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Building a better mosquito

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The East End district of Grand Cayman Island bills itself as an offbeat paradise for divers, a place where you can swim past spectacular coral reefs, practise yoga under water, and even get married in the process. But last summer, the wildest action was taking place on land, in a quiet village a couple of kilometres from the beach. Here, amid the town's modest pastel bungalows, pest-control officials arrived with an unusual group of eager visitors: three million genetically modified mosquitoes.

They were brought in to fight a terrifying disease—dengue fever, which is racing through the tropics, infecting over 50 million people a year and killing more than 12,000 of them, often young children. You can't prevent dengue, or stop it from killing you, which is why the island's mosquito-control department treats the insect that spreads dengue, the yellow fever or Aedes aegypti mosquito, as a lethal invader. Insecticide was winning the war until 2006, when hurricane Ivan tore through the island and left debris that served as perfect nurseries for a new generation of local Aedes aegypti mosquitoes. That was when the island's Scottish-born mosquito- control chief, Dr. Bill Petrie, decided to take radical action.

The problem clearly was the mosquito, the transmitter of disease, so maybe the solution was to get rid of it in a new way, without the blunt instrument of insecticide. An English company, Oxitec, was tweaking the DNA of mosquitoes in its Oxford lab, and its scientists had invented a new biological system called RIDL—Release of Insects carrying a Dominant Lethal. It was effectively a morning-after pill carried by the males. It would work like this: when a genetically modified male mated with a wild female, they would still produce progeny, but the offspring would die within a few days. This was a death sentence for the mosquito population—or at least it was in the lab.

Petrie signed on, and launched the world's first test of GM mosquitoes in the wild on Grand Cayman. The results were promising—an 80 per cent reduction of the Aedes aegypti population. Researchers now hope that the GM mosquitoes like the ones from Oxitec will finally do what insecticides, drugs, vaccines and even bed nets have been unable to do—control the most dangerous creature on the planet, the mosquito. They're starting with the mosquito that spreads dengue, but the biggest and ultimate target is the Anopheles family of mosquito that spreads malaria and kills 800,000 people a year, mainly small children in sub-Saharan Africa.

Malaria is a wily and innovative mass killer: both the mosquito that spreads it and the tiny parasite that causes the fever can adapt and change their physical form to outfox human interventions. This time, though, scientists in a handful of labs in North America and Europe are hoping that their GM mosquitoes will either suppress the wild population, or take over. But now, as scientists are beginning to test their new mosquitoes outside the lab, they are confronting some key ethical questions.

When the news of the Grand Cayman experiment broke at a scientific conference last November, anti-GM activists sounded the alarm. "We're worried about the high risk," says Pat Mooney, executive director of the Ottawa-based ETC Group. What happens, for instance, if the genetic birth control spreads to other living things? "There should be a United Nations-level debate about it," says Mooney. "What if it destroys beneficial insects, damages crops and animals and turns into a biological weapon?"

Then in January, the scientific world learned that Oxitec had tested 6,000 GM mosquitoes in an uninhabited forest of Malaysia. "There are a lot of unanswered questions," says Pete Riley, campaign director of GM Freeze in the United Kingdom. If you kill one family of mosquitoes, for instance, what pest will fill the void? "History tells us if you start mucking around with the ecosystem, the consequences can be unpredictable."

The scientific journal *Nature* voiced a different concern: were the communities properly consulted? If not, "it could generate an unnecessary and unhelpful climate of suspicion" that could damage the prospects for GM mosquitoes, just as it did for GM food in Europe. But how are scientists supposed to gauge the response of communities while they're busy researching in the field and in the lab? The answer, *Nature* suggested, may come partly from Canada, from Toronto bioethicist Jim Lavery.

Lavery, 50, a former semi-pro soccer player and classically trained guitarist, dove into this issue six years ago, when he met University of California molecular biologist Tony James at a meeting in Seattle hosted by the Gates Foundation. The billionaire philanthropist was pumping $400 million-plus into the fight against infectious disease in the developing world, and he was funding scientists who promised a breakthrough. Gates had hired Lavery, along with Toronto bioethicist Dr. Peter Singer, to review the ethical, social and cultural aspects of the various projects. It was crucial to get these non-scientific parts right: if scientists don't treat people at the test site properly, they can see their trial shut down. As Lavery notes: "You lose a lot of science and you lose a lot of money when things go badly."

James, a big, friendly scientist who shared Lavery's love of the guitar, had just won a $19.7-million grant to tackle diseases borne by mosquitoes by tweaking their DNA. When he met the Toronto bioethicists in Seattle, he was eager to hear their advice on a new and audacious way to tackle the lowly mosquito. In the mosquito world, as James explained it, the mass killers are the females. They're the ones that bite humans and transmit disease. This fact had given James and his collaborators an elegant way to suppress the dengue mosquito: they would rewrite the DNA of the male mosquito so that when it mates with a wild female, the female offspring would inherit a fatal defect: they would lack the muscles to power the wings. The females, unable to fly, couldn't bite anyone, or mate. This would be a death sentence for the community.

There was just one problem: the wild females weren't impressed by the genetically modified males; they preferred the wild ones. So the scientists gave these GM males another tweak to boost their chances with the wild females. It worked in the lab and now it was time to test the GM mosquitoes outdoors, not in the wild, but in huge cages. But where?

The Mexican city of Tapachula, near the Guatemala border, looked promising. This town knew its insects. It had been sterilizing millions of Mediterranean fruit flies with radiation to combat the pest that threatens fruit and vegetables in California and elsewhere. "The idea of manipulating insects was not foreign at all," says Lavery. This might surprise people in the north, who squirm at the mere thought of GM mosquitoes buzzing around, but in a country where dengue is quickly gaining ground, that concern seemed remote, says Lavery. When people weigh the potential risk of genetic tweaking against the fear that dengue could kill their children, it's not such a hard call, he says: "The stakes are different when people are bitten by flying things and dying."

In Mexico, Lavery and James faced a more immediate challenge: how can you test GM mosquitoes in the field without exploiting people in a poor community? How do you make sure they're properly informed? Anti-GM groups are asking the same questions. They're complaining to the Malaysian government that the pretrial consultations for the GM mosquitoes trial this past winter were too skimpy to properly consult the people closest to the test area. In Grand Cayman, scientists spoke with residents but didn't hold a formal consultation. (The company that sponsored these trials did not get Gates money, or advice from Lavery.)

Lavery and James's approach was different. They held numerous meetings with the community, hired an anthropologist, and spent two years in consultations to buy land for the giant mosquito cages, a process required by local law. They spent time, with local translators in tow, getting to know farmers and nurses. They call it community engagement. "It sounds like things your mother might tell you," says Lavery, wearing jeans, sitting in his sparse downtown Toronto office. "If you're a scientist testing a new idea, how do you ensure you're a good guest?"

So, what if things go wrong? James says his GM mosquitoes cannot give genes to a butterfly, or even to another one of the world's 2,700 species of mosquitoes. (Three dozen of these transmit malaria; two spread dengue.) Genetic modification is far more precise than insecticide, he says. Besides, GM mosquitoes don't live for long or travel very far. There is one problem: even flightless females don't fix the problem forever. The wild mosquitoes are bound to return, which means that people in poor communities will have to spend money on another round of terminator mosquitoes to mate with the wild females.

There is a permanent solution, though. Instead of creating GM mosquitoes that eliminate the local population—either with a morning-after pill or by producing flightless females—you could permanently change mosquitoes. James is trying out this strategy in the lab on mosquitoes that spread malaria. He's giving each one a tiny bit of DNA from a mouse to strengthen its immune system so the mosquito can fight off malaria. "It's a true chimera," says James, "but it works"—at least in the lab. You could call it a "mousequito." The GM mousequito would still live and multiply, but when it bites a person, it would no longer deliver malaria. Eventually the GM mosquitoes would take over the mosquito population.

As for what happens if these GM mosquitoes do something unexpected in the wild, James's lab has been thinking about every conceivable risk. By tweaking the design of the mosquito, you can handle the known risks, he says. But what about the unknown? Many scientists are frustrated by this persistent question: after all, we've been changing DNA for years to create insulin and other life-saving remedies. Most of us in North America eat GM food without picketing the grocery store. But the unknown is, well, unknown.

"As a scientist, it's hard to get my head around it," says James. If something unanticipated happens, what are you going to do? "You can spray the insects," James says. "Use old technology to eliminate what's there."

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