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Time twister

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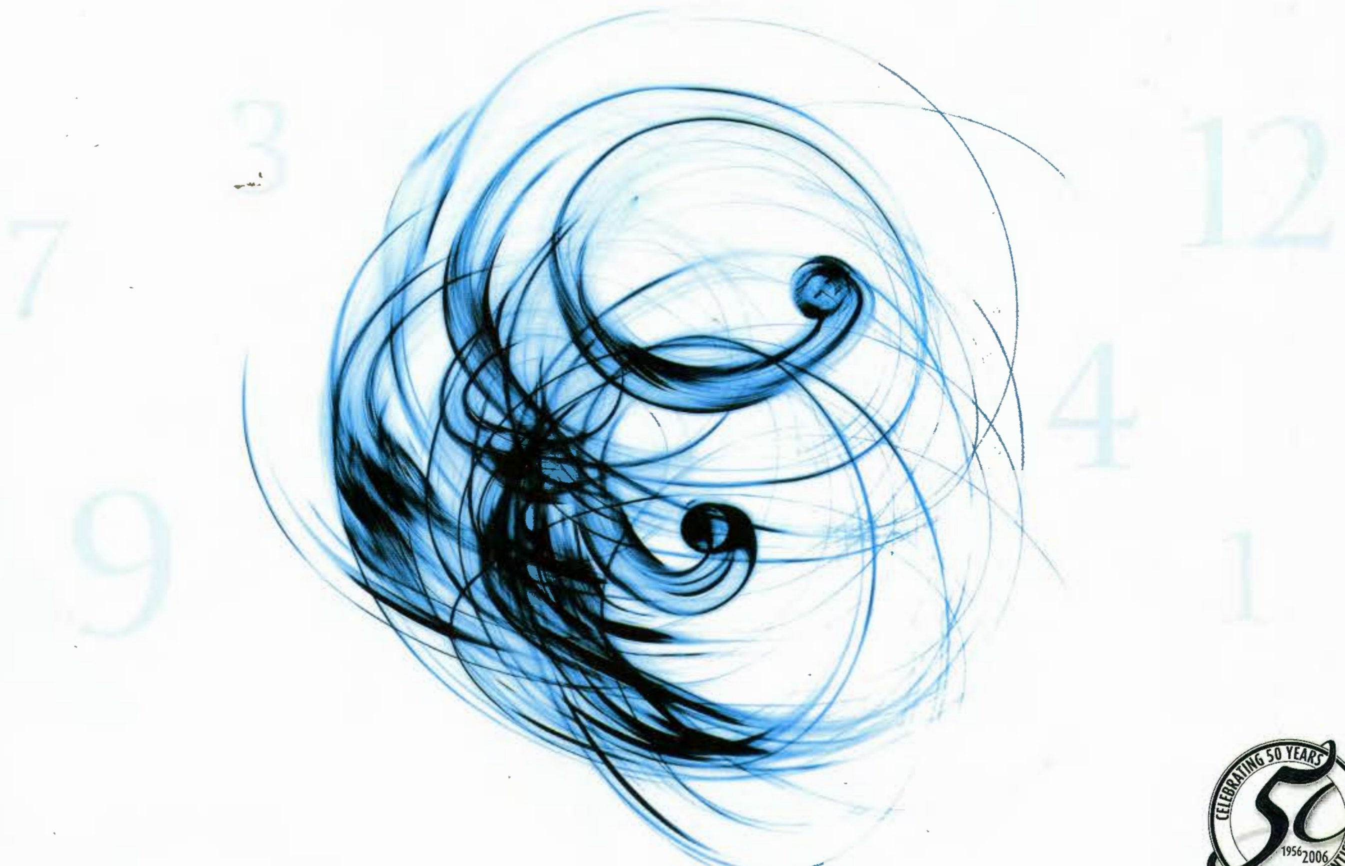

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What's your poison?

Buy a snake in a pet shop and you'll probably be told it's harmless. Don't be so sure, says Michael Tennesen

DANIEL HEUCLIN/NHPA

SNAKE-VENOM researcher Bryan Grieg Fry made his first discovery the hard way. During his PhD, he handled a snake whose venom was largely unknown. "As far as anyone knew, Stephen's banded snakes were not considered dangerous," Fry says. "I clearly proved this wrong as my body hit the ground seconds after the bite".

Several thousand snakes and more than 20 bites later, Fry, now deputy director of the Australian Venom Research Unit at the University of Melbourne, has gone one better. He now says the vast majority of snakes on the planet are venomous, even some commonly kept as pets.

Fry has spent the past five years exploring caves, climbing trees and scuba-diving for sea snakes, on a mission to catch and milk venom from as many snake species as possible. Along the way he has gained a reputation as a fearless snake wrangler and, more ▶

importantly, he has single-handedly rewritten the story of snake venom evolution.

Before Fry came along, the story went something like this. The first snakes evolved from lizards and were small burrowing creatures, less than 1 metre long. Around 60 to 80 million years ago they split into constrictor-style snakes and the advanced snakes, which are further divided into four families: Viperidae (vipers), Elapidae (cobras and coral snakes), Atractaspididae (stiletto snakes) and Colubridae (everything else).

A deadly ancestor

Leaving aside the colubrids, most of which were thought to have nothing more dangerous than slightly toxic saliva, venom was assumed to have evolved independently in each of the other three families, after they split off from their non-venomous ancestors. In these three there were thought to be a grand total of around 500 venomous species, all of which gained their venom by developing increasingly nasty saliva. Some scientists suspected there had been a common venomous ancestor to all snakes but no one had found any evidence to support the idea.

Fry began his venom-collecting mission in 2001. It was dangerous work. That year, Fry lost a friend and colleague to a snakebite, and frequently gets bitten himself. "It happens, but it doesn't make me nervous; it's all part of the job," he says, pointing out that he never goes anywhere without a doctor and a supply of antivenom.

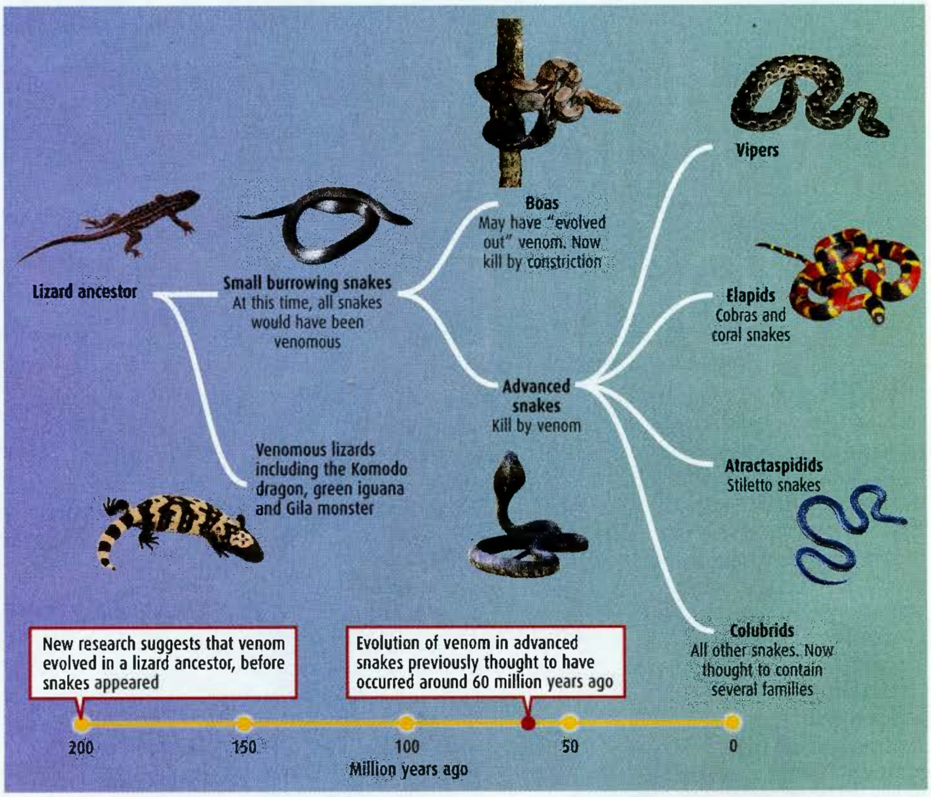
Between trips around Africa, Australia and the South Pacific, Fry set to work analysing the venoms he had collected and the glands that produced them. The idea was to create a phylogeny – an evolutionary tree based on physical similarities – of different species of snakes and their lizard relatives.

Snake venom is a mixture of toxic proteins, so to find which proteins are produced by which snakes he sequenced messenger RNA from the cells that make up the venom glands. He then compared his results with an existing snake phylogeny created by Nicholas Vidal at the National Museum in Paris, France. Vidal had traced snake evolution through DNA extracted from liver tissue, so Fry was able to check that the similarities he'd found between venoms really did reflect evolutionary relationships. Finally, he compared his new evidence to the fossil record.

Fry's phylogeny, published in the journal *Nature* in February this year, was to overturn everything scientists thought they knew about snake venom. Similarities between the messenger RNA of venom glands of advanced snakes and venomous lizards revealed that these glands did not evolve independently in three snake families, or even in a common snake ancestor, but much earlier, in a lizard ancestor 200 million years ago. Venom evolved only once, in the common ancestor of all snakes plus some other reptiles, including the Komodo dragon, the green iguana and the Gila monster.

What's more, venom didn't evolve from ever more toxic saliva but from what Fry calls "recruitment events". Rather than tweaking proteins already expressed in their saliva, snakes recruited and altered cells from other parts of the body including the brain, eye, lung, heart, liver, muscle, ovary and testis. Over generations these proteins, usually involved in key biological processes such as blood clotting or regulating blood pressure, were mutated into more potent varieties and concentrated into catastrophic overdoses. The common ancestor had nine such toxins in its venom.

REWRITING THE STORY OF SNAKE-VENOM EVOLUTION



More dangerous by the day?

Sean Bush, MD, an emergency physician and venomous-bite specialist, was on call at the Loma Linda University Medical Center in California when a helicopter brought in 23-year-old Pippin Graves, who had been bitten by a rattlesnake. Graves was unconscious, gasping for air, and the tracheotomy that the emergency crew had performed on him was not working. Rattlesnake bites normally require about 5 to 10 vials of antivenom, but Graves needed 140.

Bush wondered at the reaction. Most rattlesnake venom is thought to prevent blood clotting or attack muscle, but increasingly the poison is affecting the central nervous system of the victims who show up in hospitals in the American Southwest – something which is far more dangerous. Why should this be happening? Could snake venom be undergoing rapid evolution in response to selective pressure from humans?

Many scientists believe the increasing potency of some rattlesnakes may have nothing to do with us, but is instead a product of an arms race between the predator and its normal prey. Texas A & M University researcher John C. Perez studied 40 species of mammals that fall prey to rattlesnakes and found that 16 had proteins in their blood that could block the effects of the venom of the western diamondback rattlesnake. Snakes could be countering this by developing ever more dangerous venom.

Bryan Grieg Fry, who has studied venom evolution in a number of snakes, thinks that people are moving into snake country and learning the hard way how potent and varied rattlesnake venom can be. Bush has come to agree. "It may be more a case of rapid discovery than rapid evolution," he says.

ALEXIA FRY

Bryan Grieg Fry has spent the past five years catching some of the most venomous snakes in the world

"The venom of a pet rat snake contains a neurotoxin as potent as that of a cobra"

Modern snakes have recruited 17 more.

The upshot of all this is that while the supposedly non-venomous colubrids were widely believed to have only mildly toxic saliva, Fry's work shows that they actually possess true venom. In fact, Fry has found snakes in pet stores whose venom glands "have enough poison in them to kill a human". The venom of the rat snake, for example, a common choice of pet, contains a neurotoxin which is as potent as the cobra equivalent. Fortunately for would-be pet owners, the rat snake has no front fangs, leaving these snakes with a rather crude venom-delivery system. Garter snakes, American racers and radiated rat snakes drip venom from their back teeth, so unless you plan on sticking your hand down a snake's throat you would be unlucky to get a deadly bite. What's more, these snakes are primarily interested in smaller prey than humans, and what is lethal to a 2-gram frog may be fairly harmless to a 70-kilogram human.

According to evolutionary ecologist Martin Kreitman of the University of Chicago, Fry's findings shed a new light on the snake evolutionary tree. "It means that venom may have evolved first, and that what separates other advanced snakes from the colubrids are simply more advanced delivery systems for injecting the venom," he says.

That implies that snakes which crush their prey, such as king snakes, pythons and boas, may have lost their venom as they evolved to kill by constriction. Fry has found evidence that some snakes are now "evolving out" certain venom components, perhaps because it takes a huge amount of energy to create them. The venom of the marbled sea snake, for example, has become only 1 to 20 per cent as toxic as that of similar species since it began to feed exclusively on fish eggs, rather than fish.

"The vast majority of the colubrids are perfectly safe," says Fry, but be careful of any unusual snakes for sale from Asia, Madagascar and Latin America. Previously sold as pets, the olive sand snake has huge venom glands and big teeth, for example, and although the Egyptian cat snake only has small rear fangs, it is as toxic as a cobra – and there's no antivenom.

Caution at the pet store is not the only spin-off from Fry's work. Snakebites account for tens of thousands of deaths each year in South America, Africa, the Middle East and south-east Asia. The more venoms that are catalogued and understood, the greater the chance of the right antivenom being available at the right time.

Snake venoms are also making a positive contribution to human health as a source of new drugs. Captopril, developed from the venom of a lancehead viper, is one of the most widely used medications for high blood pressure. A promising new drug from the venom of the Gila monster, marketed as Byetta, may soon start stabilising the blood sugar of people with diabetes. Researchers at the University of South Australia, Adelaide, and elsewhere are researching the venom of a number of deadly Australian snakes which appears to stunt the growth of tumours by disrupting their blood supply.

In addition to 450 elapids, vipers and atractaspidids, there are over 2000 colubrids, accounting for over half the snake species on the planet. Fry estimates that well over 2000 species are venomous, and if he's right that's a lot of potential new molecules that could work as drugs.

The Stephen's banded snake that bit Fry early in his PhD turned out to immobilise its prey using a hormone that is almost identical to one that is used in the human body to regulate blood pressure. Fry recently patented the venom component that does this in both Stephen's banded snake and the inland taipan and hopes it will one day be used to treat patients with congestive heart failure. There may be many more potential drugs waiting in the wings.

Despite Fry's success, don't expect a mad rush of scientists to join him in the field. "It's a dangerous job," says Kreitman. "Fry is truly a modern adventurer, one of a bunch of guys who think it's great to travel to the most remote places in the world and risk death." ●

Michael Tennesen is a science writer based in Lomita, California