UNNATURAL SELECTION

How We Are Changing Life, Gene by Gene

EMILY MONOSSON

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INTRODUCTION

Life-Changing Chemicals

A leukemia patient who once ran marathons, now barely able to walk down the block, waits anxiously as his doctor struggles to find a drug that can outsmart chemo-defying cancer cells. An Iowa farmer scratches her head, wondering how to save her corn crop from weeds now resistant to the “once in a century” herbicide. A father paces anxiously by his daughter’s bedside, hoping that this next round of antibiotics will do the trick. Bedbugs spread throughout a home, tucking into floorboards and bedding—feeding on its slumbering inhabitants and driving them nearly insane. These aren’t scenes from the latest dystopian sci-fi novel; they are real problems, affecting people everywhere, and they all have one thing in common. We beat life back with our drugs, pesticides, and pollutants, but life responds. It evolves.

When I was in school, evolution was the descent of man, the glacially slow transformation of life from single-cell organisms to complex sentient beings, from a few species into Darwin’s “endless forms most beautiful.” This was evolution writ large, read through fossils found layered in the earth’s crust and, increasingly, through ancient DNA caught in amber or scraped from the bones of a long-dead ancestor. Underlying those large changes are subtle ones: a slightly longer finger bone in a bat; a minor change in the pattern on a butterfly wing; a deeper purple in a flower’s petal. This is evolution writ small.

If we could peer into life’s inner workings, whether bacteria, bug, fish, or frog, we would see that the very code of life is more fluid than once imagined. Most often, changes in DNA or its expression are unnoticeable or unimportant, but every once in a while, a doozy of a mutation pops up: a lethal strain of bacteria gains the ability to chew up and spit out the last effective antibiotic; or a malaria-carrying mosquito brushes aside DDT, unaffected; or the daughter of prehistoric farmers finds she is able to tolerate milk into adulthood. While such variations may well be the spice of life, evolution requires favorable conditions for the selection of these new flavors. A mutation that detoxifies DDT is only helpful when mosquitos are under pressure from insecticide; digesting milk only helps where milk is available and when drinking it contributes to a brighter future for the whole family. And a trait’s surviving under pressure is of little use to the larger population unless it is a trait that can pass from one generation to the next. When beneficial heritable characteristics, whether through mutation or other means, arise in the right place, the right time, and in the right species, they may sweep through populations.

This is evolution in the fast lane, and species with explosive population growth—the bugs, bacteria, and weeds (or in the case of cancer, cells)—have the advantage over those of us who reproduce more slowly. When mosquitos, bedbugs, and

houseflies evolved resistance to DDT in the virtual blink of an eye, other species such as eagles, peregrines, and pelicans faced extirpation. We won't see the evolution of tusk-free African elephants in heavily hunted populations, or contaminant-resistant polar bears (as top predators, polar bears are among the most contaminated animals on earth) in "contemporary" time, but we are certain to encounter plenty of chemically resistant pests and pathogens.

This book begins with our relationship to those species living life in the fast lane. Some of the more infamous cases of rapid evolution are introduced in the first section, "Unnatural Selection in a Natural World." Organisms like staph bacteria, agricultural weeds, and even bedbugs are evolving in direct response to our actions. It is a completely natural phenomenon, but it's occurring in a human-tainted unnatural setting. Remove the human element and you remove a good portion of the selection pressure. Each chapter of this first section reveals a different facet of our experience with rapid evolution, from discovery to prevention to resurgence of species once controlled by our chemicals. By better understanding the processes at work, we can do a better job preventing or fixing the ensuing problems. Rather than risk heading off into a near future filled with "superbugs," we can change how we interact with pests and pathogens, reduce the pressure, and still maintain some degree of control.

Though we tend to be most concerned with how evolution directly impacts *us*, it is becoming increasingly clear that our evolutionary influence extends well beyond bugs and bacteria to wildlife. In rivers, ponds, and lakes toxic enough to kill—whether contaminated with pesticides, toxic metals, or PCBs—the flash of a fin, clutch of eggs, or frog song is signaling that rapid evolution isn't just for the spineless. Species with a backbone are also evolving in response to chemically altered environments. When I first proposed this book, reviewers expressed concern that writing about evolution in response to pollution would provide industries fighting billion-dollar cleanups and pollutant controls with an excuse—if contaminated fish are fat and happy, why bother cleaning up?

By the end of this book I hope the answer will be clear. Those surviving fish will have subtle genetic differences from their pre-industrial-age ancestors. Yet how those differences—the result of our chemical influence—will play out in the long run is anyone's guess. What happens when tolerant fish or frogs loaded with chemical contaminants pass their toxic burden on to more sensitive species like the hawks and minks that feed upon them? Or when survival comes with a price tag? Perhaps a toxic-tolerant population is more sensitive to temperature swings, starvation, or predation. Some of those species surviving today may be gone tomorrow. We are laying the groundwork for a game of *Survivor: Planet Earth*, and the outcome may not be to our liking. With a century of industrial-age pollutants behind us, and billions of pounds of toxicants released into air, water, and land each year, the stories of fish, frog, and salamander told in the second section of this book, "Natural Selection in an Unnatural World," are unfolding as you read. As long as industry remains wedded to the false dichotomy of profit over protection, and we keep choosing cheap over sustainable goods, pollutants will continue to settle near and far across the globe, changing life.

If the rapidity of evolution in response to drugs, pesticides, and pollutants isn't enough to make us think twice about our chemical dependence, here is another reason: epigenetics, the heritable changes in gene *expression*, without any changes in the DNA

sequence itself. Evidence is piling up that some environmental stressors leave their mark on plants and animals, including humans, for generations to come by altering how and when genes are turned on and off. The last section, “Beyond Selection,” offers a speculative yet disturbing scenario. Epigenetic change may provide an incredibly rapid source of variation in a single generation. And the stressors shown to cause epigenetic changes range from temperature to nutrition to toxic chemicals. If variation induced by stress, including chemical exposures, can pass from one generation to the next—could these changes influence the course of evolution? And if so, how might exposed species, including ourselves, fare?

We cannot turn back the clock, nor would most of us want to return to pre-industrial, pre-antibiotic days. But we can learn to live in balance—to manage pests without creating insects invulnerable to our safest and most effective insecticides; to protect individuals from disease without inviting epidemics; to benefit from technology and modern chemistry without threatening the health of future generations. The first step is understanding how our choices impact life’s evolutionary course. And so we begin close to home, with an impending public health disaster: antibiotic resistance.

PART I

Unnatural Selection in a Natural World

CHAPTER 1

Discovery: Antibiotics and the Rise of the Superbug

"I see resistant staph all the time," says nurse practitioner Maggie G. Her enormous blue eyes convey both the compassion and the weariness of someone who has seen it all. Over the course of 25 years, the Western Massachusetts nurse has treated farmers, hill-town hippies, and teens seeking treatment for STDs and fevers, as well as men, women, and children who walk for miles and wait patiently with festering wounds and suppurating tumors in the Sierra Leone clinic that she visits once a year. One constant throughout all of Maggie's experiences is methicillin-resistant staph, or MRSA. Back in the late eighties, when Maggie was just finishing nursing school, MRSA was rare. But over the years she has witnessed the rise of this drug-resistant bug, tending to countless cases—one of the most memorable involved a young camp counselor whose infected toe turned into a life-threatening hole in her heart. When we spoke, Maggie was working with recovering addicts at a psych hospital. MRSA spreads so easily in needle-using addict populations through needle sharing or festering open wounds that Maggie says addicts are often treated "presumptively"—meaning the staff doesn't always test but assumes drug resistance. It's a reasonable assumption. In some places, nearly 50 percent of the needle-using population may be positive for community-acquired MRSA.[1]

First recognized as a "healthcare-associated infection" limited to patients and caretakers, MRSA made its way out of the hospital into the community a decade or so ago. The bacteria can spread from mother to daughter, throughout a high school locker room by way of an infected towel, from pet to owner, and between hospital patients on the hands of a caregiver. It is a parent's worst nightmare: a small bite or scrape turns into an angry red trail streaking up a child's leg, and one antibiotic after another fails. A once easily treatable infection is now potentially fatal. Of the roughly 75,000 Americans who become infected with MRSA each year, an estimated 9,700 will die.[2]

We live in dangerous times. Infectious diseases are rapidly evolving beyond our medicinal reach, returning us to the pre-antibiotic age. In just over a century, we have rendered impotent some of our most precious therapies, and there is plenty of blame to go around. Whether it be doctors pacifying pushy, anxious parents; the agricultural industry preventively treating livestock, or worse, simply encouraging livestock growth; or hospitals fending off recalcitrant infection—we have all contributed to the rise of the superbug. Each year nearly 37 million pounds of antibiotics are used in the United States. Some 7 million pounds go down the throats of our kids, up the arms of hospital patients, and into infected addicts; a few hundred thousand pounds are

consumed by our pets; and the rest is used by the ag industry.[3] And though MRSA is the poster-bug for resistance, it has plenty of company. A once-curable pneumonia recently killed seven patients at a well-regarded national hospital.[4] Tuberculosis that is completely drug resistant has surfaced in India, Italy, and Iran. In Japan, a strain of gonorrhea has shaken free from all antibiotics. That a fully antibiotic-resistant STD may once again rage throughout the world ought to strike fear into all of us, even those who consider ourselves beyond its reach—if not simply because "you just never know," then because some bacteria can easily swap resistance genes. And that means that resistance in a venereal disease may one day transfer to a bug that causes pneumonia or a skin infection. Bacteria may be among the most primitive life forms on earth, but they have proven to be among the most formidable opponents.

The story of antibiotic resistance is one of great advances and impending loss. It begins a little over a century ago with two of the most important discoveries in modern medicine: that disease can be caused by bacteria, and that bacteria can be killed selectively. Yet almost as soon as antibiotics hit the market, one after another began to fail. Antibiotic resistance touches us all, so it is a good place to begin an exploration of evolution in our time.

Discovery

Before we can cure (or better, prevent) disease, we must recognize the cause. The French chemist Louis Pasteur was just a boy in 1831 when cholera killed nearly 20,000 souls in Paris, roughly 250 miles (400 kilometers) from his hometown. These were the days when epidemics raged—infecting and killing until new victims were too few in number to sustain the spread of disease. Cholera killed millions worldwide. Bubonic plague flared up every few hundred years or so, at one point taking over a third of Europe's population. There was plenty of disease to go around, particularly in dense and well-traveled populations. When Pasteur entered the world, physicians and scientists attributed the cause of infectious disease in large part to "miasma"—poisonous vapors in the air. Disease, like the winds, weather, and the stench of a fetid river, seemed to travel, hovering here and there for days, months, or years before moving on. A few practitioners insisted that disease spread through contact as a tangible entity rather than some amorphous gas—but without proof, the miasma theory ruled. Louis Pasteur's research eventually focused on revealing the invisible causes of disease, moving medicine from the intangible to the treatable. With the goal of preventing spoilage in wine, Pasteur showed that exceedingly small *micro*organisms —"germs"—infected wine and other fermented products.

When he published the results in the 1860s, many believed that infection, whether of wine, meat, or a human body, arose spontaneously. Pasteur disproved spontaneous generation and unveiled the true nature of infectious disease, rendering it vulnerable to attack. It is not difficult to imagine making the connection between a festering piece of meat and an infected wound. In the hospital wards of nineteenth-century Europe, too often patients succumbed to bacteria that spread through the hands, tools, and clothing of surgeons. Joseph Lister, a contemporary of Pasteur's and a founding father of modern surgery, summed it up when he noted that "the same probe was used for the wounds of all patients during rounds to look for pockets of undrained pus."[5] In our

germophobic society such a scenario is hard to imagine. Inspired by Pasteur's work and his own observations of the wounds that did heal, Lister developed and encouraged the use of surgical antiseptics. (Listerine, marketed in the late nineteenth century as everything from a mouthwash to floor cleaner, was not Lister's invention but rather was named after the surgeon.) Together with Pasteur, Lister worked to raise awareness of the tangible nature of infection and the very real potential to prevent it, urging surgeons to wash their hands and sterilize their tools, and perhaps change their blood-and-guts-stained coats once in a while. Prevention was one of the first outcomes of Pasteur's discovery. But all too often, prevention is not enough.

A decade or so after Pasteur's discovery, the German physician Robert Koch developed a series of steps to isolate and identify the *causative agent* of infectious disease. Koch's so-called *postulates* remain critical to disease sleuthing today. Anthrax, a common disease of farm animals in Koch's district, was the first bacterium to be caught in the act. The microbe poisons the blood by secreting toxin and forms spores that enable it to lie in wait for decades for a suitable host.[6] By culturing bacteria from infected animals, re-infecting healthy animals, and once again isolating the original bacterium, Koch declared anthrax guilty not by association but by causation. If you have ever had the back of your throat unceremoniously scraped and cultured to confirm that you've got strep, you might thank (or curse) Koch. Louis Pasteur may have led medical science to infection's doorway, but it was Robert Koch who provided the keys to identify the diseases that had stalked humanity for hundreds if not thousands of years. By the end of the century, pathogenic bacteria—staph, strep, anthrax, diphtheria, tetanus, and syphilis—emerged from the shadow of "miasma," made visible by the advances of Pasteur, Koch, and others. We now know that a staggering number of bacteria live within us, on us, and around us. We know things about bacteria that would stun those medical giants, including the fact that the bacteria we carry on and within our bodies outnumber our own cells by a factor of ten. Most are harmless, many are essential, and some can kill us.

The fraction of bacteria that make us sick, the pathogens, are products of an eons-old process of coevolution. They invade and use our bodies, and we fight them off. Simply defined, pathogens are microbes that cause disease through infection. If there is one shared feature among pathogens, it is strength in numbers. Should the staph bacteria inhabiting a speck of skin on an addict's arm or a child's elbow gain entrance, whether by needle prick or playground scrape, an initial infection of hundreds can explode into millions if not billions of cells within hours. As the invasion progresses, the immune system kicks in, combating and destroying the trespassers. Sometimes that does the trick; other times the infection wins and we get sick. Visit any pre-twentieth-century cemetery filled with the graves of the young and you can sense the urgency that must have spurred Pasteur, Lister, and Koch to put an end to infection. The power of singling out infectious bacteria was not lost on Koch, who envisioned a day when medicine wouldn't just prevent but *cure*, leaving the host alive and well. Just one year before Koch's death, the first antibiotic drug was introduced to the world.

Target Practice

Antibiotic (or, more accurately in this case, anti*bacterial*) use is chemical warfare

waged on a microscopic field. The trick is to destroy the pathogen, yet leave our own cells unharmed. But there is a catch. Having shared a common ancestry for over a billion years, our cells have much in common with bacteria, which makes identifying a specific target akin to playing "Spot the Difference." Even in these days of genomics and advanced analytical chemistry, it is a difficult game. Singling out bacteria at the turn of the last century would have been like playing the game blindfolded.

And so scientists exploited the very few differences they *could* see. By the late 1800s, industrial chemical dyes had begun to make the invisible visible, tagging biological structures with red, blue, and purple. For the first time ever, a physician could both differentiate animal cells from bacterial cells *and* distinguish one class of pathogen from another. If chemical dyes clung to one cell type while ignoring another, could these chemicals also be used to kill pathogens while leaving host cells unharmed? Was there a way "to aim chemically"?[7]

Turn-of-the-century German physician Paul Ehrlich was the first to investigate this central question. Connecting the dots between chemistry, bacteriology, and medicine, Ehrlich assembled a team and took aim at one of the more infamous diseases of the day, syphilis. After running hundreds of chemicals synthesized by the German dye industry through their paces, the scientists discovered that compound number 606 was the winner, curing infected rabbits with a single dose.[8] It was 1909, and within a year number 606, renamed Salvarsan, made its way to the clinic. Syphilis, a chronic and potentially fatal disease for the ages, had become curable.[9] Salvarsan singled out a pathogenic bacterium and, when it was administered properly, caused relatively little collateral damage.[10] The antibiotic age had just begun: synthetic products were poised to make their way into medicine cabinets, hospitals, and our bodies. The uneasy relationship between human and bacterial pathogen, shaped by millions of years of coevolution, was about to change. But it would take two world wars before humans finally gained the advantage.

As the twentieth century dawned, Pasteur's, Koch's, and even Ehrlich's discoveries notwithstanding, eating, drinking, or getting a simple puncture wound could still send one to their grave. Syphilis was but one disease, and hygiene could only go so far in disease prevention. Infections we rarely think about today—cholera, typhus, strep, and staph—continued to run their course, killing and maiming. For pathogens, World War I, like so many other wars, was a war of opportunity. As bullets and bombs shredded skin and tore limbs from bodies, infectious bacteria thrived. Aspiring physicians had few options but to amputate infected limbs and watch helplessly as young men died. If they didn't die from infected wounds, there were plenty of other diseases, like cholera and typhus, waiting in the wings. Gerhard Domagk, a volunteer and medic in the German army, had ample opportunity to observe the quick work that bacteria made of men. Years after the war, inspired by Ehrlich's vision of a "magic bullet" cure, Domagk turned his attention to finding the magic in industrial dyes. The target was *Streptococcus*, a common cause of skin infections that could quickly take a turn for the worse. One red dye proved particularly effective at curing strep-infected mice, yet any fanfare would have to wait for human testing. But before those tests could be completed, an odd twist of fate intervened. Domagk's six-year-old daughter, Hildegard, fell ill with a life-threatening infection. She had punctured her hand with a

sewing needle. Hospitalized with fever and infection progressing up her arm, she faced the standard treatment—amputation with no guarantee of survival. Desperate, Domagk treated Hildegard with the dye. Days later she recovered. It soon became apparent that the dye targeted not just strep but a number of other infections as well. Within a few years, the dye, packaged and sold as Prontosil, became the first commercially available sulfa drug. Its derivatives remain in use today. The discovery offered a cure for illnesses from child-bed fever to pneumonia, skin infections, and gonorrhea. It was 1935, and for the first time in human history a whole range of once-fatal infections could be cured.[11] Less than five years later, Domagk took home a Nobel Prize.

Two chemicals discovered nearly two decades apart, both products of a chemical industry delirious with newfound ability to synthesize novel chemicals and scientists willing to test one after another, offered a world of change. Yet evolution had already produced a far more effective antibacterial chemical, as Scottish physician Alexander Fleming would discover.

Penicillin

Like Domagk, Fleming returned home from World War I bent on disease prevention, only to discover by sheer accident one of the most valuable antibiotics of the century. His is the now-classic story of accidental discovery: a summer vacation trip, stacks of petri dishes dotted with colonies of staph bacteria left in the sink, an observation, and the historic follow-up. Cleaning the lab after returning from vacation, Fleming noticed that an invisible conflict was playing out on plates that been left to molder. Where spots of one particular mold contaminated the plates, bacterial colonies failed to grow. Fleming's genius was to ask why this particular mold (subsequently identified as a *Penicillium*) cleared the surrounding bacteria. Follow-up studies showed that it produced soluble chemicals that killed not only staph but an assortment of other bacteria.

What Fleming couldn't have known was that penicillin hit bacterial cells where it really hurt—the cell wall. Like a chicken-wire frame for a papier-mâché sculpture, the wall protects bacterial cells from bursting under their own internal pressure. If the wall is compromised, bacteria pop like overfilled balloons. Bacteria like staph and strep with thick cell walls are most sensitive, while others with thinner cell walls, like *Salmonella* and *coliform*, are less sensitive. Our animal cells lack cell walls and so avoid damage. Penicillin is a tribute to the ingenuity of nature. When bacterial cells grow and divide, the wall is broken down and rebuilt. Penicillin prevents that molecular frame from linking back together.

Penicillin's discovery would have been a watershed moment for antibiotic development. But available technology was insufficient for isolating or producing quantities of active chemical, preventing Fleming from putting it through its paces. He published his findings in 1929, but the work slipped quietly into the literature.[12] Nearly a decade later, it piqued the interest of a trio of scientists: Howard Florey, Ernst Chain, and Norman Heatly. Finally able to produce enough of the "mold juice" to test, the group treated mice infected with a lethal dose of strep. The results were impressive. Untreated mice died. Those given penicillin lived.[13] Human testing followed. In 1941, Police Constable Albert Alexander entered a hospital in Oxford,

England, after a rose prick blossomed into a raging, life-threatening infection. Penicillin turned the tide, for a while. Unfortunately for Alexander, no one knew how much of the new drug was needed to beat back an advanced infection. With only enough to treat the constable for several days, despite extracting it back from his urine, Alexander succumbed. Yet this was enough to confirm penicillin's efficacy in humans. Fleming's all-but-forgotten discovery soon took center stage in the war against bacteria. Those early trials, combined with another world war, the desperation of battlefield medics, and the increasing failure of sulfa drugs (the first antibacterials to fall to resistance), helped turn an astute observation into one of the greatest discoveries of the twentieth century. But the triumph was short-lived.

Resistance!

As the Second World War came to a close, the great technology transfer began. From nuclear power to plastics, pesticides, and antibiotics, the era of "Better Living through Chemistry" had arrived. Penicillin was ripe for exploitation. Just as everything today, from mattresses to shopping-cart handles, is impregnated with antimicrobials, industry envisioned toothpaste, chewing gum, lozenges, face creams, and even vaginal *crèmes* infused with penicillin. In his 1945 Nobel acceptance speech, Fleming warned that penicillin's overuse and under-treatment of disease could result in resistant bacteria.[14] But it was already too late. Our first lesson in moderation had come and gone, as resistant strains of staph, strep, and pneumonia cropped up during the war. Penicillin had imposed a powerful selection pressure. Pathogens that could not evolve would die. But in hospital wards both here and in Europe, penicillin-resistant staph began making the rounds, along with sulfa-drug-resistant bacteria. One could almost watch resistance evolve.[15] Attempting to control dangerous strep infections in new recruits, the US Navy treated hundreds of thousands of trainees with prophylactic doses of the drug sulfadiazine. Rheumatic fever, scarlet fever, and respiratory disease incidence dropped almost immediately, but sulfa-resistant strep emerged just three *months* after the initial phase of treatment.[16] Similarly, penicillin was losing ground. As Fleming had feared, one of the greatest factors in the decline of antibiotic effectiveness proved to be overuse.

Then, in 1950, as if to throw fuel on fires of resistance, scientists discovered that antibiotics added to livestock feed accelerated growth, moving animals more quickly from farm to table. Even better, antibiotics helped cut production costs.[17] It was an apparent win-win for the farmers struggling to meet the booming postwar demand for meat and for customers craving an affordable, protein-packed meal. Antibiotics weren't just for the sick and dying anymore—they had become an integral part of "what's for dinner."

The medical world's failure to heed Fleming's warning was a combination of hubris and naïveté about genetics and evolution. Medicine was on a roll: if one antibiotic failed, another would surely take its place. If evolution worked to the bacterium's advantage, human ingenuity would work toward ours. Penicillin was one of the first drugs to be improved. Under penicillin's pressure and through the process of natural selection, bacterial populations acquired a gene for an enzyme capable of snipping apart the drug's key chemical structure—called a beta-lactam ring. In response, drug

developers created methicillin. Like having a portcullis to block the castle gate, methicillin contained a molecule that protected the bacterial-busting beta-lactam structure from destruction. This so-called super-penicillin did the trick. That was in 1959. By 1961, reports of methicillin-resistant staph emerged in England and Europe.[18] The invaders had found another way around. By 1968, researchers at Boston City Hospital had isolated 22 methicillin-resistant strains from 18 patients.[19] Most had become infected after admission to the hospital. It was the dawning of the age of hospital-acquired MRSA.

Several modified versions of penicillin followed, as did the discovery of other natural and synthetic drugs including bacitracin, streptomycin, rifampicin, erythromycin, and polymyxin. The majority were discovered during the antibiotic golden years, 1930–1950. Today, they are fast becoming obsolete, and unfortunately, the next best thing isn't around the corner. Many of our current antibiotics, like penicillin, are beta-lactams that inhibit cell-wall synthesis. Some inhibit the production of proteins, and others alter bacterial cell membranes. At prescribed dosages, most target bacteria while leaving our cells intact and relatively healthy. One increasingly recognized downside of antibiotics, though, is their inability to distinguish the pathogenic bacteria from the "good" bacteria, some of which may even help fend off disease. And while most MRSA patients, including those in Maggie's psych clinic, may benefit for now from next-generation drugs, those options are not available to all. "People in Sierra Leone die from infections," says Maggie, weary with resignation. "We're still using first-line antibiotics there—if we even have them."

The majority of medically important microbes now resist one antibiotic or more, and words like "nightmare" and "catastrophic" are increasingly cropping up in the medical literature. It is not just hyperbole.[20] Like Aesop's Hare, whose overconfidence led to a predictable loss against Tortoise, our hubris may very well cost us our health—if not our lives. Certainly our current situation is not for lack of understanding; we know far more about bacteria and evolution than Pasteur, Koch, or Ehrlich could have even dreamed. Yet we continue to play whack-a-mole—simply changing antibiotics as resistance pops up. It is time to reconsider our strategy and pay homage to evolution. Not the dusty old process of evolution that we equate with the descent of man and speciation but the wild, DNA-swapping, mutating ways of bacteria.

Unveiling the Machinations of Evolution

A single *Staphylococcus aureus* cell, like most bacteria, can within days give rise to millions, if not billions of daughter cells. Bacteria reproduce by cloning. The parent cell divides into two daughters that in turn generate their own daughter cells on and on as one cell exponentially yields hundreds, thousands, and then millions of new cells—by any measure, an impressive amount of DNA replication. Not all of it perfect, though. With each new generation comes the potential for mutation. And mutations are a source of variation for evolution. This is true no matter the species, whether bacteria, bedbugs, elephants, or humans. Only some enjoy the advantages of new gene variants in the course of a few months or years while others like us might require centuries. And though most mutations are of little or no benefit, it only takes one alteration in the right place, and *voilà*, an enzyme is no longer a suitable target for chemical attack.

When these advantageous traits are selected, evolution happens.

The explosive population growth of bacteria means that a beneficial mutation can infiltrate a population within hours. Contrast that with the thousands of years required for a random yet beneficial mutation to take hold in a human population. When hospitalized patients are treated with antibiotics for weeks or months, there is potential for myriad new (or *de novo*) mutations, which in turn become feedstock for the evolution of resistance. As rare but helpful mutations arise—particularly in bacteria under the influence of antibiotics—resistance isn't futile, it is inevitable. In one case, researchers caught evolution in action as the staph infecting a patient treated with vancomycin acquired 35 sequential mutations, diminishing the antibiotic's efficacy as mutations accrued.[21]

As impressive as rescue by *de novo* mutation may be, bacteria have an even more efficient means for acquiring resistance. For so-called sexless organisms, bacteria are incredibly agile genetically. Japanese researchers were the first to catch a glimpse of the acrobatics. During the Second World War, and in the years that followed, *Shigella dysenteriae* became epidemic in Japan. Even if dysentery didn't kill, it knocked the survivors flat. Sulfa drugs worked at first, but by the early 1950s, *Shigella* had evolved resistance. Then Japanese researchers observed something that should have beat some sense into scientists and physicians around the globe. Some strains of *Shigella* were resistant not only to sulfa drugs but to other, newer, drugs as well.[22] They would be the first reported multi-drug-resistant bacteria. The response by the Western medical world was underwhelming. Evolution of *any* resistance over the course of treatment was believed to be a low-probability event. According to antibiotic pioneer Julian Davies, "The notion of multiple drug resistance was heretical."[23] And that wasn't all.

A scientist working in the United Kingdom had isolated bacteria that were, oddly enough, resisting *novel* antibiotics right off the bat.[24] Resistance, it seemed, had spread from one strain to another. Follow-up studies suggested that bacteria were sharing resistance through contact. The findings, as Davies recounts, challenged the prevailing ideas about the process of evolution. *If* evolution simply proceeded by way of one random mutation at a time, and resistance required selection pressures like an antibiotic, then how could these findings be explained? As with the finding of multi-drug-resistant *Shigella*, the reception was unenthusiastic at best, doubtful at worst.[25] But then, how else could resistance to so many drugs evolve so quickly? And why would bacteria carry resistance to a novel antibiotic? The answer lies in the so-called sex lives of bacteria.

When bacteria reproduce, much like us their genes are handed down from parent to offspring, vertically. Just as we carry our genes on linear double-stranded chromosomes, bacteria, too, carry their genes on a double-stranded chromosome—but the bacterial chromosome is a single loop of DNA. Bacteria also possess extra bits of DNA on small rounds called *plasmids* that are central to the DNA trade. Like modular storage units, plasmids contain 20 or 30 "auxiliary genes" that encode biological toxins, enzymes enabling the digestion of novel food, or antibiotic resistance, among other things. When bacteria reproduce, just as the single chromosome is copied and passed on to offspring, plasmids can be passed from parent to daughter. But here is where things get weird. While we humans hold tight to our genetic stock, passing it