The past 18 months were very good ones for hypnotists, yoga teachers and acupuncturists. For many chronic pain sufferers, promises of relief from various forms of alternative medicine seemed like rational options amid the unending stream of negative reports about Vioxx, Celebrex, Aleve and Rush Limbaugh’s addiction to painkillers.

Not all was lost for patients who prefer medicine to meditation. With little fanfare, the Food and Drug Administration approved in late December two new drugs intended to treat a form of pain that often proves resistant to anti-inflammatories and opiates—the two predominant classes of pharmaceuticals for analgesia. Medical specialists welcomed their arrival. “It’s an embarrassment that we’re treating pain with opiates and aspirinlike compounds,” notes Edwin McCleskey of the Oregon Health and Sciences University. “Opiates are more than 2,000 years old, and aspirin is nearly 200 years old.”
CONE SNAIL injects venom into prey using its harpoon-tipped proboscis, as it is offered a meal in a laboratory at the University of Utah.
Intractable pain often gets addressed with drugs first approved for other conditions. Pfizer’s Lyrica (pregabalin) received FDA endorsement on December 31 for neuropathic pain caused by nerve damage resulting from diabetes and shingles. Anticonvulsants, a class that includes Lyrica, have been used for palliation, sometimes without regulatory approval. Last year Pfizer agreed to pay $430 million in criminal and civil penalties because its Warner-Lambert division had illegally promoted an epilepsy drug, Neurontin, for neuropathic pain and other unapproved uses before it was acquired by Pfizer in 2000.

The other such analgesic that the FDA approved in December has none of Lyrica’s blockbuster potential. Prialt (ziconotide) from Elan requires that a pump be implanted or used externally to send the drug by catheter into the spinal fluid, a technology often reserved to deliver morphine to critically ill AIDS and cancer patients. Prialt may not dazzle Wall Street, but from the perspective of neuroscientists and pharmacologists, it is by far the more interesting of the two compounds. “It could be argued that this is the first drug for pain that went from animal tests into patients, rather than going from a patient using it for something else back into animals to get validated for pain,” remarks Allan I. Basbaum, a professor of anatomy at the University of California at San Francisco. “It’s a proof of principle that there really are new drug targets worth going after.”

Prialt, a synthetic copy of a toxin from the Magician’s cone snail, Conus magus, a mollusk from the Indo-Pacific region, is also one of the first pharmaceuticals that demonstrates the promise that marine life, particularly invertebrates, holds for drug developers.

The route to Prialt began in the early 1970s, when Baldomero Olivera, who had recently completed postdoctoral work at Stanford University, returned to his native Philippines to set up a laboratory. At Stanford, Olivera had helped isolate and purify DNA ligase, the enzyme that joins pieces of DNA. He wanted to continue his research on the enzyme in the Philippines but was unable to procure the necessary equipment. A shell collector, he wondered whether poisonous cone snails might contain molecules that could block nerve channels—and that could be used by neuroscientists in the same way the toxins from puffer fish or a Taiwanese snake are. “I got started without any grand vision,” Olivera recalls. “I was mainly looking for a project to work on productively.”

Eventually he made his way to a teaching position at the University of Utah and planned to sideline studies on snail toxins in favor of his previous work on DNA. In 1978, a few years after Olivera’s return, Craig Clark, a 19-year-old undergraduate working in his lab, showed an interest in the snail toxins. Clark wanted to test what would happen if just one or a few of the 100 or so peptides that make up the venom of a highly lethal cone snail, C. geographus, were injected directly into the brains of mice instead of into their abdomens, the protocol for earlier experiments. Olivera was not optimistic but let Clark proceed. To everyone’s astonishment, the pep-
tides elicited a variety of behaviors. One peptide made a mouse sleep; another made it shake. Still another induced scratching.

A growing recognition of the diversity of cone snails and cone snail toxins—at least 50,000 peptides produced by 500 species (compare that with the 10,000 alkaloids identified in all plants)—prompted Olivera to abandon the DNA work. He then devoted himself to pursuing where this evolutionary variation came from in a comparatively short 50 million years. He was also trying to understand how ion channels function in the nervous system and how these toxins might be deployed in neuroscientific studies and drug development. “The snails are nature’s neuropharmacists,” he observes.

In Search of Venom

The publications from Olivera’s group intrigued George Miljanich, a biochemist at the University of Southern California who was studying the transmission of neural signals across synapses, the contact points between neurons. Miljanich was involved in helping to identify and classify different types of calcium channels that convey chemical signals to cells in the nervous system. He had received a grant from the National Institutes of Health to try to develop cone snail toxins as probes to determine the function of different molecular pathways. His inability to get more than a drop of the precious venom, procured only after painstakingly milking a snail in Olivera’s lab, made a job offer in 1988 from a start-up company especially enticing. The company, Neurex, which was formed in 1986 by two Stanford professors with the goal of melding biotechnology and neuroscience, had also hired top-notch peptide chemists from U.C.S.F., where Miljanich had worked while a postdoctoral student.

Miljanich persuaded colleagues in Neurex’s research department to undertake the difficult task of synthesizing omega-conopeptides—toxins that block certain calcium channels. The channels normally respond to a change in voltage across a cell membrane by allowing an influx of calcium ions, thereby facilitating transmission of a chemical signal across the synapse between nerve cells. Some omega-conopeptides come from C. magus, which is toxic to fish but not to humans. Originally skeptical about Miljanich’s project, the Neurex management lost its reticence when its earlier, unfocused goal of isolating medicinally useful peptides from cow brains hit a dead end. Within a short time, Neurex was able to manufacture synthetic omega-conopeptides in gram quantities.

By then, Miljanich had made a list of possible uses of drugs that might be developed from one especially interesting conopeptide, first isolated by Olivera’s laboratory. Analgesia was not first on the list but moved up fast. Though promising in test-tube studies as a possible epilepsy treatment, the favored omega-conotoxin, dubbed SNX-111 (and later Prialt/zi-conotide), proved an utter flop when tested in mice. It actually induced shaking. The next item on the list called for administration of the drug intravenously to protect brain cells against the damage that occurs from lack of oxygen during stroke or head trauma. The company began the first phase of a neuroprotection clinical trial in 1993, but the FDA shut down the study temporarily when SNX-111 caused blood pressure to drop.

Getting desperate as it burned through cash, Neurex started preparing a clinical trial of SNX-111 for severe pain. The company’s scientists had postulated that the compound might

<table>
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<tr>
<td>Cognetix</td>
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<tr>
<td>Elan</td>
<td>Prialt [ziconotide]</td>
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<td>Metabolic Pharmaceuticals</td>
<td>ACV1, for neuropathic pain and for accelerating recovery of injured neurons</td>
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<tr>
<td>Xenome</td>
<td>Xen 2174, for diminishing chronic pain</td>
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</tr>
<tr>
<td></td>
<td>TIA, for benign prostatic hyperplasia and for neurodegenerative and cardiovascular disorders</td>
<td>Has yet to enter human trials</td>
<td>Alpha-1-adrenergic receptor</td>
<td>C. tulipa (fish eater)</td>
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Phase I clinical trials are designed to assess the safety and tolerability of a drug and its effects in the body. Phase II trials examine drug effectiveness and safety.
serve as an analgesic because of new findings showing that one way morphine works is by shutting down indirectly the activity of a specific subtype (the N-type) of calcium channel. Radiolabel and electrophysiological testing of SNX-111 demonstrated that it binds selectively to the N-type calcium channel. This obstructing action prevents the channel from opening and allowing an influx of calcium ions. The ions precipitate transmission of a stimulus across the synapse into the spinal cord and then into the brain, where it is perceived as pain. “This was the smoking gun that allowed us to move forward,” Miljanich comments. Subsequent animal tests indicated that the drug candidate exerted its effects with a thousandth the dose of opiates and without creating tolerance or addiction.

Nature’s Gift

In 1995 Neurex started a clinical trial of SNX-111 for patients with severe pain who had not been aided by intrathecally delivered opiates—those channeled by catheter from an implanted pump into the spinal fluid. The same pump delivered the synthetic snail peptide to select patients, restricted by the FDA to only those who were terminally ill, because of the previous side effects in the earlier trial. Following years of fiddling with the peptide’s amino acid sequence, the drug that patients received in both clinical trials was the precise synthetic copy of the peptide found in the snail. “After testing hundreds of analogues, we came back to what nature gave us,” Miljanich remarks.

Once the pain trial began, it became clear very quickly that the dosing regimen was wrong. Some patients encountered severe adverse side effects, ranging from a lack of coordination and allowing an inrush of calcium ions. The ions precipitate transmission of a stimulus across the synapse into the spinal cord and then into the brain, where it is perceived as pain. “This was the smoking gun that allowed us to move forward,” Miljanich comments. Subsequent animal tests indicated that the drug candidate exerted its effects with a thousandth the dose of opiates and without creating tolerance or addiction.

In 1998 drugmaker Elan initiated a takeover, and Neurex quickly embraced the bid. Even though the results of two late-stage clinical trials demonstrated that SNX-111 provided significantly more pain relief than a placebo, Neurex officials knew that the FDA would probably ask it for another clinical trial before approval because of the drug’s history of side effects. A Neurex late-stage study to protect brain cells from trauma had been put on hold until 2000 because of unimpressive results from earlier studies. An unrelated hypertension drug that Neurex had licensed to bring in some revenue might not have been enough to tide the struggling firm over until it received approvals for its two principal drugs.

SNX-111, now Prialt, went through another successful
Genes for cone snail toxins may be the fastest-evolving on earth. Their diversity constitutes

A POTENTIAL PHARMACOLOGICAL GOLD MINE.

have failed,” says Michael Leong, a physician who has supervised clinical trials of the drug and also served as a paid consultant to Elan.

Prialt is most likely Elan’s last venture into snail peptides. The company did not preserve its capability, inherited from Neurex, to research cone snail toxins. Yet cone snails may still have much to offer as nature’s combinatorial chemists. An article by two Harvard University biologists that appeared in 1999 in the *Proceedings of the National Academy of Sciences USA* found that two species of cone snails have toxin genes that could be the fastest-evolving on earth, an adaptation to changing prey that inhabit tropical reef ecosystems.

A few companies are planning to exploit these riches. Olivera, a father of the field, is a founder of Cognetix in Salt Lake City. Two Australian biotech outfits—Xenome and Metabolic Pharmaceuticals—have begun development or actual trials on snail peptide–based drugs, primarily for chronic pain. In some cases, Prialt and other peptide drugs in the works may be overtaken by development efforts that use small organic molecules, delivered orally, to target calcium and other ion channels.

Still, even small-molecule designers may use the snail peptides as a starting point for formulating new drugs. As appreciation grows for cone snails’ chemical creativity, their home countries may become more proprietary about these genetic gold mines. Philippine newspapers have at times raised the specter of biopiracy. And a 2003 letter to *Science* written by researchers from Harvard Medical School, York University and the University of Chicago Pritzker School of Medicine decried the danger to cone snails and their habitats from collectors, coastal development, pollution and climate change, among other causes. The letter estimated that hundreds of thousands of the animals may be processed yearly by U.S. researchers, although a response to the letter calculated that on average not more than 5,000 cone snails a year need to be sacrificed to extract toxins that are analyzed and then synthesized. One laboratory even maintains a cone farm, enabling the milking of the mollusks without killing them.

Bioweapons may be as much of a worry as biopiracy. Since September 11, 2001, scientists engaged in cone snail research have found that rules for working with the toxins have grown much harsher, even though some venoms do not harm humans. “We’re always terrified that we’re breaking rules that we don’t know about,” Olivera says. Some caution may be warranted. The small size of the peptides, which makes them easy to synthesize, has at times held an allure for manufacturers of biological weapons. Before President Boris Yeltsin ordered the shutting down of Russia’s bioweapons program in 1992, investigators there were trying to insert the gene for a lethal *C. geographus* peptide into the genome of the smallpox virus, which would have delivered a devastating double punch to victims. The Russian team failed in fashioning this bizarre smallpox-conotoxin hybrid, which could have approached 100 percent lethality. Chillingly, they probably just ran out of time. “The problems could have been solved,” says Serguei Popov, a former top bioweapons researcher who is now a biology professor at George Mason University.

The tale of the cone snail, a lowly mollusk that has ascended toward the top of the marine food chain, will continue to fascinate. In 1998, under the pen name of Paul Adirex, a prominent Thai politician wrote a book, *The King Kong Effect*, about a plot to assassinate an American president using cone snail venom. Biologists have no need to resort to fantasy. The 50,000-plus cone snail peptides will keep them pondering this evolutionary wonder for decades to come.

MORE TO EXPLORE


A prodigious resource for all things cone snail, maintained by Bruce Livett, professor of biochemistry and molecular biology at the University of Melbourne, can be found at the *Cone Shells and Conotoxins* site: http://grimwade.biochem.unimelb.edu.au/cone/index1.html