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CONTENTS

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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

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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.

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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

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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

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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

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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.

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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.

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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

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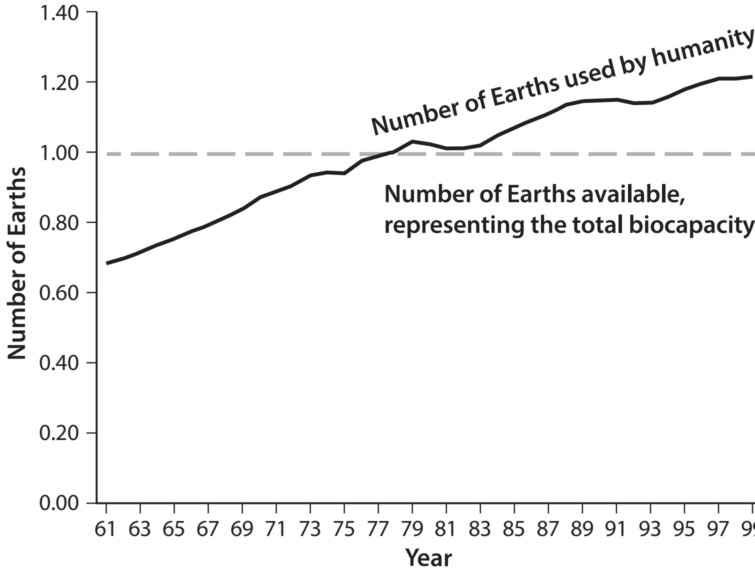

FIGURE 2 The trend in humanity's ecological demands relative to the Earth's production capacity. We are now overshooting what the planet can regenerate by about 50 percent.

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.

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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.

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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.

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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

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INDEX

Page numbers followed by "f" indicate figures and images.

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