signals, and other complex types. All previous searches required that the signal be a simple, continuous wave.

Just when, if ever, NASA will be able to turn on this electronic marvel remains to be seen. SETI researchers hope it is soon. Any extended delay would not only make their electronics designs obsolescent, but it would also exacerbate problems of radio frequency interference from terrestrial sources. Michael Klein, a SETI manager at the Jet Propulsion Laboratory, estimates that the allocation of microwave frequency bands to everything from spacecraft telemetry to cellular phones is doubling every decade.

But the battering SETI received in the House doesn't bode well. NASA had asked for $12 million in 1991, triple the expenditure on SETI this year. Much of the increase would allow NASA to begin building the multichannel spectrum analyzer, which the agency is hoping to turn on in 1992—the 500th anniversary of Columbus's discovery of the New World. But even before the bill got to the House floor, the appropriations committee had halved the request; Machtley's amendment excised the rest.

SETI supporters are now working in the Senate in the hope that it will take substantial SETI funding to a House-Senate conference. But NASA must still get its budget through the Senate appropriations subcommittee chaired by Barbara Mikulski (D–MD). She is already "outraged," in her words, that NASA blew the focusing of the Hubble Space Telescope.

Then again, SETI researchers have survived other funding crises. In 1982, then Senator William Proxmire was instrumental in eliminating funding altogether, but intense lobbying by SETI proponents won the restoration of funds the next year. SETI enthusiasts believe they must prevail again. "I would bet my house on interstellar communication," says Klein of JPL, "but I can't tell you when. The only way to distinguish between science fact and science fantasy is to do experiments." ■ RICHARD A. KERR

Science Digests the Secrets of Voracious Killer Snails

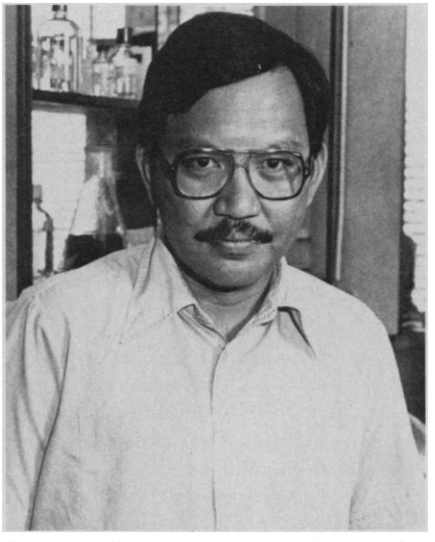
The cone snails have evolved a remarkable array of toxins that bring them dinner—and offer neuroscientists a bag of new tools

YOU'RE A SNAIL. You're hungry. And the only food around is a fast-moving fish. You could starve. Or you could fire off some potent nerve toxins to stop your dinner dead in its tracks.

That's a solution the cone snails have perfected. This genus of unlikely predators includes species that specialize in killing and eating fish, and others that prey exclusively on mollusks or worms. To be effective hunters, these snails—which live on tropical coral reefs—have evolved deadly and unique brews of nerve toxins that paralyze prey before it can escape.

The venoms are valuable not only to the snails but also to neuroscientists. Researchers find them a rich source of new, exquisitely precise chemical probes for dissecting and manipulating the protein channels that allow ions to pass into and out of nerve and muscle cells.

The general approach of using natural toxins to study ion channels is time-honored. For decades, toxins from sources as diverse as marine dinoflagellates and venomous snakes have been used to block or alter the function of specific ion channels (or neurotransmitter receptors, many of which are just neurotransmitter-activated ion channels), to help define their roles in normal nerve or muscle function. Labeled toxins can be used to find the pattern of distribution of their targets, and in some cases toxin binding has provided an assay by which the target proteins could be purified.



Cone snail cognoscento. *Baldomero Olivera of the University of Utah.*

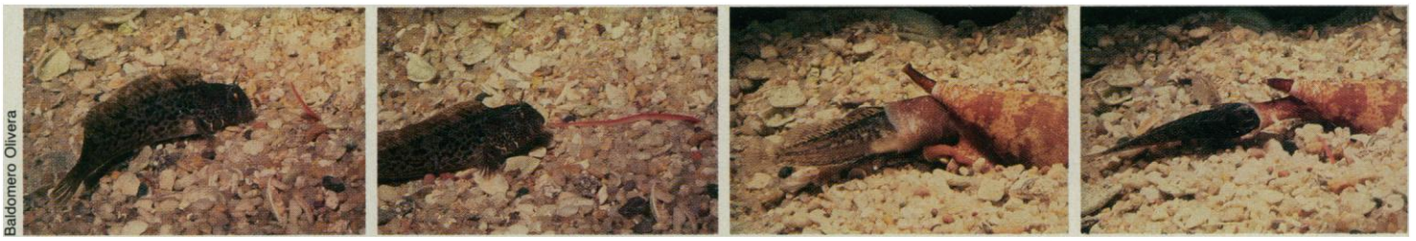
But while such approaches have been fruitful for studying some ion channels and neurotransmitter receptors, the demand for new toxins is ever increasing as researchers discover new receptors and channels at a rate that has outpaced the availability of toxins to distinguish among them. There may be as many as eight different types of calcium channel, for example, and neuroscientists are eager for new and more specific toxins to help tell them apart.

That's where cone snails come in. Their venoms represent "the biggest recent gold mine" of new and potentially useful toxins according to Stanford ion channel researcher Richard Aldrich. And since there are more than 500 species of cone snails, only a few of which have been investigated, the surface has just been scratched. Already the snails have yielded an important toxin for distinguishing among calcium channels, and those close to the field expect that more exciting finds will follow.

In spite of their value, this obscure family of snails might have been overlooked altogether had it not been for an enterprising scientist working in a developing country, without even a centrifuge in his lab. But what that scientist—Baldomero Olivera—did have was a unique background that enabled him to recognize the value of the cone snails. During his youth in the Philippines, Olivera had been fascinated with the beautiful, deadly snails (some of which have been known to kill humans). In his college studies, and his further training in the United States, another piece of the puzzle fell into place, as Olivera learned of the contribution natural toxins had made to understanding ion channels.

But it wasn't until returning to the Philippines that these pieces came together in a research project. After receiving a Ph.D. in chemistry from California Institute of Technology and doing a postdoc in biochemistry at Stanford, Olivera went home in 1970 to accept a position as assistant professor at the University of the Philippines. "I ended up in a lab that had essentially no equipment," he recalls. "No ultracentrifuge, no scintillation counters, no cold room. It was fairly clear that we wouldn't be competitive in any kind of molecular biology. So we decided to look for a research project for which there would be some local advantages." Cone snails seemed like a good bet.

Olivera (now at the University of Utah) says he initially had modest expectations for the cone snail toxins, which he dubbed conotoxins. He expected, he says, to find a single toxic component in the venom and



What's for dinner? *In this series of photographs, a cone snail extends a proboscis that looks edible, which tempts a fish. The fish nibbles the "meal" and is immediately stung, paralyzed, and engulfed by the cone snail.*

hoped its characterization would provide an easy project to get his lab off the ground. What he found instead was a far more complex picture, which he reviews in an article on page 257 of this issue of *Science*.

Part of that complexity stems from the fact that each of the handful of cone snail species studied so far has its own unique concoction of a dozen or more small, toxic peptides, each 10 to 30 amino acids in length. Some are specific inhibitors of the acetylcholine receptors responsible for muscle contraction. Others block channels regulating the flow of potassium, sodium, or calcium ions across the membranes of nerve or muscle cells. One type of toxin binds to a class of glutamate receptors called NMDA receptors, which are triggered by glutamate or its analog *N*-methyl-D-aspartate to allow calcium ions to flow into nerve cells. Other conotoxins cause behavioral changes in mice or other animals—such as aggressiveness, convulsions, or incessant scratching—but their biochemical targets have not been identified.

Olivera believes the great diversity and specificity of toxins in the venoms of the cone snails are due to the intense evolutionary pressure on the snails to stop their prey quickly, since they can't chase it down. To this end, the snails have evolved batteries of small, rapidly diffusing poisons, targeted to multiple subclasses of ion channels whose simultaneous inactivation will be sure to paralyze their prey swiftly.

In addition to the paralytic peptides, individual cone snail species have also developed some toxins apparently specialized for particular means of trapping prey. The King Kong peptide, for example, comes from a species of cone snail that preys on other snails. The King Kong molecule got its name from the bizarre aggressive behavior it triggers when injected into lobsters. In snails, however, it causes a convulsive movement into and out of the shell. Since injured snails normally retreat into their shells, Olivera hypothesizes that the function of the King Kong peptide is to cause a harpooned snail to come out of its shell so the cone snail can gobble it up. The channel or receptor that the King Kong peptide acts on is not yet known.

Cone snails that prey on fish have also evolved some remarkable toxins to complement their hunting strategies. One species, which engulfs the fish before stinging it, makes a venom component that seems to serve as a local anesthetic, keeping the fish from sensing the sting and thrashing wildly in a way that could injure the snail. This family of peptides is called the "conantokins"—after the Filipino word "antokin," or "sleepy"—because they put mice to sleep. The conantokins turned out to be specific for NMDA receptors, which play a role in the sensory systems of fish.

Other fish-hunters entice their prey by extending a tasty-looking proboscis. When a fish is attracted to the "tender morsel," the snails fire a harpoon into the fish's mouth. These "hook and line hunters" don't use the local anesthetic. They apparently have a fast-acting toxin that confounds the fish's escape reaction long enough for the paralytic poisons to take effect.

And how has this remarkable specificity and variability evolved? Olivera says the snails apparently have a genetic mechanism for varying the target-binding parts of the toxin while keeping the basic structure and shape intact. That mechanism—not yet understood—has made the snails into drug factories in which a huge range of possible toxins has evolved and been tested, with evolutionary pressure selecting the ones that are effective. That evolutionary pattern—which yields both great variety and great specificity—is good news not only for the snails, but also for neurobiologists in search of better ion channel probes.

To date, the most useful conotoxins have been those that target calcium channels, according to Richard Tsien, who studies calcium channels at Stanford University. Until recently, the most studied calcium channel was the L-channel, for which there are several good inhibitors. Important in heart muscle function, the L-channel is also found in nerve cells, but researchers were disappointed when they discovered that L-channel blockers do not check calcium-triggered neurotransmitter release—implying that the calcium that causes neurotransmitter release must enter nerve cells through a different class of calcium channel.

Researchers suspected that the channel responsible for neurotransmitter release was the neuron-specific N-type calcium channel. But it was the cone snails that finally provided proof. A class of conotoxins called the ω-conotoxins—the first known specific blockers of N-channel function—also block neurotransmitter release, demonstrating that calcium flow through the N-channels is necessary for the release to occur. Using labeled toxin, researchers have also found that the N-channels are clumped together in patches on the surface of individual nerve cells and are found in most neurons of the brain—discoveries that were not possible before conotoxins provided a specific N-channel probe.

Another research area that may benefit from conotoxins is the study of the NMDA receptor, a protein of great interest because of its putative role in learning and memory. The receptor, which has not yet been cloned, is likely to come in several forms, says University of Utah researcher Thomas Parks. "In every case, if you're going to do functional studies, you need to have selective and potent drugs to manipulate the functions of the [subtypes]," Parks says.

Researchers are banking on sources like the cone snails to provide those drugs, not only for calcium channels and NMDA receptors, but for many more unstudied and perhaps as yet undiscovered neurotransmitter receptors and ion channels. But Stanford's Tsien interjects a note of caution. The specificity evolved by the snails, he says, may not always serve the purposes of scientists. Examples have already arisen of conotoxins that work for the cone snail but not for the lab scientist.

For example, the conantokins, which block NMDA receptors, don't bind tightly enough to the proteins to be used in purification procedures. Olivera suspects that is because the conotoxins evolved to paralyze fish and snails—not the mice and rats that are the experimental animals of choice in the lab. But even though the utility of a particular conotoxin is something of a hit-or-miss proposition, Olivera and others expect that, as a result of the sheer number and diversity of conotoxins, there will surely be plenty of hits. ■ MARCIA BARINAGA