania, I could not see anything outside in the pitch-black, moonless night. Maybe the wind had toppled a tree? I checked the clock—4 a.m.—and rolled over, hoping to get a couple of more hours of rest.

Then I heard heavy footsteps, crunching at first in front of the tent, then on all sides of us, accompanied by occasional low rumbling, almost purring noises. They were *really close.* My wife Jamie was now awake.

A family of elephants had hiked up the slope from the riverbed to browse on the trees and shrubs on top. With no natural predators, the animals walked wherever they desired, and at 8,000 pounds or more with strong, forklift-like tusks, they simply bulldozed their way through any thicket. As we heard branches and trunks splinter, I wondered about the thin canvas that separated us. With utter disregard for the resting humans nearby and, thankfully, no interest in

FIGURE 1.1 Elephant! Bull moments after a bluff charge, Tarangire National Park.

Photo courtesy of Patrick Carroll.

our rectangular refuges, they munched past dawn before heading back down the hill to drink.

As daylight came, we stepped carefully outside to photograph one straggler. Boy, elephants look even bigger when there is nothing between you and them. This bull was *huge*, more than ten feet tall at his shoulders, with giant ears. Stripping branches and leaves off of small trees, while ignoring the paparazzi peering around the corners of several tents, he seemed content. [Figure 1.1]

Until some noise from a tent spooked him. He trumpeted, pivoted to his left and took some quick steps in our direction.

There is more than one account of what happened next.

In my version, we dashed for the nearest tent, barreled inside, and instantly closed the zipper behind us (because four-ton elephants can't open zippers). We then just stood inside trembling and muttering, trying to regain our composure.

In the biological version of those few seconds, a remarkable number of things happened in my brain and body. Before my mind could even form the thought "Mad elephant! Run!" a primitive part of my brain, the amygdala, was signaling danger to my hypothalamus. This almond-sized command center just above the amygdala promptly sent out electrical and chemical signals to key organs. Through nerves, it signaled the adrenal glands that sit on top of my kidneys to release norepinephrine and epinephrine, also known as adrenaline. These hormones then circulated quickly through the bloodstream to many organs including: my heart, causing it to beat faster; my lungs, to open up airways and increase breathing rate; my skeletal muscles, to increase their contraction; my liver, to release stored sugar for a quick supply of energy; and smooth muscle cells throughout my body, causing blood vessels to constrict, skin hairs to stand on end, and blood to shunt away from the skin, intestine, and kidneys. The hypothalamus also sent a chemical signal, corticotropic releasing factor (CRF), to the nearby pituitary gland that triggered it to release a chemical called adrenocorticotropic hormone (ACTH) that traveled to another part of the adrenal gland and triggered the release of another chemical—cortisol, which increased blood pressure and blood flow to my muscles.

All these physiological changes are part of what is known as the "fight-or-flight" response. Coined and described a century ago by Harvard physiologist Walter Cannon, these responses are aroused by both fear and rage, and quickly prepare the body for conflict or escape. We opted for escape.

SCAREDY CATS

Cannon first became interested in the body's response to fear while conducting pioneering studies on digestion. X-rays had just been discovered when Cannon was a medical student; a professor suggested that he try to use the new gadget to watch the mechanics of the process. In December 1896, Cannon and a fellow student successfully obtained their first images—of a dog swallowing a pearl button. They soon experimented with other animals including a chicken, a goose, a frog, and cats.

One challenge to observing digestion was that soft tissues, such as the stomach and intestines, did not show up well on X-rays. Cannon found that feeding animals food mixed with bismuth salts made their digestive tracts visible, because the element was opaque to the rays. He also explored the use of barium; it was too expensive at the time for research work but was later adopted by radiologists (and still is used in gastroenterology today). In a classic series of studies, Cannon was able to observe for the first time in living, healthy, nonanesthetized animals, as well as in people, how peristaltic contractions move food through the esophagus, stomach, and intestines.

During the course of his experiments, Cannon noticed that when a cat became agitated, the contractions promptly stopped. He jotted in his notebook:

> *Noticed sev times very distinctly (so absol no doubt) that when cat passed from quiet breathing into a rage w struggling, the movements stopped entirely. . . . After about ½ minute the movements started again.*

Cannon repeated the experiment again and again. Every time, the movements resumed once the animal calmed down. The second-year medical student now had another finding to his credit. In what would become the second classic paper of his budding career he wrote, "It has long been common knowledge that violent emotions interfere with the digestive process, but that the gastric motor activities should manifest such extreme sensitiveness to nervous conditions is surprising."

Cannon's knack for experiments soon derailed his plans to become a practicing physician. His talent, rigor, and work ethic so impressed the distinguished faculty of the Department of Physiology at Harvard that he was offered an instructorship on graduation.

THE NERVOUS STOMACH

In his own laboratory, Cannon aimed to figure out how emotions affected digestion. He observed that emotional distress also ceased digestion in rabbits, dogs, and guinea pigs, and from the medical compared blood samples of cats taken before and after they had been exposed to the stress of barking dogs. They discovered that the blood of frightened cats contained a substance that when applied to a small strip of isolated intestinal muscle stopped it from contracting. This was the same effect observed when adrenalin was applied to the muscle strip.

Epinephrine was one of the components of "adrenalin" produced by the adrenal glands. Cannon and his colleagues also found that epinephrine sped up heart rate, the release of sugar from the liver, and even blood clotting. These same effects were triggered by pain, as well as by fear or anger. None of these effects occurred when the adrenal glands were removed, or when the nerves leading to the adrenal glands were cut. Thus, the sympathetic nervous system and adrenal glands worked in concert to modulate other body organs in stressful conditions.

Cannon suggested that the responses induced by epinephrine reflected the "emergency" function of the adrenal glands in preparation for fight or flight, or in response to pain. A firm adherent to Darwin's principle of natural selection, Cannon interpreted the roles of the adrenal system through that lens:

> The organism which . . . can best muster its energies, can best call forth sugar to supply the laboring muscles, can best lessen fatigue, and best send blood to the parts essential in the run or fight of its life, is most likely to survive.

Cannon's student Philip Bard subsequently demonstrated that the hypothalamus is the critical part of the brain for control of the so-called involuntary (autonomic) functions of the nervous system, including digestion, heart rate, respiration, and the fight-or-flight response. Both this part of the brain and these emergency responses are ancient. This same set of responses helped our ancestors avoid lions and hyenas on the savannah, just as they help pedestrians to dodge taxis in New York today, or tourists to run from elephants.

A SCIENTIST-SOLDIER

Cannon was an Ivy League but not an Ivory Tower scientist. In 1916, three years into World War I, as the battlefield in Europe turned into a horrific stalemate that produced enormous casualties, it seemed increasingly likely that the United States might be drawn into the conflict. Cannon was asked to chair a special committee of physiologists to advise the government on ways to protect the lives of soldiers and civilians. He learned that one of the most serious problems in battlefield medicine was the development of shock in wounded soldiers. Cannon recognized some of the shock symptoms—rapid pulse, dilated pupils, heavy sweating—from those he had observed in his experimental studies of animals under stress. Wounded soldiers who exhibited these symptoms often went downhill quickly and died. "Are there not untried ways of treating it?" he asked a fellow physiologist.

Cannon was so taken with the problem of shock that he began some animal experiments to see whether he could figure out ways to mitigate the syndrome. When the United States did finally enter World War I in April 1917, Cannon was forty-five years old and the father of five, and could have easily been excused from service. Instead, he volunteered as a member of a Harvard Hospital Unit that was one of the first American medical teams to go to Europe. Cannon requested to serve in a shock ward near the front lines in northern France.

Cannon said goodbye to his family in Boston, took a train to New York, and boarded the troopship *Saxonia* bound for England. The voyage overseas would take eleven days. To avoid detection by German submarines, the ship was blacked out at night, with all of its portholes closed. While ships usually have lights at both ends so as to avoid collisions, the *Saxonia* lit only its stern, to help draw any torpedo off target. Eight days into the voyage, as the ship drew nearer to the English coast, the orders came to sleep in one's clothes; if hit, it was better to jump into the lifeboats fully dressed. As the ship hit choppy seas in rain and fog, Cannon was relieved, "not a favorable condition, I should say, for good hunting," he wrote to his wife Cornelia. The appearance of a British destroyer escort further eased anxieties.

After arriving safely in England, Cannon continued on to the first of several field hospitals. A wave of casualties soon arrived from a major British offensive. Although Cannon had not practiced any medicine since his graduation from medical school seventeen years earlier, he asked to assist in the operating room, dressed wounds, and worked in the wards.

Cannon then moved to a hospital nearer to the front. He watched helplessly the heartbreaking, rapid decline of scores of soldiers. Why the soldiers died was a mystery that Cannon and several other American and British physiologists were hell-bent to solve.

One important clue to shock came from the then-novel approach of measuring soldiers' blood pressures, not just their pulses. Healthy soldiers had pressures of about 120–140 (mmHg; the abbreviation stands for millimeters of mercury), while shock patients had pressures below 90. It was learned that if this fell to 50–60, the patient did not recover.

A low blood pressure meant that vital organs would have difficulty obtaining sufficient fuel and disposing of waste. Early in his time in France, Cannon decided to measure the concentration of bicarbonate ions in the bloodstream of shock patients, a critical component of the blood's buffering system. He discovered that the patients had lower levels of bicarbonate, which meant that the normally slightly alkaline blood had become more acidic. And he found that the more acidic the blood was, the lower the blood pressure and the more severe the shock were. Cannon proposed a simple possible therapy: administer sodium bicarbonate to shock victims.

Cannon reported the first results in a letter to his wife Cornelia in late July 1917, just two months after his arrival in Europe:

> Well, on Monday there was a patient with a blood pressure of 64 (the normal is about 120) millimetres of mercury and in a bad state. We gave him soda [sodium bicarbonate], a teaspoonful every two hours and the next morning the pressure was 130. And on Wednesday a fellow came in with his whole upper arm in a pulp . . . such cases usually die. At the end of the operation he had the incredibly low pressure of 50; soda was started at once and the next morning the pressure was 112.

Cannon described three other soldiers who had been treated that same week and also had been "snatched from death," including one who was given the sodium bicarbonate intravenously and whose rapid respiration and pulse eased quickly.

Cannon and the Allied medical command were thrilled by this innovation. Since shock was often brought on by surgery, the use of bicarbonate was adopted as a standard preventative measure in all critical cases. Cannon and his colleagues also advocated other procedures for warding off the development of shock, including protecting wounded soldiers from exposure by wrapping them in warm blankets, giving warm fluids, transporting on dry stretchers, and using lighter forms of anesthesia during surgery.

To promote these methods, Cannon organized the training and deployment of "shock teams" to treat shocked soldiers on or near the battlefield. To see how the teams performed in battle, he went on an inspection tour close to the front.

In mid-July 1918, he was visiting a hospital near Chalons-sur-Marne, in eastern France. After spending an evening socializing with other doctors, Cannon retired to bed. He could hear guns firing in the distance, but that was typical. Just before midnight, Cannon was jolted awake by "the most stupendous, the most terrific, the most inconceivably awful roar . . . like thousands of huge motor trucks rushing over cobblestones." He jumped to his window and saw entire horizon lit up with gunflashes and shellbursts. He heard the zip-sish sound of a shell passing nearby, which exploded near the hospital. Shells continue to hit within a mile of the building, one about every three minutes for four straight hours.

In the middle of the massive German assault, Cannon was called to the shock ward as the first few casualties were brought in. Then came a flood of wounded—eventually more than 1,100 would arrive that day. As the shock ward filled, Cannon heard a deafening crash—a shell struck the next ward, just twenty feet away, blowing off the roof and sending shrapnel through the walls of his ward. Dust, smoke, and gasses from the explosion filled the air, but Cannon and the rest of the teams stayed at their stations until all patients had been attended to and moved to safer quarters behind the front.

The battle ended up being a turning point in the war. The German drive stalled, and the Allies pushed eastward over the following weeks and months. Cannon followed the leading front into formerly German-held territory. He saw French towns in complete ruins, desolate landscapes denuded of all greenery, and longs columns of enemy prisoners. At last, the streams of Allied wounded coming into the hospitals slowed to a trickle, then stopped altogether; the war was over. Cannon wrote to his wife, "There is satisfaction now in knowing . . . that we were serving the wounded close to the center of the struggle which changed the whole history of the world."

Cannon's exemplary performance during the war was recognized by a series of promotions. In a span of just fourteen months, he went from first lieutenant to captain, then to major, and finally to lieutenant colonel. He was awarded the Order of the Bath by the British and cited by General Pershing, the leader of the American forces in Europe: "*For exceptional meritorious and conspicuous services as instructor in shock treatment.*" After a joyous celebration in Paris, he sailed back home to the United States, his wife, children, and Harvard laboratory in January 1919. [Figure 1.3]

THE WISDOM OF THE BODY

Cannon's experiences in France had a profound impact on the physiologist. They gave him a poignant, first-hand understanding of the important parameters for the maintenance of human life. Combined with his knowledge of the control of digestion, respiration, heart rate, and the responses to stress in animals, Cannon was provoked to think about the body's ability to react to disturbances and yet to maintain critical functions within fairly narrow ranges.

To Cannon, it appeared that many activities of the nervous and endocrine systems served to prevent wide oscillations and to hold the internal conditions of the body—temperature, acidity, water, salts, oxygen, and sugar—fairly constant. He knew too well that if these narrow limits are breached, serious illness or death often follows. For example, blood pH, a measure of acidity, is maintained near 7.4; if it drops to 6.95, coma and death result, and if it rises to 7.7, convulsions and seizures occur. Similarly, calcium levels are maintained around 10 milligrams per 100 milliliters of blood; half that level causes convulsions, double that level causes death.

Cannon began to speak of the innate "wisdom of the body" in lectures and papers. "Our bodies are built to take very effective care of themselves, in many ways which we have become aware of only in

Grounded in Cannon's body of work on digestion, thirst, hunger, fear, pain, shock, and the nervous and endocrine systems, and made accessible by his lucid writing, homeostasis became a fundamental concept in physiology and biology. Some compared it to Darwin's principle of natural selection as one of the seminal integrative ideas in biology.

Cannon believed that the implications of homeostatic mechanisms to medicine were far reaching and very positive. He shared his "Reasons for Optimism in the Care of the Sick" in an address to Boston-area physicians that was subsequently published in the *New England Journal of Medicine*. He began his presentation with typical modesty:

> That you, a group of physicians who are daily confronting the practical problems of sick men and women, should ask me, a physiologist, a laboratory recluse, to address you is a surprising fact. Perhaps my presence here calls for some explanations from you—and for some apologies from me! . . . All that I propose to do as a physiologist is to draw forth some suggestions from years of research and reading and thinking about the workings of the organism . . . that may be useful as laying a basis for optimism in medical practice.

Cannon then recounted how when some factors

> tip the organism in one direction or the other, internal adjustments have promptly been called into service which have prevented the disturbances from going too far and have tipped the organism back to its normal position. Note that these are not processes which [sic] we manage ourselves. They are automatic adjustments.

In light of these marvelous powers of self-regulation Cannon asked, "If the body can largely care for itself what is the function of the physician?"

He explained that doctors' services are called for when these mechanisms are overwhelmed or malfunctioning. Cannon emphasized how many of the newer therapies available to physicians—insulin, thyroxin, antitoxins—were natural components of the body's self-regulatory system. The physician's role was thus to reinforce or to restore the natural homeostatic mechanisms of the body. Cannon suggested that the power of these mechanisms, and the increasing ability of physicians to bolster them, were cause for optimism in medicine.

Cannon had the powerful ideas that regulation is the central matter of physiology, and that abnormal regulation is the central issue of medicine. Coincidentally, at the very same time that Cannon was expressing these pivotal ideas, another biologist was reaching the conclusion that regulation was the central issue in nature on a much larger scale.

CHAPTER 2

THE ECONOMY OF NATURE

[T]he study of the regulation of animal numbers forms about half the subject of ecology, although it has hitherto been almost untouched.

—CHARLES ELTON

The charge was a bluff. The elephant took only a few steps, just enough to let us know which mammal was boss of that hilltop.

Once our heartbeats returned to normal, and after he worked his way down the slope, we ventured back outside to survey the aftermath of the night's raid. There was a wake of broken trees, naked branches, and the lingering aroma of dung (theirs, not ours). Elephants are prodigious producers of the latter: their hundred-foot-long intestines manufacture up to 200 pounds of manure per day to keep up with the more than 200 pounds of food and fifty gallons of water they consume.

Given the absence of any natural predators, and their enormous appetites, one might ask why East Africa is not overrun with, or stripped bare by, elephants? Perhaps it is because African elephants, the largest of all land animals, reproduce very slowly? Females do not mature until their teens, they give birth to just a few young in their lifetimes, and it takes twenty-two months of gestation for a 250-pound baby elephant to develop.

It was Charles Darwin who famously dispelled that explanation in *On the Origin of Species*:

> The elephant is reckoned the slowest breeder of all known animals, and I have taken some pains to estimate its probable minimum rate of natural increase; it will be safest to assume that it begins breeding when thirty years old, and goes on breeding till ninety years old, bringing forth six young in the interval, and surviving till one hundred years old; if this be so, after a period of from 740 to 750 years there would be nearly nineteen million elephants alive, descended from the first pair. Indeed, in fewer than 50 generations or about 2500 years, the total *volume* of elephants would exceed that of the planet.

That figure is ridiculous. But consider the other end of the size spectrum. A typical bacterium, such as the *Escherichia coli* that populates our intestines, weighs about one-trillionth of a gram (one trillion bacteria weigh one gram; an elephant weighs about four million grams). Based on a maximum doubling time of twenty minutes, one can calculate how long it would take for one bacterium to give rise to enough bacteria to equal the weight of the Earth. The answer: just two days.

But the world is not made of solid elephants or bacteria.

Why? Because there are limits to the growth and numbers of all creatures.

Darwin recognized that. And he understood it because Reverend Thomas Malthus stated it long before in his landmark *Essay on the Principle of Populations* (1798):

> Population, when unchecked, increases in a geometrical ratio. . . . The germs of existence contained in this spot of earth, with ample food, and ample room to expand in, would fill millions of worlds in the course of a few thousand years. Necessity, that imperious all pervading law of nature, restrains them within the prescribed bounds. The race of plants and the race of animals shrink under this great restrictive law.

But just how are these "bounds" set? And how are they set differently for different creatures? Darwin did not know. These questions were