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When the Lab Rat Is a Snake

Why Burmese pythons may be the best way to study diabetes,heart disease and the protective effects of gastric-bypass surgery in humans.

As Amit Choudhary opened the package of snake blood, the first thing he noticed was its color. It looked like yogurt. The blood plasma, harvested from a Burmese python shortly after feeding, was so clogged with fatty acids that it was not clear but milky white. An oily mess like that should be toxic, Choudhary thought. Indeed, when he smeared the same amount of fatty acids on a plate of human pancreatic cells, the kind that supply the body with insulin, they self-destructed from the stress. Yet he knew the snake could somehow thrive, even as its plasma turned to yogurt after every single meal.

It was the late fall of 2012, and Choudhary, then a postdoctoral fellow at Harvard University, had become interested in the Burmese python on account of its extraordinary physiology. The animal is essentially a slithering digestive tract: In the wild, it often spends a month or two in silent ambush; then, when the moment is right, it wraps its coils around a monkey, a pig, an antelope and swallows its prey head first. A single meal for a full-grown python may contain more than 50,000 calories, a tidal wave of nutrients and fatty acids that could be deadly to another species. But the python has adapted to the overload. For the week or so that follows feeding, its body turns into an engine of digestion: Its intestine thickens; its liver and kidneys nearly double in mass; its insulin level shoots up; its temperature increases by six degrees Fahrenheit; its pulse triples; and its metabolism jumps. Once all the food has been absorbed, the python's organs shrink back to their quiescent state.

In his lab, Choudhary wondered if there might be something in a python's yogurt blood that helps it undergo this protective transformation. He dabbed a few drops on a rodent's pancreatic cells to see how they would respond. "The results were mind-blowing," he recalled on a recent April afternoon in Boston, where he now does research at Harvard and M.I.T.'s Broad Institute. Choudhary used an antibody kit to measure how much insulin the rodent cells produced. The assay works by color: Insulin turns a sample very slightly yellow, a change researchers detect using a specialized instrument. But after Choudhary treated the cells with snake blood, they started spurting so much insulin that he could *see* the sample changing color. The python's fatty

plasma didn't just insulate the pancreas from fatty acids; it appeared to juice it up.

Growing up in a farming area several hours from Kolkata, India, Choudhary had always been afraid of snakes. "I was told not to mess with those creatures," he says. Now he realized they might hold a cure for diabetes. The pancreatic cells he used in the lab were beta cells, and diabetes is a beta-cell disease. In the early-onset (Type 1) form, the body's immune system turns against these cells and nearly wipes them out. Without a source of insulin, a patient can't control the sugar in the bloodstream. In Type 2 diabetes, the version of the ailment linked to Western diets and obesity, it goes the other way: The patient loses sensitivity to the insulin being produced, and the beta cells become overcharged to compensate, until eventually they weaken or die. What if Choudhary could find a chemical in snake blood that worked to bolster the beta cells and reverse the condition?

Choudhary knew the stakes as well as anybody. In India, they call diabetes "having sugar," and his family seemed at special risk: Nearly every one of his male relatives, and some females, too, had sugar, and many died from its complications. Even he and his younger brothers, all of whom now live in the United States, may be doomed to the condition in their later middle age. So after completing his dissertation work in quantum chemistry and biophysics, Choudhary started looking into diabetes.

Until that point, he found, much of the research into therapies for beta cells had been done on laboratory rodents. After years of work on rats and mice, scientists had come up with lots of drugs that energized a rodent's pancreas, but very few of these showed any promise when it came to treating humans. We don't yet know why, but one reason may be that the pancreas of a mouse or a rat is a bit peculiar. For one thing, its beta cells are livelier than ours and more likely to divide. They are also grouped together in one place in the pancreas, while ours are a bit more scattered. And rodents have a pair of genes encoding insulin, while we have only one.

In spite of these discrepancies, rats and mice remain the most common research animals for the study of diabetes, as they are for all of biomedicine. In part because of their proximity to humans on the evolutionary tree, in part because of their small size and in part because of our facility at playing with their DNA, Mus musculus and Rattus norvegicus have become the default choice for biomedical experiments. But if sickly diabetic mice and rats were useful models of the disease, Choudhary thought, might there be even greater value in a species that evolved to be the opposite — a model of good health, resistant to whatever makes a rodent or a person fall apart?

Choudhary had the snake blood and a plate of beta cells on steroids. But before he allowed himself to dream of wonder cures, he tried the same experiment again — putting milky drops into a petri dish — this time using plasma from a different snake. Once again, the beta cells were sent into a riot.

If Choudhary were to start a brand-new research program using laboratory pythons, he would need to be absolutely certain that he hadn't messed things up. "When the results are too good," he said, "you always worry that something must have gone wrong." He ran the experiment four more times. It always worked.

The idea of using pythons to understand metabolism got its start 100 years ago, on the very same street as Choudhary's Harvard office. Opposite the medical school on what is now called Blackfan Circle, a physiologist and professional magician named Francis Gano Benedict embarked on a landmark 17-year study of absorption in the snake.

Benedict came to Boston on behalf of the Carnegie Institution to found a laboratory for the study of nutrition. He brought with him a state-of-the-art device that he helped develop while at Wesleyan, known as the respiration calorimeter. An airtight chamber lined with zinc and copper, it could be used to calculate the energy in food — i.e. its "calories" — and study how exercise or eating might affect a person's metabolic rate. He soon discovered that his measurements of energetics could be applied to nearly any animal — he once built a mammoth version of the chamber for an elephant — and used to answer endless questions on nutrition, important or mundane. At one point, he calculated the energetic cost of thinking: "The cloistered scholar at his books may be surprised to learn that the extra calories needed for one hour of intense mental effort," he announced in 1930, "would be completely met by the eating of one oyster cracker or half of a salted peanut."

As part of his grand project on behalf of Carnegie, Benedict set out to construct a bestiary of metabolic rates. In 1915, he traveled to New York City to install a respiration chamber in the reptile house at the Bronx Zoo. He hoped to use the snakes — including the zoo's 17-foot python — to understand how and why an animal's body temperature might fluctuate. Eventually, he predicted, this work could help explain the mysteries of human fever.

By the following spring, Benedict had begun a study of the snakes' response to eating. It intrigued him that pythons and other constricting snakes, in particular, could ingest an "inconceivably large mass" at one time. He had them gobble rabbits whole, or hunks of beef fat wrapped in the pelts of guinea pigs, and tested them in his giant-snake-size chamber. The resulting bumps in heat — and fivefold increase in carbon-dioxide production — left him dazzled. "With no other animals in the world, certainly among the vertebrates, can one expect such economy in the taking of food," he wrote in his monograph from 1932, "The Physiology of Large Reptiles." A photograph of Benedict, published that same year, shows him in a lab coat and bow tie, proudly holding an eight-foot python by its neck.

For Benedict, the python's Olympian feats of digestion made it worthy of study, but he was nearly as impressed by its placid disposition — a highly valued trait in a laboratory animal. Special credit went to the python he

examined at the National Zoo in Washington: “In the entire series of experiments with this animal she gave but one sign of agitation,” he wrote, “which was a heavy, deep breath, approximating a hiss, in the middle of an afternoon session.”

Yet despite Benedict’s efforts to proselytize, the python barely made its way into the labs of other physiologists. In fact, the details of its digestive tract and their implications for our understanding of metabolism were more or less ignored for 60 years, until a young biologist named Stephen Secor started tracking rattlesnakes in the Mojave Desert.

Secor, who grew up on a horse farm, planned to be a veterinarian, but a love of snakes derailed him. At first, he tried to study their behavior in the lab (the mating habits of the speckled king snake), but he found the research boring. So for his Ph.D. at the University of California, Los Angeles, Secor headed out into the field to track a pair of wild species — the coachwhip and the sidewinder rattlesnake — and learn how they managed their metabolism in a natural setting. As eaters, these snakes were polar opposites. Secor noticed that the coachwhip, whose form is long and slender, was always on the move, chasing little lizards through the Kelso Dunes. A sidewinder waits for its dinner: It sits in ambush until a kangaroo rat happens to come hopping by, and then it has a banquet.

When Secor presented his observations at a 1991 scientific meeting at White Mountain Research Center, a few hours north of Los Angeles, Jared Diamond raised his hand. Diamond, now better known for his work as a geographer and historian (he is the author of “Guns, Germs and Steel”), was at the time a physiologist in the mold of Francis Gano Benedict. Since the early 1980s, he had been working on a grand survey of animal digestion. His lab had looked at rats and mice, cats and minks, frogs and fish. He had even studied how a hummingbird handles so much nectar in its small intestine.

Diamond thought of the intestine as something like a muscle, lifting substances into the bloodstream. If you had to do more lifting, he reasoned, you would need to have a stronger muscle. So Secor’s talk about the sidewinders, and their feast-or-famine diet, made him wonder if the animals’ intestines were endowed with superhero strength. As it happens, Secor had tried to measure the rattlesnakes’ metabolism, but the numbers he got were so high that they seemed impossible. A mammal’s metabolic rate typically rises by one-quarter or one-half after feeding. The largest such increase anyone had ever measured in a reptile was a fourfold or fivefold change. But Secor’s data showed that sidewinders could increase their metabolism by almost eightfold — a bigger jump than anyone had seen in any species. A prominent scientist at U.C.L.A., who would later serve as Secor’s mentor, told him that he must be doing something wrong. “Leave the physiology to physiologists,” the professor said.

But when Diamond looked at Secor's numbers, he believed them. "This is the most exciting data I've seen in five years," he announced. As soon as Secor finished his dissertation, he moved his work to Diamond's lab. It soon became apparent that, as research animals, Secor's three dozen wild rattlesnakes were not ideal. "Every now and again, he'd get bitten, and then he'd get a little dizzy," Diamond remembers. Secor says the venom didn't bother him much, but U.C.L.A.'s administration was not keen on housing a colony of sidewinders. So Secor and Diamond set out to find a safer snake with an athlete's intestine. Secor tested a Noah's ark of options — a pair of water snakes, a pair of corn snakes, a pair of black racers, a pair of Burmese pythons — before he found his champion. The python's gut looked even more impressive than the rattlesnake's. After feeding, the intestine blew up like a bodybuilder's, doubling in mass.

And if the python's meal was very large, its metabolic rate would increase not just eightfold, like the rattlesnake's, but by a factor of 44. The only comparable metabolic increase Diamond knew of had been identified in a galloping racehorse. The most impressive short-term increase he had seen in humans — measured in water-polo players and cyclists in the Tour de France — was no more than five or six times their resting rate. "These pythons made the Tour de France cyclists and water-polo players look like wimps," he says. What's more, the python could sustain that level of metabolism for several days.

Secor kept a pair of 12-footers in his home, Linus and Bob; he knew pythons were easy to acquire and maintain. The pet trade in the Burmese python had been booming since the 1980s. So he reached out to a guy he knew in Oklahoma, who happened to be the nation's biggest python breeder, and put in an order for 100 snakes. Over the next few years, Secor worked on tracing how a Burmese python's body transforms itself after feeding. Nearly every facet of digestion was exaggerated, he found, from the way the python fills its stomach with hydrochloric acid to the way its organs thicken and expand. For him and Diamond, the scale of these effects had a scientific value of its own. It made the process of digestion easier to study, because every nuance could be seen in high relief.

But as Secor finished this initial round of work, Diamond was preparing to move on. "The future of the world does not depend on intestines and gallbladders," he had decided. In the fall of 1998, he and Secor summarized their research on pythons in the journal Nature. Their article was half-prospectus and half-plea — a call to fellow physiologists to make the Burmese python a standard laboratory animal. The snakes were practical, the article said, on account of their infrequent feeding and inexpensive upkeep, their convenient "linear anatomy," their easygoing nature and their relative lack of moral standing. (Snakes "do not arouse the controversy associated with medical research on similarly sized mammals," Secor and Diamond noted.)

But the Burmese python's greatest value — its raison d'être as a laboratory species — derives from its special way of eating.

"The history of biology illustrates the importance of selecting exceptionally suitable species as models," Secor and Diamond wrote. The fruit fly, for example, with its rapid reproduction, helped scientists understand genetics; the squid, with its peculiarly gigantic axon fibers, allowed scientists to examine the workings of a single nerve cell. Could pythons, with their astounding feats of regulation, become the next great model animals?

Secor now runs his own lab, bustling with reptiles, at the University of Alabama, in Tuscaloosa. Since 1998, he has published 30 papers on the python. His lab has studied, among other things, how the python's microbiome changes in response to eating; how its metabolism responds to meat depending on whether it has been ground up like hamburger or cooked in a microwave oven; how it regulates its blood flow after feeding; and how it keeps a rising tide of gastric acid from lapping into its throat.

For most of his career, Secor's work has been unadulterated by the need for real-world applications. People rarely bothered him with plans to plumb the python as a source of pharmaceuticals or as a means to better human health. "I don't care about the medical aspects," he says he might have told them at the time. "That's not what I do. I just love these animals because I'm interested in their biology."

Then, all at once, the field began to change. First a group based at the University of California, Irvine, led by a comparative physiologist named James Hicks, published data showing that the python's heart can grow in size by 40 percent as the animal digests. Not long after, Leslie Leinwand, who studies cardiac disease at the University of Colorado, became interested. Leinwand knew that in humans, an enlarged heart can be a sign of good health — athletes get bigger, stronger hearts from working out — but it can also signal that the organ is diseased. With help from Secor, she and her postdoctoral researcher, Cecilia Riquelme, found that after feeding, a python's heart swells the way an athlete's does, with no ill effects. Then they tried pouring snake blood on a dish of rat heart cells and found it bulked them up, like liquid exercise. A subset of the fatty acids in the python's blood seemed to function as a cell-expanding cocktail, one that worked even in living mice.

In early 2012, Leinwand presented her research at the Broad Institute, where Choudhary had just begun to think about the python as a tool for treating diabetes. The python's heart might swell by 40 percent after feeding, he thought excitedly, but its pancreas would double. Leinwand had found a signal in a python's blood that makes heart cells big and strong. What if he could do the same, or more, for pancreatic beta cells? Later, in 2013, another researcher, Nicholas Stylopoulos of Boston Children's Hospital, whose office

happens to be just down the street from Choudhary's (and from the site of Francis Gano Benedict's), decided that the python might be a useful model for his work on the science underpinning gastric-bypass surgery and its benefits for diabetics.

Why did it take so long for medical researchers to see the value in the python? For one thing, the conditions the python might help to treat have become more prevalent. In 1998, when Secor and Diamond's essay first appeared, 10.5 million Americans were found to have diabetes. By the time Leinwand published her results, that number had nearly doubled. Obesity rates have also climbed during that span. Our worsening diets have made the python's way of eating more germane.

Leinwand has begun to investigate whether the snakes themselves get fat and sick. In the 25 years since Secor started work in Diamond's lab, escaped or discarded Burmese python pets have found their way into the Everglades in Florida. With no natural predators, they have flourished on the region's supersize supply of birds, raccoons and opossums, as well as bobcats, deer and alligators. Leinwand wants to know whether the Burmese python — or the Burmese-American python, really — might be getting ill from all this food. (And if it isn't, then what, exactly, is protecting it?) "Their diet is different, they're eating things that they're not normally eating and they're eating way more often," Leinwand says. "So one of the experiments that we're working on right now is asking, Is this a bad thing for them, or a good thing, to be exposed to such huge amounts of food and fat?"

It's not clear when Leinwand's and others' newer projects might develop. Python research has been very slow, especially compared with the work done on rodents. It took Leinwand and Riquelme several years just to make sure that antibodies they used for their mouse research would work the same for snakes. And while a round of lab mice can be bred in a matter of weeks, new python hatchlings arrive only once per year. That glacial pace makes the work on snakes "a very high-risk, high-reward project," Choudhary says. Last year, he and Secor and a third researcher, Bridget Wagner, secured a grant of $2.5 million from the National Institutes of Health, from a special fund for "innovative, unconventional, paradigm-shifting research projects." They have started by setting up what Choudhary calls a "snake infrastructure," so they can rear and analyze the pythons as efficiently as possible.

The work is on the verge of getting easier for another reason too. When Leinwand and Riquelme started on the Burmese python, the animal's genetic code had not been mapped. They did their best by comparing bits of python RNA to published genomes of the chicken and the lizard. But just before they published their research, a group of snake biologists put out a first draft of the sequence for the Burmese python. Now Leinwand's lab, as well as Choudhary's and Stylopoulos's, has a detailed atlas of the python's DNA. That means they can feed a Burmese python in the lab and then use a simple probe to analyze tissue from its heart, pancreas or small intestine to see which genes

are tuning up or down within each cell. Choudhary has been using this approach to figure out the genes behind the beneficial changes to a python's beta cells. These might be useful targets for a future diabetes drug, he says.

If all this work on snakes continues to expand, the python may one day be as central to our understanding of disease — or at least those illnesses that stem, in part, from overeating — as the laboratory rodent. Eventually, in some respects, it might even overtake the mouse. Perhaps that would be fitting. As she raises the baby Burmese pythons for her lab, Leinwand has them on an all-mouse diet.