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Toxic Treasure

Poisons and venoms from deadly animals could become tomorrow's miracle drugs. And few places on Earth harbor so many deadly animals as Australia's Great Barrier Reef.

By Robert George Sprackland

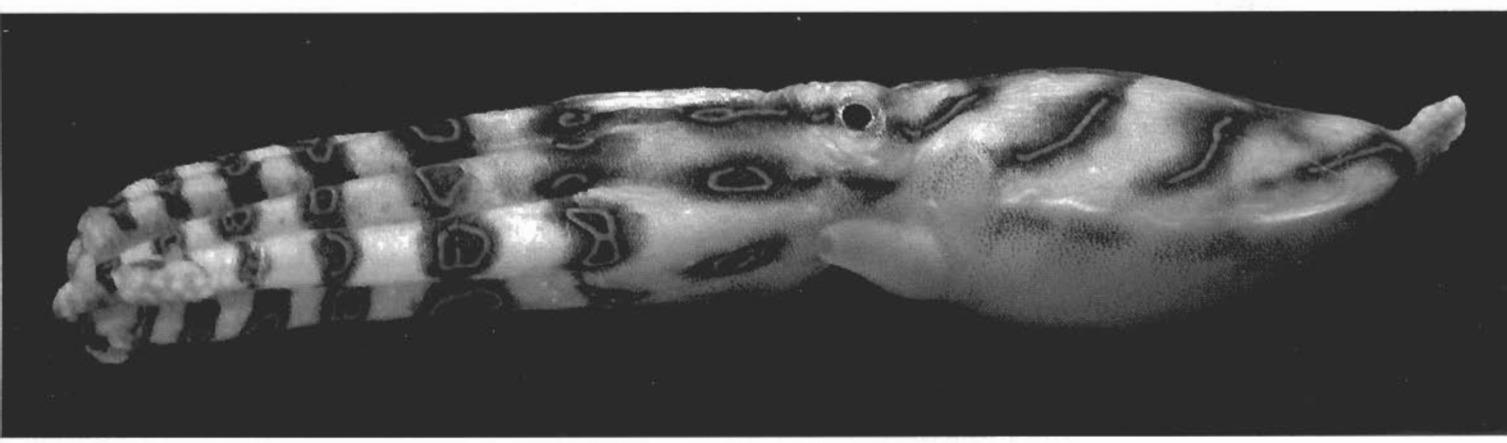
[Australia] has more things that will kill you than anywhere else. . . . This is a country where even the fluffiest of caterpillars can lay you out with a toxic nip, where seashells will not just sting you but actually sometimes go for you. . . . It's a tough place.
—*Bill Bryson,* In a Sunburned Country

Raised, as you probably were, on film or video footage of drowsy koalas hugging eucalyptus trees, or kangaroos bouncing happily around the outback, you might wonder just what country Bryson is talking about. But consider the unassuming cone shell—just the kind of malicious mollusk that will "actually sometimes *go* for you."

The cone shell is a marine snail that lives in tropical regions worldwide, including the waters around northeastern Australia's Great Barrier Reef. The snail aggressively reaches out to sting prey or would-be predators, injecting toxins that are among the most powerful in the animal kingdom. Even a diminutive member of the genus *Conus* can carry enough venom to kill a dozen people; a single careless encounter can bring death in less than thirty minutes. What's more, the radula, a harpoonlike stinger that delivers the venom, can strike with enough speed and force to pierce a diver's wetsuit. There is almost no pain associated with a cone-shell sting, because the venom contains a strong analgesic. That's the good news. The bad news is that the toxin is a nerve agent for which there is no known antidote.

Why would anyone intentionally seek out a creature whose venom packs such a wallop? Answering that question goes a long way toward explaining why Australians, whose continent is well known for its gold and opals, have begun studying their richly varied animal populations with renewed interest. Latter-day prospectors on the continent are searching for biologically active chemicals throughout Australia's biting, stinging, venomous fauna. Those chemicals and their derivatives could turn out to be both a pharmaceutical bonanza and the foundation of a multimillion-dollar industry.

In Brisbane, for instance, laboratory workers at a six-year-old biotechnology company called Xenome



Blue-lined octopus (Hapalochlaena fasciata), *photographed at night, shows its displeasure at being disturbed by flashing a vivid array of iridescent indigo rings and lines along its mantle and arms. In spite of its diminutive size (adults typically measure only six inches long), the octopus can be a nasty meal for predators: it defends itself with a potent nerve agent, tetrodotoxin. It deploys a second kind of toxin—much less potent than the first—while hunting the crabs on which it feeds.*

Spotted porcupine fish (Diodon hystrix) *is considered poisonous but not venomous: it does not bite or sting, but it is highly toxic if consumed. Like its puffer-fish cousins of the genus* Fugu, *which are prized (and feared) by Japanese gastronomes, the porcupine fish is toxic not by nature but by nourishment. As it feeds, it ingests bacteria that contain tetrodotoxin, which accumulates in the fish's liver and other organs.*

Ltd have the unenviable task of "milking" cone shells. The job is not an easy one. Because the snail can bend its proboscis to sting from virtually any angle, there is no safe way to hold a live cone shell. To get the venom, the technicians dangle a small fish from forceps for the snail to sting. The snail's venom kills the fish, but it can then be safely extracted from the fish's tissue. In spite of that roundabout—and costly—procedure, Xenome's efforts have been worthwhile. The company is developing a drug based on cone-shell toxin for treating severe long-term pain. Its effects are similar to those of morphine, but because of its potency, effective doses are smaller, and so far at least, it seems not to be addictive.

Xenome's work is an outgrowth of a major bioprospecting project in Australia, initiated in 2003 by Peter Beattie, the premier of Queensland, and his government. Known as the Queensland Bioscience Precinct, the project aims to encourage the discovery of new biochemicals that might spawn major pharmaceutical products. What sets apart the Queensland bioexplorers is that they focus on molecules derived from animals, instead of from plants. At least 25 percent of the medicines currently avail-

Geography cone shell, Conus geographus, *is one of some 300 species of cone shells that occur in the waters off Australia—all of them with a ready answer to the biblical query, "O death, where is thy sting?" The probelike structure extending to the right is a siphon, used to detect prey. The cone shell also has a flexible proboscis, inside which is a harpoonlike barb called a radula that can pierce a diver's wet suit. A single untreated jab can kill an adult human in thirty minutes.*

able come from plant products, but relatively few animals so far have been assessed for medically useful chemicals. Thus, animal bioexplorers are entering largely uncharted territory, and the odds are good, they believe, that a mother lode is still out there, waiting to be discovered.

Animals, like plants, have long been known as a source of a vast array of chemicals, many of the with great potential for human use. Many frogs, for instance, secrete compounds through their skin that have powerful antibiotic properties, enabling them to thrive in stagnant water teeming with pathogens. Clown fish—immortalized in the 2003 movie *Finding Nemo*—wear a coat of slime that informs the anemones with which they live that clown fish is *not* on the anemone menu. Corals exude chemicals that protect them from sunburn at low tide; derivatives of those chemicals are already being marketed as sunscreens. Even compounds from sponges have led to valuable drugs: acyclovir, a treatment for herpes, and cytarabine, for a kind of leukemia.

In some cone shells, the venom needed to kill a dozen adult humans would fit on the head of a pin.

The chief attraction of animal biomolecules, particularly the toxins, is their staggering potency: they are often hundreds of times more powerful than plant compounds that deliver a similar medicinal effect. For example, the analgesic alkaloid epibatidine, derived from South American dart-poison frogs, is about 200 times more powerful than an equal amount of morphine, derived from poppy flowers.

But why seek potency for its own sake? Why not play it safe, and simply use more of some less potent agent? After all, it goes without saying that the more powerful the toxin, the less of it is needed to achieve its effect, and so the greater the risk of an overdose.

The answer lies in the highly specific way that the most potent animal toxins attack certain kinds of cells or cellular processes. That very specificity of chemical action is often a highly prized medicinal property. It enables a drug to attack the site of a disease—a highly localized cancer, for instance—without crippling side effects. A precisely targeted drug can also act as a carrier for some other drug, bringing the second agent to the part of the body where it can do the most good. Hence, investigators reason, pharmaceuticals derived from modified but potent toxins may prove useful in targeting drug treatments.

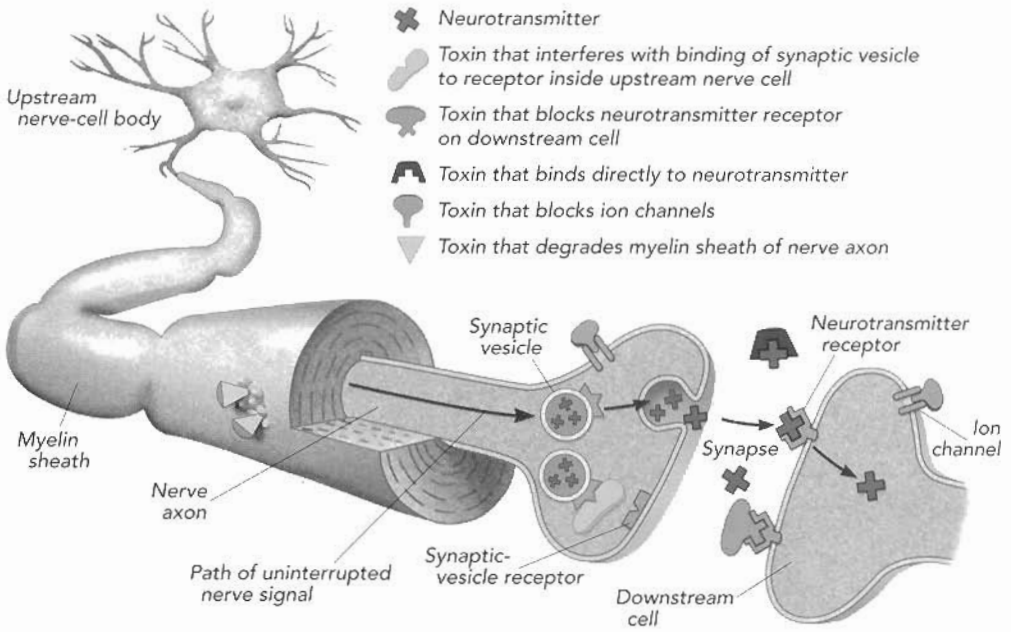
Many animal toxins, for instance, have evolved that exploit the vulnerability of nerve cells. That makes sense—from the point of view of the attacker—partly because nerve cells, in most cases, cannot be replaced or even repaired. But nerve cells have two other liabilities that make them particularly vulnerable to even small-scale structural problems. First, they can be shut down by minor interference with any one of several critical components [*see illustration on opposite page*]. For example, a toxin could block neurotransmitter sites either upstream or downstream from the synapse between two nerve cells, making it impossible for a nerve impulse to travel across the synaptic gap. A toxin could bind to the neurotransmitter molecules themselves, rendering them useless. Or a toxin could block the channels that enable sodium and potassium to pass through the nerve-cell membrane, and thereby halt a neuroelectrical impulse along the length of each nerve cell. Finally, a toxin could degrade the myelin sheaths that insulate the axons of a nerve cell, causing the nerve impulses to lose strength and dissipate.

The second liability, related to the first, arises simply because part of each nerve pathway is usually made of a single strand of nerve cells in sequence, like the links in a chain. If any single nerve cell is shut down, the entire pathway is neutralized. That's why the system is so readily sabotaged by minute doses of highly target-specific animal neurotoxins. In some cone shells, for instance, the venom needed to kill those

dozen adult humans would fit on the head of a pin.

Because a given toxin may target only a specific section of a particular kind of nerve cell—say, the myelin sheath of cardiac nerve cells—bioexplorers have to screen many toxins to identify which ones attack which targets. Suppose, for instance, screening leads to the identification of a toxin that attacks myelin. That toxin then becomes a key factor in a strategy for repairing some of the damage caused by myelin-degenerative disorders, such as multiple sclerosis.

One way to use the toxin might be to modify or remove just its toxic part, while leaving the myelin-seeking part intact. Then, in place of the toxic part, the bioexplorer might substitute a therapeutic chemical agent, which could restore or mimic the function of myelin. Because the newly engineered drug would be so target-specific, virtually all of it could act only within the nerve cell's axonal region, making it an efficient fix in small doses. Similarly, other drugs might be designed to retard or alleviate the symptoms of diseases such as Alzheimer's and Parkinson's.



Nerve cells can be attacked by animal toxins in any of several ways, as shown in the schematic diagram. Nerve signals depend on the opening and closing of ion channels along the nerve axon, and on a mechanism that enables neurotransmitter molecules to cross the synapse, or gap between upstream and downstream cells. Interference with any one of the mechanisms can cut off an entire signaling pathway.

If animal toxins, and their therapeutic potential, are such underexplored pharmaceutical territory, why do so many bioexplorers converge on Australia? Things that sting and bite, after all, occur around the world. The answer is as straightforward as the whereabouts of a gold rush: you go where the yield is most likely to be high. Not only do countless venomous animals live Down Under, but some, such as certain species of cone shells, may also produce toxins with a lengthy list of ingredients. (By contrast, the venom of a typical highly venomous snake may include only a handful of chemical components.) Bill Bryson was exaggerating only slightly when he claimed to have looked up a particular animal in the fictitious "*Things That Will Kill You Horridly in Australia,* volume 19."

Part of the scientific recognition that Australia is such a rich potential source of new animal toxins can be traced to the work, in the 1950s, of Hugo Flecker, a naturalist and physician living in Cairns, Queensland. Ever since records began to be kept, occasional deaths had been reported just off the northern beaches of Queensland. In Flecker's day, the cause of the deaths was still a mystery, but he suspected that they were the work of a jellyfish.

In January 1955, a young boy was fatally stung in the shallow Queensland surf. The local police, acting on Flecker's hunch, set nets to capture the killer. What they caught in the nets were jellyfish, which they turned over to Flecker. Flecker, in turn, sent the specimens to Ronald V. Southcott, another naturalist-physician, who determined that the animal was, indeed, a species of jellyfish previously unknown to science. He named it *Chironex fleckeri*, after Flecker—and so introduced science to the sea wasp.

The sea wasp was dramatic proof that there were still dangerous unknown creatures to be discovered and studied. Since Flecker's time many other toxic marine organisms have been described, and their study has been conducted in a more systematic way. A great many of those animals, as it happens, live in and around Queensland.

Generally speaking, some of the most fertile grounds for bioexploration are tropical reef communities. Such reefs harbor a phyla-spanning host of organisms that produce powerful toxins. So it is no surprise that Queensland, whose coastline includes the entire Great Barrier Reef, is home to the widest array of toxic creatures in Australia. Some 300 species of cone shells live in and around the reef, each with a venom that may

Worker "milks" the venom from an olive sea snake, Aipysurus laevis, *captured along the Great Barrier Reef. Australia is home to all ten of the world's deadliest sea snakes, and the olive sea snake—which can grow to more than six feet long—is among the commonest of them.*

include as many as a hundred distinct chemicals—yielding perhaps several thousand biochemically interesting compounds. Also among the well-armed sea fauna of Queensland are all ten of the most dangerous sea snakes in the world. Many other Queensland creatures—including various species of fishes and mollusks—hold the distinction of being the most venomous of their kind. Among the jellyfish, Flecker's sea wasp, also known as "the stinger," is arguably the most dangerously venomous animal on the planet [*see "One Touch of Venom," by Jamie Seymour, September 2002*].

The diversity of wildlife in Queensland is hardly limited to sea creatures. In the rainforest of the tropical north, more species of flowering plants are thought to occur within a few typical acres than are found in all of North America. Among the land fauna are nine of the ten most venomous land snakes in the world. And new species from northern Queensland are still being discovered and formally described every year; many more are still unknown to science. There is plenty in Queensland to keep bioexplorers busy for a long time.

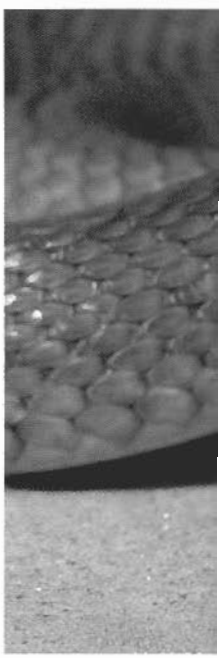
In those circumstances, bioexplorers are well advised to seek the help of seasoned systematists—taxonomists with a solid grounding in the evolution and natural history of organisms. For one thing, the chemicals that a species produces by itself must be distinguished from the ones it gets from its diet or its environment. And if the target animal isn't ingesting the right bacteria or other toxin producers at the right time, bioexplorers may not be able to extract the chemicals they want.

Some toxin carriers, for instance, including sea slugs and puffer fish, feed on toxic species only seasonally. Bioexplorers once noted, to their dismay, that long-term-captive and captive-bred dart-poison frogs produced less potent poisons than their wild counterparts—or even no poisons at all. Systematists were able to resolve the puzzle. Many precursor chemicals for the poisons come from specific prey insects. Deprived of their natural prey, most of the frog species became harmless.

Systematists can also save both time and money once a particular species has been identified as a source of a particular biomolecule. It is then well worth determining whether a close relative of the species might produce an even more useful version of the molecule. But related species—particularly the ones belonging to the so-called lower taxa—may be hard or impossible to pinpoint without the knowledge of a qualified systematist.

Ranging even more widely through the tree of life, systematists might also help show the way to multiple, alternative sources of a specific biomolecule. Tetrodotoxin, also known as TTX, is a powerful nerve agent, first identified in the tissues of certain puffer fish of the family Tetraodontidae. In Japan the fish is best known for those puffers belonging to the genus *Fugu*, an expensive, high-thrill delicacy, which is served after the poisonous bits have been skillfully carved away—or so the diner hopes—by specially licensed chefs. (Alas, there are some 50 to 150 accidents each year, in which the *Fugu* feast becomes a last meal.)

After tetrodotoxin was identified in



Coastal taipan (Oxyuranus scutellatus) *is reputed to be the third-most-venomous land snake in the world. Yet because of its large fangs, size (some grow longer than nine feet), and nervous disposition, the coastal species is considered more dangerous than its inland relative,* O. microlepidotus, *even though the venom of the inland taipan is the more potent.*

puffers, it started turning up in a variety of places around the globe. In 1982 the ethnobotanist and independent scholar Wade Davis announced that TTX is a major component of the voodoo elixir that turns people into zombies. (A person in a zombie state cannot move, but is fully conscious of everything around him.) TTX was later identified in the skin secretions of the American rough-skinned newt (genus *Taricha*), an amphibian often kept as a pet, and in the venom of Australia's tiny blue-ringed and blue-lined octopuses (genus *Hapalochlaena*). Perhaps most remarkably, it also turned up in the feathers of two genera of birds, *Pitohui* and *Ifrita,* in New Guinea. The source of the toxin turned out to be bacterial. Such microorganisms readily disperse across great distances and throughout a variety of habitats. Thanks to studies by systematists, bioexplorers no longer need to find a particular species of puffer fish in order to obtain TTX.

The question remains, however, whether expertise in taxonomy and biological systematics will be available for the long term. Amid proliferating budget cuts and under increasing pressure to produce "employable" graduates in applied sciences, Australian universities, like many universities elsewhere, have cut back on numerous subjects in the basic sciences. The University of New England in New South Wales is now the only university in eastern Australia to offer courses specifically in biological systematics.

Fortunately, government and commercial interests are stepping into the breach. At the heart of Peter Beattie's Queensland Bioscience Precinct is a partnership between the Institute for Molecular Bioscience, at the University of Queensland, and the Commonwealth Science and Industrial Research Organization. The program has already received $12 million (in U.S. dollars) for the design and construction of a research facility, as well as a ten-year, $60-million commitment for operating funds from the Queensland government. A second project is the Natural Product Discovery Programme, operated in Brisbane by Griffith University, which has received more than $75 million from the London-based pharmaceutical company AstraZeneca.

Such projects have attracted numerous experts in biochemical and pharmaceutical research and development, who are building an industry close to where the raw biomolecules occur in nature. Perhaps some future, revised edition of Bryson's book will mention a very different reference work, something called *Things That Will Save Your Life Derived from Australian Creatures That Can Kill You Horridly.* □

SPECIES	LETHAL DOSE
Anthrax toxin	*0.0002*
Geographic cone shell	*0.004*
Tetrodotoxin in:	
Blue-ringed octopus (venom)	*0.008*
Puffer fish (poison)	*0.008*
Inland taipan snake	*0.025*
Eastern brown snake	*0.036*
Dubois's sea snake	*0.044*
Coastal taipan snake	*0.105*
Beaked sea snake	*0.113*
Western tiger snake	*0.194*
Mainland tiger snake	*0.214*
Common death adder	*0.500*

Various animal toxins are listed by potency (anthrax-toxin potency is shown for comparison). The lethal dose is the so-called LD_{50}, the dose that kills 50 percent of the animals tested with the toxin, in units of milligrams of toxin per kilogram of the victim's body weight.