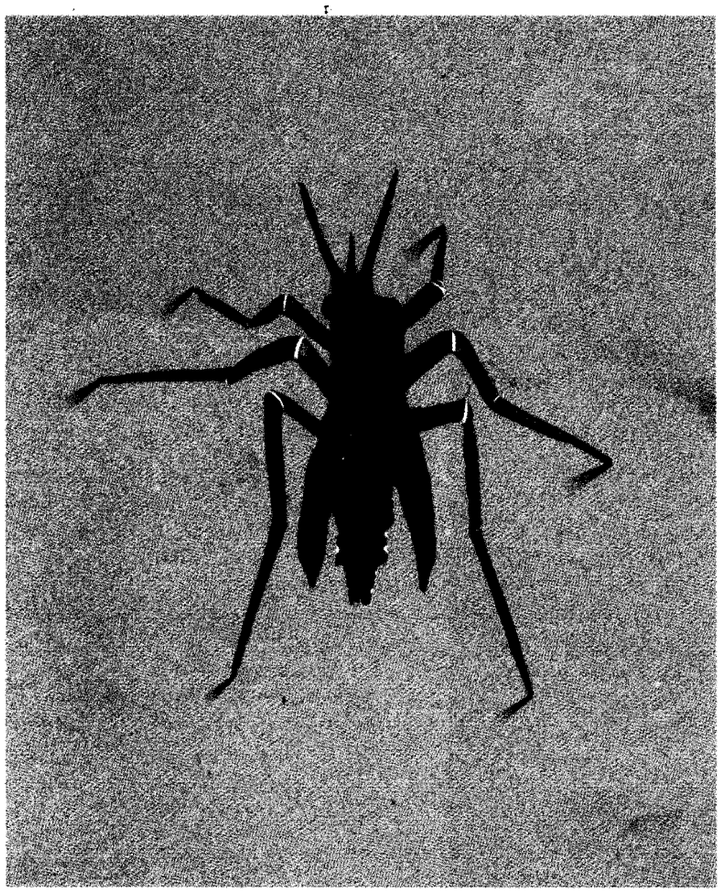
ANNALS OF SCIENCE

THE MOSQUITO SOLUTION

Can genetic modification eliminate a deadly tropical disease?

BY MICHAEL SPECTER



Few people, unless they travel with an electron microscope, would ever notice the egg of an *Aedes aegypti* mosquito. But the insects follow us nearly everywhere we go. *Aedes* can breed in a teaspoon of water, and their eggs have been found in tin cans, beer bottles, barrels, jugs, flower vases, cups, tanks, tubs, storm drains, cisterns, cesspools, catch basins, and fishponds. They mate in the dew of spider lilies, ape plants, guava trees, palm fronds, in the holes of rocks formed from lava, and in coral reefs. More than any other place, perhaps, *Aedes aegypti* thrive in the moist, hidden gullies of used automobile tires.

As adults, the mosquitoes are eerily beautiful: jet black, with white spots on the thorax and white rings on their legs. Yet *Aedes* are among the deadliest creatures on earth. Before a vaccine was discovered in the nineteen-thirties, the mosquito transmitted the yellow-fever virus to millions of people, with devastating efficiency. During the Spanish-American War, U.S. troops suffered more casualties from yellow fever than from enemy fire. The mosquito also carries dengue, one of the most rapidly spreading viral diseases in the world. According to the World Health Organization, dengue infects at least fifty million people a year. For the fortunate, a case of dengue resembles a mild form of influenza. But more than half a million people become seriously ill from the disease. Many develop dengue shock syndrome or a hemorrhagic fever that leaves them vomiting and, often, bleeding from the nose, mouth, or skin. The pain can be so excruciating that the virus has a commonly invoked nickname: break-bone fever.

There is no vaccine or cure for dengue, or even a useful treatment. The only way to fight the disease has been to poison the insects that carry it. That means bathing yards, roads, and public parks in a fog of insecticide. Now there is another approach, promising but experimental: a British biotechnology company called Oxitec has developed a method to modify the genetic structure of the male *Aedes* mosquito, essentially transforming it into a mutant capable of destroying its own species. A few weeks ago, I found myself standing in a dank, fetid laboratory at Moscamed, an insect-research facility in the Brazilian city of Juazeiro, which has one of the highest dengue rates in the world. A plastic container about the size of an espresso cup sat on a bench in front of me, and it was filled with what looked like black tapioca: a granular, glutinous mass containing a million eggs from Oxitec's engineered mosquito. Together, the eggs weighed ten grams, about the same as a couple of nickels.

Oxitec, which is short for Oxford Insect Technologies, has essentially transformed Moscamed into an entomological assembly line. In one tightly controlled, intensely humid space, mosquitoes are hatched, nurtured, fed a combination of goat's blood and fish food, then bred. Afterward, lab technicians destroy the females they have created and release the males to pursue their only real purpose in life: to find females in the wild and mate with them. Eggs fertilized by those genetically modified males will hatch normally, but soon after, and well before the new mosquitoes can fly, the fatal genes will prevail, killing them all. The goal is both simple and audacious: to overwhelm the native population of *Aedes aegypti* and wipe them out, along with the diseases they carry.

The engineered mosquitoes, known officially as OX513A, lead a brief but privileged life. The entire process, from

Designed and folded by Robert J. Lang. Photograph by Bartholomew Cooke.

creation to destruction, takes less than two weeks. The eggs, oval spheres no longer than a millimetre, are milky white when laid. Within a couple of hours they harden, forming a protective cuticle and turning shiny and black. Looking around the lab, I saw long white sheets lining the shelves; each sheet was covered in tens of thousands of pin-sized dots and resembled some sort of computer code. The eggs can survive that way for a year; after four days, however, they are plunged into jam jars filled with water at twenty-seven degrees Celsius—a temperature that enables the eggs to hatch in less than an hour.

"These mosquitoes are relatively easy to breed and cost almost nothing to transport," Andrew McKemey, Oxitec's chief field officer, said as he led me around the lab. McKemey, a lanky man who was dressed in a green madras shirt and khaki cargo pants, spends much of his time in Brazil, teaching local scientists how to manufacture the company's prize product. The lab churns out about four million mutant eggs a week, and will soon increase production to ten million. "That's a start," McKemey said. "In theory, we can build hundreds of millions of mosquitoes in this place."

The field trial, which began a year ago, is a collaboration between Moscamed, Oxitec, and the University of São Paulo. Preliminary results have been impressive: the group recently collected a sample of eggs in two neighborhoods where the engineered mosquitoes had been released, and found that eighty-five per cent of them were genetically modified. With a large enough number of those eggs, the *Aedes* population would fall, and so would the incidence of dengue. "This is not a panacea," Giovanini Coelho, who coordinates the Brazilian Ministry of Health's National Program for Control of Dengue, told me. "I am not saying this alone will solve the problem or that there are no risks. There are always risks—that's why we start with small studies in geographically isolated neighborhoods. But people are dying here, and this mosquito is resistant to many insecticides. We really do need something better than what we have."

In Juazeiro, where few families remain unaffected by dengue, the Moscamed team and its mosquitoes are treated with reverence. The researchers drive around in white vans that have pictures of mosquitoes and the word *transgenico* painted on the side. They try to visit every house in areas where they release mosquitoes, to explain that OX513A "are friendly bugs that protect you against dengue" and that, because the scientists are targeting *Aedes aegypti* where they live, under sofas and in back yards, the engineered mosquitoes can kill their brethren without harming any other plant or animal.

It's an elegant approach to a health crisis that threatens much of the world, but it will take more than biological success to make it work. That's because OX513A is not like other mosquitoes. In fact, it's like nothing else on earth—a winged creature, made by man, then released into the wild. Despite the experiment's scientific promise, many people regard the tiny insect as a harbinger of a world where animals are built by nameless scientists, nurtured in beakers, then set loose—with consequences, no matter how noble the intention, that are impossible to anticipate or control. "This mosquito is Dr. Frankenstein's monster, plain and simple," Helen Wallace, the executive director of the British environmental organization GeneWatch, said. "To open a box and let these man-made creatures fly free is a risk with dangers we haven't even begun to contemplate."

There are more than three thousand species of mosquito, but the vast majority take no interest in us; they feed mostly on rotting fruit and other sources of sugar. Only a few hundred species, including *Aedes aegypti*, need blood to survive. (The males never bite, but without a blood meal the females would be unable to nourish their eggs.) Mosquito mating habits can be brutal. "In the most successful encounters, the pair may become so tightly locked together that the male has some difficulty escaping in the end," the late Harvard entomologist Andrew Spielman wrote in his 2001 book, "Mosquito: The Story of Man's Deadliest Foe." "An unfortunate few males manage to get away only by leaving their sex organs behind." Yet Spielman also noted that the briefest exchanges can be highly productive: "A single minute or so of

passion allows her to produce all the fertile eggs she will ever lay."

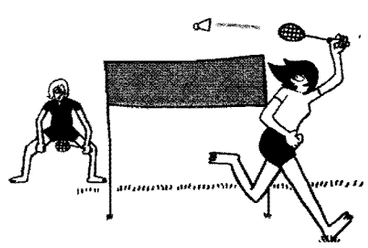
There has never been a more effective killing machine. Researchers estimate that mosquitoes have been responsible for half the deaths in human history. Malaria accounts for much of the mortality, but mosquitoes also transmit scores of other potentially fatal infections, including yellow fever, dengue fever, chikungunya, lymphatic filariasis, Rift Valley fever, West Nile fever, and several types of encephalitis. Despite our technical sophistication, mosquitoes pose a greater risk to a larger number of people today than ever before. Like most other pathogens, the viruses and parasites borne by mosquitoes evolve rapidly to resist pesticides and drugs. Many insecticides once used against *Aedes aegypti* are now considered worthless.

Aedes aegypti is an invasive species in the Americas. It most likely arrived on slave boats from Africa in the seventeenth century, along with the yellow fever it carried. The mosquitoes bred easily in the casks that provided drinking water on sailing ships. During the eighteenth century, a severe yellow-fever epidemic swept through New England and Philadelphia, as well as other American port cities; it took another century to discover that mosquitoes were the bearers of the disease.

Traditional mosquito control all but eradicated *Aedes aegypti* (and the diseases it carries) from the United States fifty years ago. But globalization has been good to mosquitoes, particularly species like *Aedes aegypti*, which travel easily and can lie dormant in containers for months. In recent years, the mosquito and dengue have returned to Texas, Hawaii, and Florida. The disease has also been transmitted for the first time in France and Croatia. "We have dragged mosquitoes around the world in billions of used tires," Paul Reiter told me. Reiter, a professor of medical entomology at the Pasteur Institute, in Paris, is one of the world's experts on the natural history of mosquito-borne diseases. Before moving to France, he spent more than two decades in the Dengue Branch of the Centers for Disease Control, devoting a surprising amount of his time to studying tires. He found that they are ideal incubators for mosquitoes: tires absorb heat, trap rainwater, and nurture bacteria in the puddles they create. The exponential growth of dengue fever—the number of cases reported to the World Health Organization has increased thirtyfold since 1965—can, at least in part, be attributed to the enormous increase in tire exports.

Aedes aegypti don't fly far or live long; a major traveller would move a few hundred yards and, on average, survive as an adult for ten days. But it is a particularly wily insect. Most mosquitoes are noisy enough to wake a sleeping man and slow enough that one bite is all they'll get before escaping or being crushed with an angry swat. *Aedes aegypti* feed during the day and strike in silence; they mostly stay low to the ground, preferring to bite people in the ankles or legs. The mosquito is highly sensitive to motion—as you move, it will, too, often stabbing its victim several times during each feeding, depositing pathogens with every bite and, in turn, increasing its chances of picking up dengue from infected people to pass along to others. (Unlike most mosquitoes, which can lay hundreds of eggs in a single raft the size of a grain of rice, *Aedes aegypti* usually deposits its eggs in multiple locations, thereby raising the odds that some will survive.)

Dengue has always been considered a tropical illness. But its mode of transport, the mosquito, rarely lives more than a hundred yards from the vector's principal source of sustenance—us—and as our demographics have changed so have those of the mosquito. *Aedes aegypti* has adapted to the city with great dexterity. Even the most effective modern larvicides



often miss the mosquito's well-hidden urban breeding grounds. "Dengue is a terrible disease, just terrible," Reiter said. "Its danger is impossible to exaggerate. And none of the methods used right now for dengue control are working. None."

It is not easy for an egg to become an OX513A. Most were originally modified in Oxitec's laboratories, in the English countryside not far from Oxford, where scientists, working with glass needles so small they can be seen only under a powerful microscope, insert two genes into eggs no bigger than a grain of salt. One gene carries instructions to manufacture far too much of a protein required to maintain healthy new cells; the results are lethal. Scientists keep the gene at bay, and the mosquitoes alive, by placing the antibiotic tetracycline in the insects' food. The drug latches on to the protein and acts as a switch that can turn it on or off. As long as tetracycline is present, the mosquitoes live and reproduce normally and can be bred for generations. Once they are released from the lab, however, the antidote is gone; the lethal gene goes unchecked. Within days the males, along with any eggs they help to create, will perish. In fact, Oxitec has already modified all the *Aedes aegypti* eggs the world may ever need.

The other gene is a fluorescent marker—the molecular version of a branding iron—that helps distinguish normal mosquitoes from modified ones. The naked eye sees nothing, but under the microscope the larvae give off a rich red glow, like a soft neon sign. Most of the altered eggs will die. Others will fail to incorporate the new genes into their DNA; these are useless, because the process succeeds only when the genes work their way into the critical germ cells the eggs need to reproduce. The task is difficult and tedious: the technicians can go through thousands of eggs to hit on just one that will pass the new genes to the next generation of mosquitoes. But once a sufficient number of eggs have been correctly modified they can, after many generations, produce millions of mutant mosquitoes.

OX513A are raised in the relative splendor of the laboratory. After they hatch, they are moved from petri dishes to plastic tanks the size of a home aquarium. Males are fed sugar; females, first lured by the smell of human sweat, feed on goat's blood obtained weekly from a nearby abattoir. "Thank God for that place," McKemey said with a laugh. "You can't make mosquitoes without blood." He stood in the close quarters of the rearing room as all around him eggs were morphing into larvae, hatching in the type of long trays bakers use to store loaves of bread. Across the room, in transparent, water-filled pails covered with cheesecloth,

thousands of larvae, known to biologists as wrigglers, were frantically trying to work themselves out of their cases and emerge as pupae, the final stage before becoming an adult.

Adolescent mosquitoes have enormous heads and prominent eyes; under the microscope they look like sea horses or miniature versions of E.T. While the mosquitoes are still sheathed in their cases, their transparent wings are pinned behind their bodies. By this point, the mosquito has begun breathing through its syphon, a curling, segmented tube that pokes above the surface of the water like a snorkel. When the moment is right, the pupae inhale, expand their abdomens, burst their cases, and emerge head first as adults. "It's thrilling to see," McKemey said, as we watched the young mosquitoes take their first tentative flights. "I never tire of it."

The Oxitec mosquito grew out of a pest-control method called sterile insect technique, or SIT, which has been used for decades. Billions of insects, all sterilized by intense bursts of radiation, have been reared in laboratories like Moscamed and released to mate in the wild. In 1982, SIT, which prevents the organism from reproducing, successfully eradicated the screwworm—a parasite that attacks the flesh of warm-blooded animals—from North America. But radiation is difficult to use properly on insects as small as mosquitoes. Administer too little and they remain virile; zap them too powerfully and the insects are left so weak that they are unfit to compete for mates.

In the early nineties, Oxitec's chief scientist, Luke Alphey, was investigating the developmental genetics of *Drosophila*, the common fruit fly. One day, Alphey, now a visiting professor of zoology at Oxford, bumped into a colleague who was talking about sterile insect technique. Alphey, who knew little about the field, began to think about how to supplant radiation with the practices of modern molecular biology. Alphey is reserved, with a mop of brown hair and pensive eyes; one can practically see his brain in motion as he works out a scientific problem. His goal was not exactly to sterilize the males but to alter their genes so that any progeny would die. If he could do that without using radiation, he reasoned, the insects should be fit to compete sexually for wild females.

THE ROSE-WAY IN GIVERNY

And in the reticulate distance
the cued inertia of Lucifer
astounds. Our feet bleed:
buoyant, the body at its task.
What you wanted was what I
wanted—slant of sun to the left,
twinkling of civilization elsewise,
and the moon (whelp of history)
to our backs, all come-hither
and dream. Motion understood
is philosophy deferred: peace,
the felt pathos of space and time.
Look, darling, at the establishing
shot. It's downright Biblical,
this thrown-together vista,
world upon world without end.

—*Virginia Konchan*

Alphey faced several scientific hurdles. He would have to engineer only males. (Female mosquitoes bite, so genetically modified females could, in theory, pass novel proteins to humans, with unknown consequences.) "I was trying to think of ways around the radiation issue," he said. "I wondered, What if the engineered lethal system could be sex-specific? It turns out that, with *Aedes aegypti*, females are considerably larger than the males. That was a lucky break, because it means you can easily separate them on the basis of their size."

Once released, the males would have to live long enough to impregnate females, and they would need to be healthy enough to compete with wild males for the right to do so. "You want the insect to breed successfully in the lab but to be dependent on an antidote that will no longer be available in nature," Alphey said. "It was difficult to know how to do that." But chance again intervened: he happened to attend a seminar at which researchers described using tetracycline as a switch to turn off a gene. "The molecule prevents the deadly gene from working," Alphey said. "It was a perfect solution."

In 2002, Oxitec was spun off as a company apart from the university. Alphey began to speak at tropical-disease meetings and in dengue-infested countries; he also gathered support from private investors and public-health philanthropies, including the Gates Foundation and the Wellcome Trust. In 2010, the company ran a series of field trials in the Cayman Islands, releasing 3.3 million genetically altered mosquitoes on sixteen hectares of land. OX513A became the first engineered mosquito set free on the planet.

The number of wild *Aedes aegypti* mosquitoes in the area fell by eighty per cent in two months. It was only a test of feasibility; no one knew how it might affect the local ecology or whether it would actually reduce the incidence of dengue. Environmental activists feared that the release of engineered insects could set off a cascade of events that nobody would be able to control.

"They don't know how it will function in the real environment," Silvia Ribeiro, the director in Latin America for an environmental organization called the ETC Group, said. "And once they release it they can't take it back." In 2010, Oxitec began a smaller trial in Malaysia. But the Brazilian experiment has been the biggest test so far, and it has laid the groundwork for Oxitec's battle over entry into the world's most significant market: the United States.

In 2009, Key West, Florida, suffered its first dengue outbreak in seventy-three years. There were fewer than thirty confirmed cases—a trifling number compared with the millions who are in-

fected each year in South America, Africa, and Asia. There are just twenty thousand full-time residents in Key West, but, with more than two million visitors each year, the town is highly dependent on tourists. I was there during spring break, which is not the best time to visit unless you have a particular interest in keggers, tequila, or Eagles cover bands.

"They feed this town," a woman who runs a cigar stand told me as we watched scores of sunburned students work their way down Truman Street and head toward Jimmy Buffett's bar, Margaritaville, ground zero for the aggressively laid-back Key West life style. "Sometimes it's a little gross out there," she said. "But take the tourists away and we are just a bunch of taco stands, bars, and beach bums."

Even a small dengue outbreak in Key West would send a troubling message. After 2009, the Florida Keys Mosquito Control District added ten inspectors to join the battle against *Aedes aegypti*. In 2010, there were twice as many cases. "Clearly, we have the potential for serious dengue outbreaks," Michael S. Doyle told me. Doyle, an entomologist, is the district's executive director. He moved to Key West in 2011, after spending five years at the Centers for Disease Control. "Part of our problem is the image of dengue," he said. "A couple of hundred cases here could be devastating to the tourist economy.

"Think about it," he continued. "Somebody in Milwaukee is cruising through Web sites and asks his wife, 'Where should we go on vacation, honey, Key West or some place in the Caribbean?' And the wife says, 'Hey, didn't I hear something about dengue in Key West?'" We were sitting in a café not far from Ernest Hemingway's house, the city's most heavily visited tourist site. Like many public buildings, the café has open windows and no screens; mosquitoes danced in the air beside us. "We live with open doors and windows," Doyle said. "And they live with us. We are an ideal host."

Doyle is a soft-spoken man with rimless eyeglasses and a neatly trimmed mustache. He pointed out that, when it comes to contracting dengue, the way people live is as important as where they live: from 1980 to 1999, Texas reported sixty-four cases of dengue along the Rio Grande, whereas there were more than sixty thousand cases in the Mexican states just across the river. "The population of *Aedes aegypti* was actually larger in Texas," he said. But Texans have screens on their windows (and keep the windows closed), drive air-conditioned cars, and spend little time outdoors.

Doyle wanted to lower the risk of a dengue outbreak in Key West, but the district was already spending more than a million dollars a year on insecticide, and he was loath to dump more chemicals in people's yards. Then a colleague attended a meeting of the American Society for Tropical Medicine and Hygiene and told him about OX513A. "I remember thinking that if this actually worked we would win in every possible way," he said. "Other approaches are more costly and more environmentally challenging. The data looked solid, and certainly we need to think differently about mosquito control than we have in the past."

In March, Doyle invited Luke Alphey, Oxitec's founder, and Hadyn Parry, its chief executive, to explain their approach at a town meeting. It would be the first in a series of hearings intended to explore the possibility of testing the mosquitoes in one relatively isolated Key West neighborhood. "I don't really know what to expect," Alphey told me early on the day of the meeting. "But I hope the people of Key West understand that they have been lucky. Because they are living in a sea of dengue."

Opponents mobilized within hours of receiving notice of the meeting. Boldly colored flyers, stating that the mosquito-control board was "planning on releasing and testing genetically modified (man-made) mosquitoes on you, your family and the environment," were pasted onto half the city's walls.

Before the meeting, I ran into Chris O'Brien, an artfully dishevelled woman with shoulder-length hair and searching blue eyes. She was dressed in the peaches and pinks one associates with southern Florida. She was also wearing combat boots. O'Brien is a "conch," a term that describes people who are born, raised, and spend their lives in Key West. Her children and grandchildren are conchs, too.

"People live with mosquitoes here,"

"What do you eat for anxiety?"

she said. "We always have. We have had no dengue for two years and maybe, at most, we will have a few cases. It's not a huge deal. Certainly not big enough to bring in an unnatural insect about which we know so little. You are in much more danger of being hit by a car."

It is impossible to predict the likelihood of a dengue outbreak based on the number of past infections. All it takes is the presence of the mosquito and the virus. Key West has plenty of the former; the rest is a matter of aggressive pest control—and chance. Once infectious mosquitoes start biting humans, an epidemic can erupt within weeks, as the virus moves from vector to host and back again. O'Brien, like many of her fellow-protesters, had been briefed by the Friends of the Earth about the concept of introducing man-made creatures into the local environment. "How do we know the females won't breed and bite people?" she asked. "They would have enzymes in their bodies that don't exist in real life. What would happen if they bit us? Getting rid of dengue would be wonderful, of course, but what would happen if we did succeed and these mosquitoes simply vanished from the earth? Isn't there a food chain to worry about?"

Those are reasonable concerns. But ecologists are quick to note that *Aedes aegypti* have been in America for only two hundred years or so; that's not enough time for a species to make an evolutionary impact. Many biologists argue that if *Aedes aegypti*, or, indeed, all mosquitoes, were to disappear, the world wouldn't miss them, and other insects would quickly fill their ecological niche—if they have one. "More than most other living things, the mosquito is a self-serving creature," Andrew Spielman has written. "She doesn't aerate the soil, like ants and worms. She is not an important pollinator of plants, like the bee. She does not even serve as an essential food item for some other animal. She has no 'purpose' other than to perpetuate her species. That the mosquito plagues human beings is really, to her, incidental. She is simply surviving and reproducing."

Not everyone agrees with Spielman's assessment. "Genetic modification leads to both intended and unintended effects," Ricarda Steinbrecher, of EcoNexus, a not-for-profit, public-interest research organization based in England, says. In a lengthy letter to government regulators in Malaysia, she stressed that there could be ancillary impacts "if the mosquitoes are eliminated altogether." For instance, what would happen to those fish, frogs, other insects, and arthropods that feed on larval or adult mosquitoes? "What if their interactions with other organisms in the environment change?" she wrote. "There is also the question of what will fill the gap or occupy the niche should the target mosquitoes have been eliminated. Will other pests increase in number? Will targeted diseases be able to switch vectors? Will these vectors be easier or more difficult to control?"

It would be irresponsible to deploy transgenic insects widely without adequate answers to those questions, but most have been addressed in environmental-impact statements and by independent research. If the results were put to the vote of biologists, the overwhelming response would be: the potential benefits far outweigh the risks. There are no birds, fish, or other insects that depend solely on *Aedes aegypti*. It doesn't pollinate flowers or regulate the growth of plants. It is not what entomologists call a "keystone" species in the United States.

"It is frankly difficult to see a downside," Daniel Strickman, the national program leader in veterinary and medical entomology at the Agricultural Research Service, told me. "My job is to try and prevent human disease by modifying behavior and killing mosquitoes. So I come at it from that perspective. I am biased against mosquitoes. And *Aedes aegypti* cause immense damage. Raging epidemics of dengue would affect our economy badly. Go back to the days of yellow fever in this country and it had real demographic consequences. Whole towns died. Life expectancies in certain areas were reduced." Strickman added, "I look at this new approach and there is nothing greener. It's targeted at one species. If the sole question is what will happen if we kill off this single species of mosquito, it doesn't seem like a close call."

Mark Q. Benedict agrees. Benedict, an entomologist at the University of Perugia, has researched genetically modified insects for years and written about them extensively. "There are unanswered questions and there always will be," he said. "But there are also unanswered questions about the effect of insecticides on children, and we use them every day to try and kill the very same mosquitoes. It's important to remember: we're already trying to wipe this species out, and for good reason. The risk involved in eliminating them is very, very small. The risk in letting them multiply is enormous."

Environmentalists have expressed concern about what might happen if some of the modified females survived and, while biting people, injected them with an engineered protein. Oxitec separates males from females, but, with so many mosquitoes, a few genetically modified females inevitably slip by—Oxitec puts the number at about one in three thousand. "This is a nightmare scenario, and we don't have any published data that answers this question," Eric Hoffman, a food-and-technology policy campaigner for Friends of the Earth, told me. Hoffman has assiduously followed the Oxitec experiments. Reiter says that none of the protein introduced into transgenic mosquitoes enters its salivary glands—which means it couldn't spread to the humans it bites. In addition, he has recognized nothing in the genetic structure of the modified mosquitoes that could cause humans harm. But he and others are eager to see papers published, by groups unconnected to Oxitec, that confirm those conclusions.

The biggest question raised by the creation of OX513A is who will regulate it and how. In Brazil, a single government body—the National Technical Commission on Biosafety—oversees the approval of all genetically modified organisms. In the United States, however, the regulatory structure is far more complex. It's not clear whether engineered mosquitoes will be regarded as animals, under the jurisdiction of the Department of Agriculture, or as drugs, governed by the Food and Drug Administration.

"I would be so eager to have a clear regulatory situation in the United States," Alphey told me, his frustration at the process barely held in check. "We do not want to move forward unless one is properly in place." To the consternation of many, Oxitec recently applied to the F.D.A. for approval of its mosquito. "We are concerned that Oxitec has been less than forthcoming in their statements to the public," Hoffman told me. "They are

saying that these mosquitoes are sterile, but they are not sterile, since they impregnate females. They are genetically modified, and the public needs to know that." Oxitec does call its mosquitoes sterile, but has not denied that they are genetically modified; almost all their literature says as much. "There is no layman's term for 'passes on an autocidal gene that kills offspring,'" Alphey said. "'Sterile' is the closest common term. OX513A is sterile in very much the same sense as radiation-sterilized insects are sterile." Hoffman stops short of calling Alphey's message deceptive, but he certainly doesn't agree. "This country just doesn't have the law or regulations necessary to move this project forward right now," he said.

In Key West, the Oxitec scientists, along with Doyle and his team from the mosquito-control district, faced a packed room at the Harvey Government Center. It was a warm, sunny day, and many in the crowd had left work early to be there. Doyle explained how a small experiment might proceed; Oxitec made its case; then the floor was opened to the public. The meeting quickly became emotional and, at times, rancorous. Oxitec—a small company that had emerged from a zoology department—was portrayed as an international conglomerate willing to "play God" and endanger an American paradise. The insects were referred to as "robo-Franken mosquitoes." More than a dozen people rose to speak; none defended the project or noted that, if successful, it would reduce a health threat and ease the county's heavy reliance on insecticides. Overwhelmingly, the people with whom I spoke said they assumed that this decision had already been made; the meeting was taken up with accusations of lies and secrecy. But nothing had been decided. Every question asked, at the meeting or later, in writing, was forwarded to state regulators for their consideration.

"It breaks my heart to think that you guys have the nerve to come here and do this to our community," one woman said. "Anything genetically modified should not be touched. I have a feeling that"—she pointed to Doyle and his colleagues on the dais—"your minds are made up. I know it. I can just sense it. I feel the vibe." She concluded to thunderous applause. Another speaker, Rick Worth, was even more direct. "I, for one, don't care about your scientific crap," he said. "I don't care about money you spend. You are not going to cram something down my throat that I don't want. I am no guinea pig."

One afternoon before leaving Brazil, I found myself inching along the rutted dirt roads of a neighborhood called Itaberaba, with Aldo Malavasi, the highly animated director of Moscamed. Itaberaba is only a few miles from the center of Juazeiro, and, as we drove, loudspeakers on the front of the car announced our arrival. "We are here to talk about the transgenic mosquito project," the speakers said. "We are here to explain this program to you and answer your questions." Malavasi, a large and charismatic man, said, "There is only one way to get people on your side: talk to them. This is a new technology. It is scary. But it also carries tremendous possibilities. People are not stupid. You just have to tell them all of that. Lay it out so they can decide." Moscamed has spoken to nearly everyone living in the affected areas. When a team leaves a house, they etch the outlines of a mosquito on the doorframe, so that colleagues will know which houses still need to be visited.

Bahia is one of Brazil's most important fruit-growing regions. We passed warehouses full of guavas, mangoes, limes, pineapples, and papayas. The scent of rotted fruit filled the humid air. People live in small, brightly painted cottages in these towns, and it seemed that at least one member of every family had had dengue. It isn't as hard to explain to them the value of a modified mosquito as it is of, say, modified corn. "You tell people you are messing with soybeans or corn and they get suspicious," Malavasi said. "This is different. They have suffered."

When it comes to genetic engineering, acceptance clearly depends on the product. Opponents often invoke a one-sided interpretation of the "precautionary principle," which argues against introducing activities into the environment that, in theory, could cause harm to human health. The sentiment is difficult to dispute, but so is the fact that dengue fever strikes tens of millions of people every year, that the threat is growing, and that there is no treatment or cure. The worry about theoretical risks tends to overwhelm any discussion of possible benefits. Many people, particularly in the rich Western world, object to modified food, but such complaints are almost never aired against the same scientific process when it is used to make insulin or heart medicine. "Sometimes I despair of these issues," Paul Reiter, who has advised Oxitec, told me. "The objections so rarely have anything to do with the science or the safety of the research. It is an opposition driven by fear. I understand that, but this technology has been used in a different form for years." He was referring to sterile insect technique. "The Oxitec approach is safer and more environmentally benign," Reiter said. "If the phrase 'genetically modified' was not attached, I don't think people would even mind."

Malavasi shrugged when I brought up the opposition. "I know this sounds like science fiction," he said. "And I am not naïve. But to get rid of the virus, we have to get rid of the mosquitoes. And, at least in this small experiment, it's working." He noted that the name of the program, the Projeto *Aedes* Transgenico—the Transgenic *Aedes* Project—was not accidental. "We put the word 'transgenic' right in the name of the program for everyone to see," he said. "We hide nothing."

We had stopped at a random spot on an unmarked road. The heat was oppressive as we emerged from the car; a small stream burbled by the roadside. "We are in mosquito heaven," Malavasi said. As he spoke, a team from Moscamed began unloading several casserole-size Tupperware containers from the back of their van. The containers had white plastic lids, and one by one they were flipped open, releasing thousands of male mosquitoes. Each time a top was removed, scores of the tiny insects would alight, briefly, on the researchers' bodies—not to bite but to orient themselves. It was the first time they had experienced freedom. For a moment, they seemed reluctant to fly away. Then, almost as a unit, they would lift off and, after hovering for a few seconds in the moist afternoon air, form a kind of flying carpet, and set off to fulfill their destiny. ♦