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Health

7. CASE STUDY: CHAGAS' DISEASE; LOCATION: GUATEMALA; Building a Better Bloodsucker

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In an Atlanta suburb, I have joined two scientists at the Home Depot to shop for some wood. There are other men in the aisle, homeowners who are wheeling their flatbed lumber carts among the forests of upright planks -- poplar, oak, pine. They are building huts for their children to play in or sheds for their tools. Their mumblings involve the important issues of length and width.

My guys fret more about glue content and stability under intense humidity. They are not building a playhouse or a toolshed. Instead, these scientists are building a simulacrum of a thatched Guatemalan hut that will sit inside a triply-protected Level Two Biological Hazard greenhouse on the campus of the Centers for Disease Control and Prevention. A few days from now, they will release into this near-natural environment a swarm of insects containing altered genes, what they cheerfully call "Frankenbugs" because they know as well as you do that it's inevitable.

For the last few years, the public debate involving the phrase "genetically altered" has remained hermetically contained within the plant kingdom. Now it is escaping the tomato vines and cornfields and jumping into the animal kingdom. The small group of scientists around the world who specialize in this new field recently held only their third annual "Insect Transgenesis" conference. Here in the United States, a handful of experiments tinkering with the genome of insects has recently received protocol clearance by the government. For example, some scientists hope to attack the pink bollworm moth, which harms cotton crops in the South, by releasing a modified male that passes along a fatal flaw while fertilizing eggs. As with this moth, most of the other tests use genetics to prompt massive, one-time collapses in the population of invasive agricultural pests.

The bug experiment in Atlanta, however, is different, and its implications are much further-reaching. The short-term hope is that the method being tested in the greenhouse will one day thwart an incurable tropical affliction called Chagas' disease. But should the technique work, the scientists may have devised a powerful, and entirely new, class of weapon in the battle to stop infectious diseases -- something on the order of the vaccine and antibiotics.

"What about cedar?" asks Ben Beard, an entomologist working on parasitic diseases at the C.D.C.

"Doesn't cedar repel bugs?" says his partner, Ravi Durvasula, an infectious disease scientist at Yale University.

Beard laughs and ambles on in search of cheap wood. He discovers some poplar listed at $4.59, perfect for his $50 hut budget. We unload a dozen towering planks. When it's our turn with the clerk who operates the table saw, he gives us the Look. "You know these boards are $4.59 a foot, right?" the clerk says as we all stare at what is suddenly a $500 trove of prime timber. A group of guys gives us that Other Look.

"Do you feel your testosterone draining away as quickly as I do?" Durvasula whispers to me. We scramble back down the aisle, load up some sheets of crummy plywood and head back to the Chamblee campus of the C.D.C.

On the way, I listen to Beard and Durvasula describe the mechanics of their idea, and right away it is clear that this tiny shack we are about to build inside this greenhouse is about a lot more than the success or failure of stopping this one disease. These two scientists are opening the genetic door for a new reason -- not to enrich a global corporation but to take command of nature at a Darwinian level and erect a microscopic fire wall between us humans in here and those diseases out there. Of course, as always, these phylum-size paradigm shifts always sound good at first: one little tweak of the gene and poof! -- Chagas' or Lyme or some other disease is gone, no problem. And doesn't it always seem that after we are deep into the changes of some innovation, we suddenly ask ourselves, Why didn't we consider the implications of this before we made it standard operating procedure? This time, maybe we can pose a few of the hard questions first.

Chagas' is a devastating parasite-borne illness that kills 50,000 people a year. About 16 million people in Latin America have it, although with the warming climate, cases have just recently begun to crop up in Texas. In most cases, you become chronically ill for a long time; in the worst cases, after that long time, the wall of your heart weakens and one day just gives way.

The way you get Chagas' is, frankly, disgusting. The "vector" for Chagas' -- that is, the means by which people get the parasite -- is a tropical insect called the kissing bug. It looks like an exotic roach when fully grown: one to two inches long, with wings that it rarely uses. There are various species: some of them blandly gray, others with fetching little spots. The bugs thrive in dark hidden places like the thatch of roofs in Guatemala or the cracks of adobe in Mexico.

As a bloodsucking insect, the kissing bug tends to search out dinner at night by parachuting out of the safety of its thatch. Nature equips the bug with a unique method for finding its meal. It can detect sources of carbon dioxide. That's the gas that you softly exhale at night while you sleep. As a result, the bug usually heads for the area near your mouth (hence its name). The kissing bug then unfolds a proboscis from beneath its head and pierces your skin, drinking heartily -- for around five minutes. After eating, the bug leaves a parasite-laced fecal droplet right at the site of the feeding. In the morning, when you awaken, all you sense is a slight itching on your face. When you scratch, you rub the parasite into the tiny wound nearby. Twenty years later, if you are unluckier still, your heart will explode.

Beard and Durvasula wondered if there was a way to interrupt this gruesome process. "What we have done," Durvasula says, "is create a kind of Trojan horse inside the bug's gut." The scientists have genetically altered a bacterium that resides inside the bug to produce a protein that fatally punches holes in the parasite.

Most of the other Frankenbug projects -- like the pink bollworm research, which is being pursued at the University of Arizona -- involve attempts to genetically alter an entire insect. (In Europe, researchers recently gained a patent on the idea of genetically altering a mosquito so that it spreads malaria vaccine with every sting.) But there are serious scientific problems with insect work. Making transgenic changes further up the chain of organic complexity tends to result not in superbugs but in hobbled critters. To make them effective often means releasing them in massive numbers to compensate for their Darwinian inferiority -- a prospect with a bit of a P.R. problem. Which is why Beard and Durvasula's work may be the breakthrough method. What they call "paratransgenesis" -- genetic modification of a bacterium inside the bug -- potentially raises less intractable problems.

The journey to this greenhouse has been long. First, Beard and Durvasula had to figure out a way to get the transgenic bacteria into the bug. Fortunately, baby kissing bugs love to probe adult fecal droplets right after birth. It is nature's way of colonizing the bug's stomach with nutrient-producing bacteria. So Beard and Durvasula created a synthetic, dunglike paste -- the Trojan horse -- filled with transgenic bacteria. Newborn kissing bugs, experiments have confirmed, will happily ingest it. The genetically altered bacterium takes up residence in the bug's gut, waiting for the appearance of the Chagas' parasite, formally known to scientists as Trypanosoma cruzi. "The paste is really fake bug feces," Durvasula says. "But that doesn't sound so good, so we call it Cruzigard."

The next question was to begin asking what might happen if kissing bugs containing genetically altered bacteria were let loose in the real world. Recently, the National Institutes of Health awarded Durvasula a $1.3 million grant to construct this biologically secure greenhouse to begin the earliest phase of testing.

Around 9 a.m., we pull up to the guardhouse at the Chamblee campus, one of six sites maintained by the Centers for Disease Control on the outskirts of Georgia's capital. Security is tight, and a visit to the campus is testimony to just how crucial disease research has become to this nation. Everywhere, offices and labs are under furious construction. Meanwhile the existing buildings -- old wooden shacks connected by overhead steam pipes -- hum with activity. Behind every other back door, empty gas canisters lean against the walls, set out like old milk bottles. Idling beside the building are specialized delivery trucks from a unique courier service equipped to overnight everything from Agent Orange to malaria parasites to the plague bacillus.

Just down from Beard's office building is the existing greenhouse, built with reinforced steel and double-paned thermal windows. Stepping into the door, you encounter a huge tent grommeted to the concrete floor with rubber gaskets to prevent any insect escape. Around the entrance flap is a perimeter of wide tape that will be treated with Tangle-Trap, a kind of insect glue to prevent Frankenbugs from escaping and normal bugs from entering.

Inside the tent is a dressing room in which Beard and Durvasula will put on completely white full-body gowns with mouth masks and eye shields. On their feet they must wear special plastic stockings (which, after the visit, will be soaked in Clorox and then burned). The researchers will then step from the dressing room into yet another tent erected inside the first one to ensure containability in the event of a rip. In this enclosed enclosure will stand the Guatemalan hut.

It takes us only a morning to build the hut, which measures 6 feet by 6 feet by 6 feet. We construct a thatchlike cover by building panels of perfectly set willow sticks. This way, the bugs will still be able to indulge their furtive habits while giving the scientists enough room to see and locate each one of them. Before laying down the six willow panels that will form the roof, Beard and I stretch a thin gauze of white organdy across the top, which will provide the baby kissing bugs with easy access to any one of the hut's four corners. In each corner will be a small hose slowly leaking carbon dioxide and beside it, pressed up against the organdy, will rest a latex condom filled with warm blood -- the schematic elements of a sleeping human face.

"The experiment has two specific goals," Beard says. "One is to understand how the transgenic bacterium will travel through the kissing-bug population. But also we want to determine what is the smallest amount of Cruzigard we will have to lay down in these huts to achieve the maximum result. Obviously, if we have to blanket an area with a paste containing transgenic bacterium, that's no good." Introducing a novel gene into a dynamic ecosytem isn't just daunting and full of multiple contingencies; it's risky. So we return to Beard's office to discuss why tinkering at the genetic level is a smart thing to do. Greeting any visitor at Beard's desk is a terrarium crawling with Madagascar roaches, the infamously huge, two-inch beasts that are startled when I look in on them. They puff up their carapaces and scuttle frantically, making a sizzling noise meant to gross me out and make me jerk my head back and cause me to retreat in fear. All of which, according to nature's mysterious design, works just perfectly.

"The first thing you have to worry about is human toxicity," Beard says of the kissing-bug experiment. In other words, will the Cruzigard make humans sick or cause allergic reactions? Those tests have been done, he reports; it is not toxic.

"The other thing that's a given in a dynamic system," Durvasula says, "is that the parasite will develop a resistance to whatever you throw at it." This is true of any remedy, including pesticides. For instance, DDT-resistant mosquitoes are now causing a profound public health crisis in India. By the same logic, natural selection dictates that the kissing-bug parasite will eventually mutate into a form that isn't vulnerable to Cruzigard. To solve this problem, the scientists have developed multiple alterations to the bacterium's genes. In addition to the gene engineered to produce the protein that punches holes in the parasite, Beard and Durvasula have created another gene that helps the bacterium harmlessly flush the parasite

out of the insect.

"The idea is to create a kind of genetic factory of different mechanisms," Durvasula explains. "Like beads on a necklace, we can shift from one to the next in order to anticipate mutations."

Another danger of the project is the possibility of having a modified gene show up in other bacteria or insects. Tests to find out what happens when the gene moves into the bug's neighbors -- crickets, bedbugs or even other bacteria -- will be the subject of Beard and Durvasula's next experiments.

Beard leaps up from his chair and stands excitedly in front of his white marker board. "This next step will involve setting up the protocol for a release of bugs with transgenic bacterium in a real field test," he says. Because the bugs would have to be released in their native habitat, this experiment would most likely take place in Guatemala in collaboration with local scientists. This stage would obviously add serious diplomatic challenges to an already complicated scientific protocol.

But right now, he is thinking science. "We'd probably build 16 huts," he says, scribbling out a map. "Then we'd cover the entire operation in a mesh net. And we'd put a goat inside to serve as a blood source." Having constructed a whole village, the scientists would be able to see if the altered gene (in their test, it will be just a marker gene) "jumps" or "migrates horizontally" -- i.e., winds up in other bacteria or insects and thereby escape the scientists' control, fleeing into the wild.

"Such an experiment," Durvasula says excitedly, "would move us to the everything-but-humans level."

The next morning, it is time to visit the Insectary, where the kissing bugs (in all of their various species) are bred and maintained. A special code is required to enter the building and then another code to enter the Insectary itself. In screened alcoves, racks of circular five-gallon cartons with mesh tops sit upon the shelves. "This is the C.D.C.'s reference library," Beard says, a bestiary of various insects bred precisely to reflect even such things as differing pesticide resistance levels from around the world.

Through yet another coded doorway is a special waiting room. A gale-force wind machine blows all the air away from the door as it closes. We wait a minute and then enter the inner sanctum of the bug kingdom. Here are mosquitoes infested with malaria or bugs that have been altered to carry the green phosphorescent gene from jellyfish. When a kissing bug is permitted to carry the transgenic bacterium, it lives here.

The morning's chore is to transfer some kissing bugs from one container to another. As we enter the cage, the sudden influx of our bodies and all that intoxicating carbon dioxide we are exhaling sends the bugs to the tops of their cartons in anticipation of fresh blood. They stick their hairlike proboscises through the mesh, waving them at us, pleadingly. It is freaky.

As Durvasula opens a carton set inside a tray edged in silicon (so that escapees will slide back down slick walls) and tweezes some very large and highly agitated bugs into another container, I decide that it's appropriate to pursue the issue of nature's unpredictable amazingness.

"It's what I call the 'what if?' problem," Durvasula says, "or the 'Jurassic Park syndrome.' We can try to anticipate every problem, and then someone can just say, 'What if?' and then you're dealing with images of 40-foot insects coming down the street and the whole thing comes to an end." The "what ifs" can be projections of our fear, largely imaginary, but they can also be rooted in real concern.

Andrew Kimbrell of the International Center for Technology Assessment argues that the work of Beard and Durvasula (along with all the others) inaugurates a new kind of pollution: biological, instead of the old kind of containable waste. "The F.D.A. cannot say, 'Oh, we had a defective design,' and sponsor a federal recall," Kimbrell says. "Biological pollution divides, mutates and changes. Our experience should teach us something. You can't impose a recall on killer bees or Dutch elm disease."

When I asked other scientists who have no connection to the kissing-bugs experiments what was their worst-case scenario for transgenic insects, their answers revealed a third kind of fear, which Beard had also confessed was his own nightmare. It was not the prospect of giant Frankenbugs wreaking havoc down Main Street (until the movie hero tricks them into walking straight into a net of high voltage wires) or an ecosystemic catastrophe.

"My fear is that we might release bioengineered insects but then find that under field conditions the altered gene turns off," says Marjorie Hoy, an entomologist at the University of Florida. "So you'd simply have released more insects into the affected area and with them more Chagas', more malaria, more yellow fever, more dengue."

Kimbrell suggests that the way to deal with all this concern, real and imagined, is to spend as much money on risk assessment as the scientists spend on genetic manipulation. "If we can do that," he says, "we can proceed with some sense that we've matured, proceed without the usual 'Gee whiz, this will cure all disease,' and then deal with the real complexity of living systems."

Durvasula argues that they are proceeding carefully, trying to account for the contingencies that occur in a dynamic system: they are testing for how the genes affect other life forms, whether they "jump," the toxicity on humans, the effect of the gene on the kissing bug itself, etc.

"What's really needed is some degree of transparency," Durvasula says, which simply means that you should tell people what you're doing as you go along. He recalls the recent Taco Bell scandal in which the public suddenly learned that their supermarket taco shells had been contaminated with a genetically altered corn approved only for animals. "Putting a genetically altered product on the market surreptitiously and then having the media blow the whistle was probably the wrong way to educate people," he says. Beard adds that too often scientists take their work to the public without explaining what the specific benefits will be. "Scientists cloning sheep were trying to clone tissues and growth factors," he says.

"But it came across as a frivolous pursuit, just tinkering with nature to no end except to arrogantly push back the boundaries. We need to explain what the other end points are."

Besides stopping Chagas', there are a number of other end points in this case. Scientists aware of Beard and Durvasula's method have already begun work on bacteria dwelling inside the tsetse fly (the vector for African sleeping sickness) and the sand fly (leishmaniasis). Finally, there is one other end point that is the furthest off.

"You know, bugs and humans aren't all that different," Durvasula says late one afternoon. Our gateway membranes -- nasal, oral, etc. -- are colonized by bacteria that stand like sentries at the portals of disease. Durvasula has already experimented with a bacterium that dwells in the human respiratory tract. In the laboratory, he has begun work on a transgenic tweak in this bacterium that would generate enough of an antibody to bind with the flu virus and flush it harmlessly from a human body. How much of a cultural shift would it take to persuade people to snort a line or two of transgenic bacteria in order to ward off the worst of the winter diseases? Probably not much. Of course, curing the flu is precisely the kind of "gee-whiz" stuff that makes Kimbrell nervous, should it go awry. It's also Nobel Prize stuff, should it not.

Because it is so early on in this work, it is easy to say that we are either at the edge of a remarkable new and useful science or that we are careering down an environmental rabbit hole. It is a good time to think about how improvements in public health have happened historically. When it was determined that the rat was the vector for plague, urban centers embarked on a campaign to create proper sewage disposal in order to keep such creatures away from where we dwelled. The era of pesticides, in which we now live, has focused solutions on a smaller scale: the insect. Today's scientists recognize that bugs are not the real cause of disease and have redirected their attention to the microscopic realm. Paratransgenesis leaves the bug alone to thrive in its habitat while surgically targeting the parasite.

There is a comforting progression here, but if the age of pesticides has taught us one thing, it is that you cannot eliminate a single nuisance species wholesale without possibly violating the law of unintended consequences. Such a dynamic might well occur at the bacterial level as well: what if the parasite Beard and Durvasula have focused on wiping out turns out to serve some critical purpose for the kissing bug? It is not improbable. In the case of the sand fly, the disease-causing parasite colonizes the bug's throat and chokes it. This forces the weakened bug to eat many small meals rather than one big one -- which is nature's way of spreading the parasite. But if paratransgenesis successfully eliminated the stress of this parasite, would the sand-fly population explode? In a similar vein, might the kissing bug's parasite affect its host in some way that we don't understand? If we eliminate the parasite altogether, will that create some other problem?

As many experiments as these scientists have performed and have planned (and this is one of the most thought-through of such projects), these contingencies don't go away. The actual risk to the environment of releasing genetically altered insects can't really be known until we release them. Of course, nature constantly causes massive disruptions that ripple through a local ecosystem, like a forest fire or a Mount St. Helens eruption. Often we cause them. The release of rabbits in Australia, where they swiftly reproduced and swarmed the entire island, has become a parable of environmental mayhem. Regardless of who's to blame, nature handily adapts every time -- no exceptions. Sometimes we don't like the adaptation at all (global warming, tropical "supercanes," a continent crammed with rabbits, regional extinction of elm trees), but the truth is, most of the time, we hardly notice. If the choice were always between a 40-foot Jurassic insect and the normal one-inch kind, it would be easy.

"The question is," Durvasula says, "can we explain to the public that we've tried to show that this technique is safe and efficacious to such a point that they will accept the risks?" The timing and the context of that possible acceptance will mean everything. Laying down blankets of insecticides over cities does not appear to have a bright future. And only 50 years after penicillin seemed a cure-all, the efficacy of nearly all of the roughly 150 antibiotics in the doctor's satchel is waning. If the arsenal for disease prevention continues emptying, the decision will become more focused: how do we weigh the fear of knowingly disrupting our own natural habitat with transgenics versus the fear of taking no action in face of a new epidemic? This is the question posed by Beard and Durvasula's work. When the time comes, they will not have to answer it. We will.

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