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REWRITING THE CODE OF LIFE

Through DNA editing, researchers hope to alter the genetic destiny of species and eliminate diseases.

By Michael Specter December 25, 2016

Early on an unusually blustery day in June, Kevin Esvelt climbed aboard a ferry at Hyannis, bound for Nantucket Island. Esvelt, an assistant professor of biological engineering at the Massachusetts Institute of Technology, was on his way to present to local health officials a plan for ridding the island of one of its most persistent problems: Lyme disease. He had been up for much of the night working on his slides, and the fatigue showed. He had misaligned the buttons on his gray pin-striped shirt, and the rings around his deep-blue eyes made him look like a sandy-haired raccoon.

Esvelt, who is thirty-four, directs the "sculpting evolution" group at M.I.T., where he and his colleagues are attempting to design molecular tools capable of fundamentally altering the natural world. If the residents of Nantucket agree, Esvelt intends to use those tools to rewrite the DNA of white-footed mice to make them immune to the bacteria that cause Lyme and other tick-borne diseases. He and his team would breed the mice in the laboratory and then, as an initial experiment, release them on an uninhabited island. If the number of infected ticks begins to plummet, he would seek permission to repeat the process on Nantucket and on nearby Martha's Vineyard.

More than a quarter of Nantucket's residents have been infected with Lyme, which has become one of the most rapidly spreading diseases in the United States. The illness is often accompanied by a red bull's-eye rash, along with fever and chills. When the disease is caught early enough, it can be cured in most cases with a single course of antibiotics. For many people, though, pain and neurological symptoms can persist for years. In communities throughout the Northeast, the fear of ticks has changed the nature of summer itself—few parents these days would permit a child to run barefoot through the grass or wander blithely into the woods.

"What if we could wave our hands and make this problem go away?" Esvelt asked the two dozen officials and members of the public who had assembled at the island's police station for his presentation. He explained that white-footed mice are the principal reservoir of Lyme disease, which they pass, through ticks, to humans. "This is an ecological problem," Esvelt said. "And we want to enact an ecological solution so that we break the transmission cycle that keeps ticks in the environment infected with these pathogens."

There is currently no approved Lyme vaccine for humans, but there is one for dogs, which also works on mice. Esvelt and his team would begin by vaccinating their mice and sequencing the DNA of the most protective antibodies. They would then implant the genes required to make those antibodies into the cells of mouse eggs. Those mice would be born immune to Lyme. Ultimately, if enough of them are released to mate with wild mice, the entire population would become resistant. Just as critically, the antibodies in the mice would kill the Lyme bacterium in any ticks that bite them. Without infected ticks, there would be no infected people. "Take out the mice," Esvelt told me, "and the entire transmission cycle collapses."

Esvelt has spoken about Lyme dozens of times in the past year, not just on Nantucket and Martha's Vineyard but at forums around the world, from a synthetic-biology symposium in Chile to President Obama's White House Frontiers Conference, in Pittsburgh. At every appearance, Esvelt tells the audience that he wants his two young children—he has a three-year-old son and a daughter who is almost one—to grow up in a Lyme-free world. But that's not really why he speaks at infectious-disease meetings, entomology conventions, and international conservation workshops. He has embarked on a mission that he thinks is far more important.

Esvelt and his colleagues were the first to describe, in 2014, how the revolutionary gene-editing tool CRISPR could combine with a natural phenomenon known as a gene drive to alter the genetic destiny of a species. Gene drives work by overriding the traditional rules of Mendelian inheritance. Normally, the progeny of any sexually reproductive organism receives half its genome from each parent. But since the nineteen-forties biologists have been aware that some genetic elements are "selfish": evolution has bestowed on them a better than fifty-per-cent chance of being inherited.

That peculiarity makes it possible for certain characteristics to spread with unusual speed.

Until CRISPR came along, biologists lacked the tools to force specific genetic changes across an entire population. But the system, which is essentially a molecular scalpel, makes it possible to alter or delete any sequence in a genome of billions of nucleotides. By placing it in an organism's DNA, scientists can insure that the new gene will copy itself in every successive generation. A mutation that blocked the parasite responsible for malaria, for instance, could be engineered into a mosquito and passed down every time the mosquito reproduced. Each future generation would have more offspring with the trait until, at some point, the entire species would have it.

There has never been a more powerful biological tool, or one with more potential to both improve the world and endanger it. Esvelt hopes to use the technology as a lever to pry open what he sees as the often secretive and needlessly duplicative process of scientific research. "The only way to conduct an experiment that could wipe an entire species from the Earth is with complete transparency," he told me. "For both moral and

practical reasons, gene drive is most likely to succeed if all the research is done openly. And if we can do it for gene drive we can do it for the rest of science."

At the meeting on Nantucket, Esvelt assured residents that he and his team fully understood the implications of manipulating the basic elements of life. He said that he regards himself not just as a biologist but as the residents' agent; if they stop showing interest in the research, he will stop the experiments. He also insists that he will work with absolute openness: every e-mail, grant application, data set, and meeting record will be available for anyone to see. Intellectual property is often the most coveted aspect of scientific research, and Esvelt's would be posted on a Web site. And no experiment would be conducted unless it was approved in advance—not just by scientists but by the people it is most likely to affect. "By open, I mean all of it," Esvelt said, to murmurs of approval. "If Monsanto"—which, fairly or not, has become a symbol of excessive corporate control of agricultural biotechnology—"did something one way," he said, "we will do it the opposite way."

There are fewer than a million white-footed mice on Nantucket, so a gene drive won't even be necessary to insure the spread of Lyme-resistant genes. Esvelt plans to release enough genetically modified mice, tens of thousands of them, to overwhelm the wild population. (Since he could never house that many mice in his lab at M.I.T., he recently mentioned the idea of breeding them on a container ship.) That approach, however, would never work for Lyme on the mainland, where there are more than a billion white-footed mice scattered up and down the Eastern seaboard.

The battle against Lyme disease is just an early stage in an unprecedented effort to conquer some of mankind's most pervasive afflictions, such as malaria and dengue fever. Despite a significant decline in deaths from these diseases over the past decade, they still threaten more than half the world's population and, together, kill nearly three-quarters of a million people each year. Malaria alone kills a thousand children every day.

The Bill and Melinda Gates Foundation has invested tens of millions of dollars in the research of a team called Target Malaria led by Austin Burt, at Imperial College, in London. In laboratory tests, the group has already succeeded in using CRISPR to edit the genes of *Anopheles gambiae* mosquitoes, which carry the parasite that causes malaria, so as to prevent females from producing fertile eggs. In theory, as those mosquitoes spread across the countries of sub-Saharan Africa and mate, the population will begin to

shrink. A few weeks ago, the Tata Trusts of Mumbai announced that it would fund a similar project in India.

Gene drives could also be used to help wipe out schistosomiasis, a parasitic disease, carried by blood flukes, that affects hundreds of millions of people each year and kills as many as two hundred thousand. In addition, the new technology could eliminate a variety of invasive species—from pests that eat up thousands of acres of crops to the mosquitoes spreading avian malaria so rapidly among the native birds on Hawaii that the Audubon Society and the American Bird Conservancy routinely refer to the state as "the bird-extinction capital of the world."

For Esvelt, though, those achievements seem almost like secondary benefits. "For a lot of people, the goal is to eradicate malaria, and I am behind that a hundred per cent," he said. "The agricultural people have the New World screwworm"—a particularly destructive pest also known as the blowfly—"they'd love to get rid of in South America. Everyone has a thing he really wants to do. And it makes sense. But I would submit that the single most important application of gene drive is not to eradicate malaria or schistosomiasis or Lyme or any other specific project. It is to change the way we do science."

That is the message that Esvelt has been selling in his talks throughout the world, and the initial response, on Nantucket and Martha's Vineyard—even from people who attended the meetings in order to object to the proposal—has been overwhelmingly positive. "I came here thinking I would say, 'Absolutely not,' " Danica Connors, an herbalist and shamanic practitioner who opposes genetically modified products, said at the Nantucket meeting. "I am the first person to say that, tinker with Mother Nature, we are going to break it." But she told Esvelt that she loved "the fact that you are a young scientist saying, 'I want this to be a non-corporate thing and I want this to be about the people.' " Seeming to surprise even herself, she said, "You know, I want to see where you go with this. I am actually very excited."

Many children grow up enamored of dinosaurs. Most move on, but Kevin Esvelt became transfixed at a young age by the idea that these extinct creatures were somehow related to us. As a boy, in Seattle, he read Michael Crichton's book "Jurassic Park," which sparked his interest in biotechnology. "The real conversion came when I

was ten or eleven," he told me last year, the first time we met, in his office at M.I.T. "My parents took me to the Galápagos. After that trip, I knew what I wanted to do."

The Galápagos trip led him, inevitably, to read the works of Charles Darwin. "I became fascinated with the idea that you have these complex systems that constantly evolve, and all in the language of DNA," he said. "I decided I wanted to spend my life learning how to rewrite the genes of organisms to make some extremely useful and interesting things. When you're a kid, of course, you might be more excited about the interesting than the useful."

Esvelt's father was an executive with the Bonneville Power Administration, and his mother taught elementary school. When Kevin was twelve, his family moved from Seattle to Portland, where he attended a small private school. "They thought it would provide a better environment for me," he said. "I wasn't the most socially connected child. I was reasonably athletic, and got along well enough with other kids, so I wasn't quite on the nerd outer limits. But I certainly preferred books to people."

After graduating from Harvey Mudd College, an engineering school with a strong humanities program, Esvelt moved to Harvard, to the laboratory of David Liu, a professor of chemistry and chemical biology who is best known for his work on the directed evolution of biological and synthetic molecules. Graduate students normally try to publish in professional journals as often as possible, as it is essential for landing prestigious jobs. Yet Esvelt produced no papers in the first five and a half of the six years he spent at Harvard. "Kevin told me on the day we met that he wanted to forgo smaller projects to accomplish something of genuine impact," Liu told me this summer, when I visited him in his office at Harvard. "I had never heard anything like this from a first-year graduate student." Liu, who is also a senior faculty member at the Broad Institute of M.I.T. and Harvard, said, "It stunned me. Kevin struck me as somebody who had all the skills and all the ambition he needed, but he also had just the right amount of naïve fearlessness."

For his doctoral thesis, Esvelt tackled one of synthetic biology's most significant constraints. Evolution unfolds over millions of years, and it can take a thousand generations before even the slightest genetic change becomes permanent. Scientists who want to redesign or augment nature need a much shorter time frame. With Liu's supervision, Esvelt developed a technique to trick certain viruses into evolving proteins

so rapidly in the laboratory that researchers could observe dozens of rounds of molecular evolution in a single day. The work earned him the Harold M. Weintraub Award, one of the country's most coveted prizes for graduate research in the biological sciences.

In 2012, Esvelt assumed a postdoctoral position at Harvard's Wyss Institute for Biologically Inspired Engineering. He began to work with George Church, who is among the world's most renowned—and outspoken—geneticists, and runs one of the largest academic laboratories in the country. Esvelt and Church established an unusual rapport, and they went on to collaborate on a number of studies, including the seminal 2014 paper that described the way CRISPR could combine with gene drives to alter many types of wild populations.

Despite his awards, publications, and influential mentors, Esvelt struggled to find a job that would help him achieve his goals as a scientist and as a public educator. To many institutions, he seemed like a strange hybrid. He had certainly demonstrated great talent as a researcher, but he had also decided to become a sort of proselytizer. He long ago concluded that telling the story of science, and the choices it presents, is just as valuable as anything he might accomplish in a lab. Élite scientists often look down on that kind of advocacy and see it as sanctimonious. "Carl Sagan, to this day, has a reputation in the science community as someone who was obviously a great science communicator," Esvelt said. "But people will say he wasn't that important a scientist. That is insane. Look at his publication record. He was a fabulous scientist."

Many universities were discouraging, in large part because they weren't sure what to do with him. "Most places told me, 'We are fine with you speaking out about open science, but not on our time,' " Esvelt said. This meant that, when it came to tenure decisions and professional evaluations, he would be judged solely on his work in the lab. "I just didn't fit into any of their normal silos," he said.

I first met Esvelt when he was still working in Church's laboratory. He is intensely focussed and rail thin, even though his exercise routine seems limited to fidgeting, which he does constantly. He regards meals, particularly lunch, as a distraction, and often downs some Soylent-like mixture at his desk. Like many of his scientific colleagues, Esvelt is not burdened by a lack of self-regard. Earlier this year, I heard one of his colleagues describe a well-known but particularly shy scientist as extremely

arrogant. Esvelt burst out laughing when I told him about the conversation. "I am a thousand times more arrogant than he is," he said, not entirely without pride. Nonetheless, Esvelt's goals are essentially those of an effective altruist. One of his favorite Web sites, scienceheroes.com, ranks scientists by the number of lives that were saved by their invention. Fritz Haber and Carl Bosch, the inventors of synthetic fertilizer, which has helped feed the world for more than a century, rank first, having together saved 2.72 billion lives. Louis Pasteur, who developed the germ theory of disease, doesn't even make the top ten. "It's an impossible list to crack," Esvelt said, the first time he showed me the site.

Last year, Esvelt took a position at M.I.T.'s Media Lab, which seemed to me an odd fit. Although the lab is influential, I had always assumed that it was more focussed on technology, art, design, and computer learning than on biology or genetics. "You have a dated view of this place," Joi Ito, who has been the lab's director since 2011, told me.

"Kevin fits here perfectly," he said. We were sitting in his office, which looks out on the Charles River. The day was so muggy that there wasn't a single jogger on the street or a scull crew on the river. Ito sees CRISPR as a logical step in the rapid march of digital progress. "It is a part of a long-term democratic trend where diminishing costs drive innovation," he said. "Cheaper prices drove computers out of the walls of these big companies—because you suddenly didn't need all that money anymore. When you take away money, you take away the requirement for permission." He compared what was going on in biotechnology with the emergence of e-mail. "Suddenly, a janitor had the ability to communicate with the chairman of the board," he said. "The filters disappeared. We are seeing the same thing today with CRISPR and biotechnology."

It may be years before animals or plants with CRISPR gene drives are released into natural environments. There will be many regulatory, political, and social hurdles to negotiate along the way. Esvelt predicts that it will be nearly a decade, if all goes well, before Lyme-resistant mice appear on Nantucket or Martha's Vineyard. But the scientific obstacles are disappearing rapidly. That makes it at least possible to envisage a day when gene-drive technology will be deployed to vanquish diseases that have killed billions of people, deter devastating pests, and protect endangered species like the black-footed ferret. (Plague has brought the ferrets to the edge of extinction, but it should now be possible to edit their genes to make them immune.) To consider

implementing such fundamental scientific changes, though, will require a tectonic shift in public attitudes about the natural world.

One of Esvelt's goals at M.I.T. is to facilitate that shift. Part of his job, as he sees it, is to challenge what he describes as "the ridiculous notion that natural and good are the same thing." Instead, he told me, we ought to think about intelligent design as an instrument of genetics. He smiled because the phrase "intelligent design" usually refers to the anti-Darwinian theory that the universe, with all its intricacies and variations, is too complex to have arisen by chance—that there had to be a guiding hand. The truth is more prosaic, and also more remarkable: for four billion years, evolution, driven by natural selection and random mutation, has insured that the most efficient genes would survive and the weakest would disappear. But, propelled by CRISPR and other tools of synthetic biology, intelligent design has taken on an entirely new meaning, one that threatens to transcend Darwin—because evolution may soon be guided by us.

For Esvelt, that moment can't come soon enough. "Natural selection is heinously immoral," he said, invoking Tennyson's view that nature is "red in tooth and claw." Unlike Rousseau, Esvelt sees nothing "blessed" about man in his natural state. In fact, romantic notions of a natural world defined by innocence and harmony repel him. "The idea that nature is the essence of goodness, is purity and truth, is so foreign to my perception of the world that I can't even conceive of how people can think that way," he said. "There is such a fantastic degree of suffering out there."

He went on to say that humans no longer need to be governed by nature, or rely on brutal and ruinous methods to control it. "When nature does something that hurts us, we respond with chemistry and physics," he said. "We spread toxic pesticides that kill problematic pests, and often kill most of the other insects in the area as well. To get rid of mosquitoes, we use bulldozers to drain swamps. It works. But it also destroys wetlands and many other species. Imagine that an insect is eating your crops. If you have a gene drive and you understand how olfaction works in that pest, you could just reprogram it to go on its merry way. The pest would still be in the ecosystem, but it would just dislike the taste of your crop. That is a much more elegant way of interacting with nature than anything we do now."

Virtually any technology that can serve a species can also harm it, however, either by accident or by design. A scientist capable of rewiring a mosquito to prevent it from

spreading malaria, dengue, Zika, or any other infectious disease would almost certainly have the skill to turn that insect into a weapon. Earlier this year, James Clapper, the director of national intelligence, listed gene editing as a potential weapon of mass destruction. Some scientists felt that he was being hyperbolic, but the authors of a report on gene drives issued this year by the National Academy of Sciences wrote, "It is not inconceivable that rather than developing a resistant mosquito, one could develop a more susceptible mosquito capable of transmitting a specific pathogen." In other words, terrorists might be able to add to the saliva of a mosquito a gene that makes toxins, which it would transmit along with malaria. Just before Thanksgiving, the President's Council of Advisors on Science and Technology warned the White House directly that it is no longer difficult to imagine how somebody might, simply by editing a gene, transform a common virus into a biological weapon. "My greatest fear," Esvelt told me one day, "is that something terrible will happen before something wonderful happens. It keeps me up at night more than I would like to admit."

Until recently, the tools of molecular biology were expensive, and few people had access to them—not to mention the ability to resurrect dead viruses or build new ones. CRISPR has already begun to change that, and will undoubtedly speed progress in many fields. But with accessibility comes a growing risk of accidents, and of sabotage. These days, sequences of DNA can be ordered on the Internet for pennies. For under a thousand dollars, any eager amateur—no matter his level of skill or training—could acquire a virus and everything needed to edit it at his kitchen table.

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For centuries—from Goethe's "The Sorcerer's Apprentice" and "Faust" to "Frankenstein," "Jurassic Park," and beyond—people have harbored a persistent fear that some powerful form of life, manufactured by man with good intentions but excessive hubris, might one day slip beyond our control. No previous scientific advance, not even splitting the atom, has made this fear more palpable. Yet the research community often regards itself as the only acceptable arbiter of the way new inventions should be used. That puts Esvelt in an unusual position, because, while he is a compelling advocate for gene-drive technology, he is also its most insistent voice of alarm. "This is where my problem begins," he told an audience earlier this year, at a forum in Cambridge. "Because, as a single scientist, I can alter an organism in a laboratory that will have more of an effect on all your lives than anything the legislature across the river can do.

"What does that mean for our democratic ideals?" he asked.

In order to flourish, Esvelt argues, the field will require a radical new approach to scientific experiments. "In medicine, we demand informed consent before we do research," he says. "That has become standard. But in the laboratory we don't even tell each other what we're doing. There is very little openness. That is going to have to change."

Laboratory research in the United States is hardly ungoverned. Experiments must be approved by institutional review boards, and researchers routinely exchange data—there are conferences every week in nearly every scientific discipline for that very purpose.

And yet the system of incentives that drives academic advancement—grants, publications, and tenure decisions—rarely rewards openness. "If you are in academia, you are constantly reinforced for maintaining some level of secrecy," Dan Hartman told me recently, when I visited him at the Gates Foundation, where he leads the team that provides technical support for clinical trials and quantitative research. "That is the way the incentive system works. You are supposed to keep your research to yourself until you publish. Even then, you decide what to publish—what to reveal and what to keep secret." Beginning in January, the Gates Foundation will require the data from all studies it funds to be published in journals that are open and freely available to anyone who wants to read them. "To do anything less is crazy," Hartman said. "Seeing data from studies that didn't work can often be as useful as seeing data from those that did."

Esvelt believes that we will have to go much further before scientists understand how to communicate with the societies they serve. To illustrate that point, he often cites one of modern science's most chilling statements. "When you see something that is technically sweet," J. Robert Oppenheimer testified in his own defense at a security hearing in 1954, "you go ahead and do it, and you argue about what to do about it only after you have had your technical success. That is the way it was with the atomic bomb." Esvelt says that, in a world where schoolchildren will soon be editing genes in biology class, this is exactly what needs to change. "We really need to think about the world we are entering," he said. "To an appalling degree, not that much has changed. Scientists still really don't care very much about what others think of their work."

An hour or so before Esvelt's meeting on Nantucket, we joined one of his graduate students, Joanna Buchthal, and Sam Telford, an infectious-disease and global-health professor at Tufts School of Veterinary Medicine, for a sandwich and some reconnaisance on Alter Rock. (At a hundred feet above sea level, it is the island's highest point.) Telford, who is one of the world's foremost tick biologists, has been studying deer, mice, and the ticks that feed on them for more than thirty years.

With wire-rimmed glasses that nearly obscure his face, Telford looks like an academic Clark Kent. He was dressed in a green felt shirt, khakis, and Wellingtons. To ride with him to the meeting, I had to wedge into the back seat of his car between two mouse cages, both of which were, thankfully, empty. As we peered across the moors and the cranberry bogs, out toward the Atlantic, Telford talked about the rising incidence of tick-borne illness. "I have been trying for years to convince people on this island that if you get rid of the deer you get rid of Lyme," he said. "That will never happen."

I asked him if he thought Esvelt's experiment would work. "I sure don't know a better place," he said. In fact, it would be hard to imagine a more ideal location in which to explore the boundaries—both physical and emotional—of such a far-reaching experiment. Islands are self-contained. Most Nantucket residents are well educated and in a good position to make reasoned decisions about whether to embark on an ecological study that might affect them all. And they are motivated by a pervasive fear of Lyme and by increasingly threatening pathogens, such as babesia and erlichiosis, that are carried by the same black-legged tick that transmits the Lyme bacterium. Even

raising the millions of dollars it would cost to eliminate the disease on Nantucket and Martha's Vineyard shouldn't be difficult.

Life without Lyme disease would bring relief to millions of Americans, but defeating mosquitoes, which have always been humanity's deadliest enemy, would be an accomplishment—and a challenge—of an entirely different order. Malaria alone—not to mention yellow fever, dengue fever, chikungunya, and several types of encephalitis—has killed billions of people. Creating a mosquito that could eliminate those diseases would rank, along with the eradication of smallpox, as one of public health's signature achievements.

And yet any group that unleashes a tool that could reconfigure an entire species is bound to encounter serious opposition. "You know, with G.M.O.s we were told, 'It's O.K., it's being done in a lab,' " Jim Thomas, a program director at the ETC Group, told me. The group, which monitors the impact of emerging biotechnologies, has long held that we should exercise more caution before releasing genetically engineered products. "Then it was: 'It's O.K., it's being done only in a limited way.' Then: 'It's O.K., because it won't survive in the wild.' And here you have a technology that is not only going to survive in the wild—it is intended to take over in the wild."

In September, at a meeting of the International Union for the Conservation of Nature, Thomas's group and others proposed a moratorium on all gene-drive research. No major scientific organization has endorsed the idea, but even the suggestion stirs a common fear among scientists: that if, through secrecy, misunderstanding, desire for profit, or arrogance, this new approach to biology comes to be viewed more as a hazard than as a salvation, people will reject it. (Early this fall, the Broad Institute licensed its CRISPR technology to Monsanto for use in developing new seeds and better crops. But the deal came with a notable caveat: Monsanto will be prohibited from using CRISPR in gene drives.)

Every new technology—whether a genetically engineered food product or a self-driving car—forces us to assess both risks and benefits. In the case of gene drives, which could alter the ecological balance of an entire continent, that debate promises to become especially divisive, in part because the technology's greatest utility will almost certainly be in Africa. And there is a long, unsavory history of Western scientists using Africans as subjects without their permission, and often without their knowledge.

Ethical choices in medicine are rarely straightforward. During early AIDS-vaccine experiments in Uganda, many Western public-health officials vigorously debated the implications of testing a risky product on Africans. Some felt that it was unethical to carry out clinical trials on people who could not possibly give their fully informed consent. The consensus among many academic researchers was that medical ethics were universal; an experiment that was forbidden in America should also be forbidden in Uganda.

That is a noble sentiment, but not one you will often hear expressed in countries that are besieged by the many diseases that have all but disappeared from the developed world. As one public-health official in Kampala told me years ago, in discussing the ethics of AIDS-vaccine trials in his country, "Principles matter to us as much as they do to Americans. But we have been dying for a long time, and you cannot respond to death with principles."

Scientists have been trying to use the tools of genetics to control pests almost since the day, in 1953, when James Watson and Francis Crick described how the language of life is written in four chemical letters—adenine, cytosine, guanine, and thymine. In 1958, the American entomologists Edward F. Knipling and Raymond C. Bushland proposed a novel approach to eliminating the screwworm (*Cochliomyia hominivorax*), the only insect known to eat the live flesh of warm-blooded animals. The screwworm has infested cattle for centuries, and it can kill a cow in less than two weeks. Employing radiation, which served as a crude but effective form of birth control, Knipling and Bushland sterilized millions of male screwworms. They released them to mate with females, who would then lay sterile eggs. Known as sterile-insect technique, it has been used widely ever since. Two years later, Knipling published an article, in the *Journal of Economic Entomology*, in which he suggested that it would be possible to use the same approach to force malarial mosquitoes and other pests to destroy themselves. Such a proposal would have required the release of billions of sterile mosquitoes, which, at the time, was not possible.

In 2003, more than forty years after Knipling's work with mosquitoes, Austin Burt published a paper in the *Proceedings of the Royal Society* which set the trajectory for all that has followed in the field. Burt, who is a professor of evolutionary genetics at Imperial College, in London, suggested, for the first time, that scientists might deploy

"selfish" genes to alter or eradicate species that "cause substantial harm to the human condition." If you cut DNA in particular locations, and inserted extra copies of the selfish genes, he wrote, those genes could be harnessed to eliminate undesirable genetic traits, such as the ability of some mosquitoes to carry disease-causing parasites and viruses.

Burt quickly recognized the biggest risk posed by this type of genetic engineering: while nobody could question the value of eliminating a disease like malaria, it might not be possible to gauge the long-term ecological impact of eradicating an entire species, no matter how deadly. Burt suggested that controlling a dangerous insect or pest would not always require scientists to kill it. "One may not want to eradicate a population, but rather to transform it genetically so that it is less noxious," he wrote in a 2003 paper, "Site-Specific Selfish Genes as Tools for the Control and Genetic Engineering of Natural Populations."

At the time, the research faced two seemingly insurmountable problems. The laws of genetics, as laid out by Gregor Mendel, dictate that genes pass between generations in heritable and predictable ways. And Darwin's law of natural selection favors genes that help their hosts survive, whereas most engineered traits do not. So a change made by scientists might last for a few generations, but eventually nature would prevail, eliminating any gene that did not improve the fitness of the organism.

CRISPR, however, privileges design over evolution—which is the central project of synthetic biology. Using CRISPR in a lab in London, Burt and a colleague, Andrea Crisanti, have built gene-drive systems to spread female infertility in mosquitoes. There are several steps and many trials left before anyone could entertain the idea of releasing them anywhere other than a highly controlled lab. But the team has developed a long-term plan to work with scientists in a variety of countries—Burkina Faso, Mali, and Uganda—to educate local communities. Ultimately, should the science prove worthy, they hope to offer the technology to other poor malarial countries in Africa, and train people so that they can decide for themselves whether and how they should proceed.

Kevin Esvelt had studied Burt's mosquito research, but realized that his approach would not quite work with Lyme disease. Editing the ticks themselves might be feasible, but it would be nearly impossible to release enough of them to have a meaningful impact. Esvelt was briefly stumped, but then he made an obvious

connection: ticks get Lyme and other infectious diseases from white-footed mice. He would rewrite the DNA of the mice to become resistant to the Lyme bacterium. The mice would mate, and, before long, all offspring and all subsequent generations would be resistant, too.

With CRISPR and gene-drive technology, it might be possible for just one engineered mosquito, or fly, or any other animal or seed, to eventually change the fundamental genetics of an entire species. As Esvelt puts it, "A release anywhere could be a release everywhere." Recognizing the possibility of an irreversible error, however, he and Church, in their earliest experiments, began to build drives capable of restoring any DNA that had been removed. Both say that if an edit cannot be corrected it should not be attempted. They also suggest retaining, in its original form, some part of any population that has been edited—a kind of molecular Noah's Ark.

Esvelt and his colleagues have developed a system to keep gene drives from spreading where they are not wanted. The plan, which he calls a daisy drive, separates the components of any gene drive into discrete parts—a genetic version of a multistage rocket. Each component contains one or more genes that contribute to the whole drive. For the system to continue to propagate, all parts need to be present. If they are not, the trait would vanish after a prescribed number of generations.

The approach, which is still in early development, could prove essential. Regulatory approvals and government licenses would have no effect on the migratory patterns or the mating habits of a mouse or a mosquito. Without some system of control, a conventional gene drive would keep spreading across state lines and international borders. If daisy drives work, they might prevent that.

The research is ingenious and promising, but it also suggests a mastery over nature that may be hard to achieve. Human generations are long, and genetic changes are slow. But with mosquitoes or mice or many of the invasive species that scientists hope to curb, the transformation could be swift. Also, genes do not always spread the way they are supposed to. Occasionally, a gene will move between species, through a process called horizontal gene transfer. A gene drive created to suppress one type of mosquito could jump to a different one, threatening it as well. Genes themselves also change constantly. If a particular gene-drive sequence mutates, it could end up affecting different targets, with consequences that would be hard to predict.

One day this summer, I had lunch with Aviv Regev in her office at the Broad Institute, where she is the chair of the faculty. Regev, one of the world's leading computational biologists, studies the ways in which the different cells in the human body function and interact in biological systems, like muscle tissues or organs. Regev compared gene-drive mechanisms, which alter the genetics of species, with cancer immunotherapy, where a person's immune cells are leveraged to attack his tumors. "With malignant cells, we can take one gene out and see what happens," she said. "We can take another gene out and see what happens. But if we take both out we cannot predict the result. The whole is different from the sum of the parts. That is also true in species ecology."

Both systems are risky, she added, but in experimental cancer treatment doctors present options to a patient. "That treatment could kill a person or save him. But it is a personal decision made by somebody who is appropriately informed about the risks." She stressed that she was not opposed to gene-drive research.

"But gene drives affect entire communities, not single individuals," she said. "And it can be almost impossible to predict the dynamics of any ecosystem, because it is not simply additive. That is exactly why gene drives are so scary."

Late in July, Esvelt presented his data to Martha's Vineyard residents at a forum held at the Edgartown Public Library. He spoke to a standing-room-only crowd, made up of prosperous summer people, mostly middle-aged and evenly tanned—the kind of people who can afford to spend a perfect vacation afternoon inside, at a town meeting.

Esvelt explained his goal by saying, "I want to drag my entire field kicking and screaming into the open." As in Nantucket, the crowd loved the presentation and the sentiment behind it. I couldn't help thinking of a similar town meeting I had attended a few years earlier, in Key West. That meeting was also packed with prosperous residents, but they were there to denounce scientists from the British biotech company Oxitec, which wanted to test *Aedes aegypti* mosquitoes that had been genetically modified to prevent the transmission of dengue. The previous year, the region had had its first outbreak in years, and Oxitec's presentation was made at the request of local mosquito-control officials.

I had just returned from Brazil, where I watched Oxitec scientists release millions of genetically modified mosquitoes into the atmosphere. Most residents there—nearly all of whom knew the agony that dengue causes—were exceedingly grateful.

The difference between the reception that Esvelt received and the Oxitec inquisition could not have been more marked. To some degree, the reason is that Oxitec is a profit-seeking venture and Esvelt wears his political opposition to corporate science like a neon badge. But there is an even simpler reason that one community may embrace what another rejects: the people in Brazil fear dengue, and those in New England fear Lyme; they are desperate for relief. The sorts of ethical distinctions made in Key West, where dengue was only a distant prospect, seem silly to them.

We have engineered the world around us since the beginning of humanity. The real question is not whether we will continue to alter nature for our purposes but how we will do so. Using a mixture of breeding techniques, we have transformed crops, created countless breeds of animals, and converted millions of wooded acres into farmland. Gene drives are different; one insect could affect the future of our species. But it is a difference of power, not of kind.

"I've been trying to encourage my thoughts to coalesce into a more coherent picture of why I'm doing everything that I'm doing," Esvelt told me. "Someone recently coined the terms 'upwinger' and 'downwinger,' technologically, and I'm of course very much an upwinger. That's partly because I view us as not having much of a choice. That is, we are already so dependent on technology, and, what's more, we are dependent on future advances. We cannot simply stop here and last it out—that won't work. We need new advances. And my problem, philosophically, with that is that it means that the human cautionary instinct kicks in." He went on, "We say if it's risky we just shouldn't do it. And that's fine, so long as you're standing on firm ground. But that's the thing: we're not standing on firm ground. And the greatest danger we could face is to assume that not doing anything to nature is the safest course." ♦

An earlier version of this article incorrectly stated the ferry's departure point.

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