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On Venom and Varmints

Why bad things might be good for us

Gila monsters do not often come up in ordinary conversation. That's a shame, because in their own quiet, unheroic way, Gila monsters have improved the lives of thousands of people. If nothing else, their contribution to mankind makes for a good story, one that illustrates the unexpected connectedness of the natural world and the sometimes chance ways in which scientific discoveries are made.

My own introduction to these creatures came in 2016, on a day trip to Biosphere 2. (Built in the remote mountains northeast of Tucson, Biosphere 2 had been the site of an experiment in enclosed, self-sufficient living and remains a research facility today.) Dr. Kevin Bonine, of the University of Arizona, happened to be giving a public lecture on Gila monsters that day, and I found myself intrigued by what he had to say.

Along with the more commonplace facts (they're the largest lizard native to North America; they're one of the few venomous lizards in the world), Dr. Bonine mentioned that Gila monsters were the source of a drug used to treat diabetes. This fact stuck with me. In 2019, while researching diabetes treatments for a friend, I remembered the Gila monster drug. I didn't recall the details, but I started searching for references. There were a surprising number of them.

If you've never heard of a drug marketed as "Byetta", you're probably not alone. But if you have type-2 diabetes, chances are that you are acquainted with it—you may even be taking it to help regulate your blood sugar. What you might not know is that

Byetta is based on a peptide (a small protein molecule) found in the saliva of Gila monsters.

If that sounds unpalatable, note that the drug is "based on" rather than being collected from their saliva. There wouldn't be enough Gila monsters in the world to fill the need —their total population is estimated at only a few thousand scattered around the Southwest. Even if you could procure enough saliva, you would be faced with the task of isolating the component responsible for blood sugar regulation. (Lest there be any confusion, this peptide functions as a hormone, a substance that helps regulate a process in the body. Not all hormones are peptides, though.)

Byetta is the synthetic version of this peptide known as exendin-4. And therein lies a tale. Part of this tale relates to how a previously feared and despised creature came to be recognized as the source of a medically important drug. The other part relates to the mysteries surrounding this elusive lizard. Why would a Gila monster, a creature found only in Southwestern deserts, produce a substance in its venom that is similar to GLP-1, a hormone produced in the human pancreas? Who would have recognized this connection? Why would a Gila monster produce venom at all? A good place to begin might be with the biology of this odd little reptile.

A Most Ingenious Paradox

Shakespeare wrote that "nature hath framed strange fellows in her time", but some seem stranger than others. The Gila monster could be thought of as the Southwest's answer to Australia's platypus, a creature so improbable that it stretches our belief in what is biologically possible. Consider some Gila monster paradoxes:

- Its skin is covered in bony, bead-like “ossicones”, set in a vivid pattern of black, yellow, and orange. But why would Gila monsters require such a colorful display when they spend more than 90% of their lives in humid underground burrows?
- When a Gila monster bites, it clamps down like a bulldog, continuing to inject venom into the wound. (The venom is produced in glands in its bottom jaw, and mixes with saliva.) Its bite, though extremely painful, is not fatal to its few predators, or to humans. Nor is the venom needed to subdue its prey, which consists of small birds, young animals and, especially, eggs. (A Gila monster will climb a tree or cactus to reach a nest.)
- Though adapted to the harsh desert environment, Gila monsters love water—some have been found paddling in suburban swimming pools. Yet a Gila monster can exist for up to 81 days without drinking. This is due to a specialized bladder that serves as a reservoir, capable of dumping water that then recirculates throughout the body.
- Gila monsters have a very slow metabolism. They can exist on as few as three large meals a year, eating about a third of their body weight each time. They store fat in their tails, rather than being able to jettison the tail (as do other lizards) if a predator grabs it. They don’t walk, they waddle. Yet they have exceptional endurance and aerobic capabilities. If placed on tiny treadmills (this has been done!), they’ll run-waddle up to a mile an hour.

Many hypotheses have been proposed to explain these paradoxes. For example, males engage in prolonged wrestling matches during mating season, at which point, it is thought, they might need high endurance.

Also, some scientists believe Gila monsters may have evolved in a wetter climate, and found themselves stranded in a harsher environment over time. There is some merit to this idea, given what is known about their evolution, but there is no solid proof of it.

Loathed and Maligned

As if the real qualities of the Gila monster were not odd enough, the fictional accounts are even stranger. Explorers and settlers regarded the reptile as ugly, dangerous and unpleasant. Myths and tall tales from the 19th century describe its "fetid breath" as bad enough to kill its prey. Not true. Newspapers of that era gave lurid accounts of fatalities caused by its bite. None of these deaths were ever properly documented. But the evil reputation of the Gila monster persisted.

Indigenous peoples of the Southwest had their own myths and legends about them. Most tribes were aware of their venomous nature; none seemed to find them edible. Many legends credited Gila monsters with the ability to cause illness in someone who had touched or killed them.

The general consensus seemed to be that, in the case of the Gila monster, nature had produced a lemon. It wasn't until the late 20th century that a medical researcher realized you might make "lemonade" from this lemon in the form of a powerful drug.

A Reputation Upgrade

In the late 1980s, endocrinologist Dr. John Eng came across studies done at the National Institute of Health (NIH) reporting that the venom from certain snakes and lizards, Gila monsters among them, caused expansion of the pancreas in humans. Eng worked at the VA Medical Center in the Bronx, treating diabetics and running

radioimmunoassays in hopes of discovering new hormones from animals. When he followed up on the NIH studies, and learned that Gila monsters could slow their metabolism and regulate their blood sugar for long periods between meals, Eng decided to run assays on Gila monster saliva. When he did, he discovered that it contained a peptide he dubbed “exendin-4”.

Eng was able to isolate and then synthesize this peptide. He determined that the chemical structure of exendin-4 was 52% identical to GLP-1, a pancreatic hormone that increases the production of insulin after a meal. But there was an important difference: exendin-4 did not degrade within minutes like GLP-1, instead its effects lasted for hours. This meant type-2 diabetics would only need to inject it daily rather than hourly, thus enhancing their ability to regulate their blood sugar. His results were confirmed by other researchers and, after a long licensing process, the synthetic version was brought to market in 2005. Like the two researchers I spoke with, Eng became a great fan of the Gila monster.

Beyond Byetta

Since its discovery, other researchers have begun to investigate whether exendin-4 might be effective in the treatment of neurogenerative diseases such as Parkinson’s, much as GLP-1 has been shown to be. Also, a computational biologist at Arizona State University, Dr. Melissa Wilson, is sequencing the Gila monster genome, which could help establish their evolutionary relationship to snakes and other lizards. Examining their genome may also help scientists solve the mystery of venom production, which is not well understood. This information could aid in the development of anti-venoms. Research on the Gila monster could fill in a number of biological blanks.

Back to Biology

"Do Gila monsters even have a pancreas?" I put this question to Dr. Bonnie, the professor whose lecture had first sparked my interest in this lizard, during a phone interview. My research had led me to wonder about some very obscure topics, including the internal organs of reptiles.

All vertebrates had a pancreas, he assured me, but Gila monsters might have one more like the "splenopancreas" found in snakes, in which the spleen and pancreas are fused. Given that Gila monsters can ingest the equivalent of a 50-pound meal for a 150-pound adult, it seemed logical that they would produce a hormone that powerfully regulates their blood sugar levels and allows these levels to remain consistent over a long period of time.

I now had an answer to the question of why the Gila monster was making exendin-4 for its own purposes. I then asked Dr. Bonine the second question that had been bothering me. "Why," I asked, would a lizard in the Southwest have evolved to produce a peptide that humans would be able to use to control their blood sugar?" His answer surprised me. "Though our species may seem vastly different, we are all biologically connected." I suppose the scientific explanation for this would be that we're all carbon-based life forms. But I suddenly felt the illusion of separateness dissolve; I never felt closer to my fellow creatures than I did at that moment.