MEDICINE FROM THE SEA

From slime to sponges, scientists are plumbing the ocean's depths for new medications to treat cancer, pain and other ailments

BY KEVIN KRAJICK

PHOTOGRAPHS BY JEFFREY L. ROTMAN

FRED RAINEY was standing aboard the 100-foot-long *Spree* about seven miles off the marshy Louisiana coast, rocking on four-foot swells. All around, oil-rig platforms rose like skyscrapers from the heaving waters of the Gulf of Mexico's "oil patch," a 64,000-square-mile stretch of shallow ocean where 4,000 steel platforms pump enough petroleum to account for one-third of the nation's production. But Rainey was not prospecting for oil. A microbiologist at Louisiana State University, he was on the trail of an unlikely quarry: slime. In particular, he sought algae, sponges, sea urchins, soft corals and other squishy, mostly immobile organisms that have attached to the oil platforms' undersides in tangled mats up to a foot and a half thick.

Scientists believe that from such lowly marine creatures a number of medications may one day be derived. Compounds from marine sources are now being tested as treatments for chronic pain, asthma and various malignancies, including breast cancer. (A new generation of industrial chemicals as well— particularly, powerful adhesives—are on the horizon.) Slime, it turns out, is absolutely brilliant at producing useful biochemicals.

Botanists and chemists have long prospected in tropical forests and other terrestrial ecosystems for unusual substances to meet human needs. But the world's oceans, which may contain as many as two million as yet undiscovered species, have remained largely untapped. Denizens of exotic, difficult-to-reach locations, such as deep-sea hot vents and seabed sediments, have hardly been documented. However, as advances in diving technology open new underwater realms to exploration, and developments in molecular biology and genetics allow labs to isolate molecules at a pace unimagined even a decade ago, the sea's potential as a biochemical resource is becoming apparent. Over the past 30 years, scientists have extracted at least 20,000 new biochemical substances from marine creatures. Dozens have reached clinical trials; a handful may soon be reviewed by the FDA for possible approval. "Because we humans live on land, that's where we've always looked," says organic chemist William Fenical, director of the Center for Marine Biotechnology and Biomedicine at the Scripps Institution of Oceanography in La Jolla, California. "But if you were to ask from scratch 'Where should we explore?' the answer would always be the sea. Now we're there."

Rainey, an easygoing native of Belfast, Northern Ireland, has collected microbes on high-Arctic islands and extremely dry deserts, including the Atacama in northern Chile. An unabashed nondiver, he claims he is unable to identify most marine specimens that aren't microbes—except perhaps starfish. "If you can see it with the naked eye, I probably can't help you," he quips. He made his first foray into marine bioprospecting in 2001, when the Department of the Interior asked Louisiana State University to survey life-forms on oil and natural-gas platforms in the Gulf of Mexico. Marine biologists (and fishermen) have long been aware that offshore oil platforms function as artificial islands, creating new frontiers especially for sessile, or stationary, organisms such as sponges and coral; these organisms typically reproduce by releasing eggs and sperm that, when fertilized, become larvae. The larvae, in turn, may drift hundreds of miles before attaching to something solid.

Recently, a research team led by Rainey that included specialists in mollusks, algae and foraminifera (tiny one-celled shell-builders) conducted a three-day collecting expedition aboard the *Spree,* a chartered vessel. They embarked from Port Fourchon, Louisiana, a hamlet surrounded by saltwater bayous that are punctuated by giant oil-industry installations and the occasional Cajun fishing shack. The plan was to collect samples at five oil-rig platforms. The researchers and several divers pulled up to the dock with piles of gear and a six-foot-high freezer for storing specimens. They winched it onto the *Spree*'s upper deck and lashed it down with industrial-strength straps. The skipper, who insisted on being addressed as Captain Frank, was a large, gruff man with flaming red hair; his feet were bare, his toenails painted purple. He resembled a Viking marauder who had changed into shorts and T-shirt.

We cast off and met in the cabin to talk strategy. At each rig, the divers would chisel off a few pounds of whatever was growing on the platform legs at depths of 60 feet and 30 feet and at the sea-air interface. They would also use large sterile syringes to collect seawater (and thus the microbes inhabiting it). The waters around oil platforms are dangerous environments. Tidal surges and currents can bash a diver's head against a steel platform. The platform's legs and crossbraces harbor remnants of commercial fishing nets, not to mention lines fitted with fishhooks. Some platforms are equipped with large intake pipes that draw vast quantities of water; a diver who strays too close could be sucked in and drowned.

Within an hour we were in open water, though on all sides a city of steel oil platforms stretched to the horizon. At some points, I could count 50 at a time. The smallest consisted of just a few girders and pipes, rising 20 or 30 feet out of the water. The largest—gargantuan contraptions fitted with stairways, piping systems, winches, sheds, tanks and satellite dishes—towered 100 feet or higher. Helicopters buzzed from one to another, ferrying crews. Fishing boats bobbed everywhere: the platforms are piscine magnets. Some fish come to hide from predators, others to feed off organisms that have made the platforms home.

The first platform we visited, 42-C, was a rusty yellow monster 16 miles offshore in about 100 feet of murky green water. It sat on three massive legs, its nine well-stems, thick as utility poles, plunging through the center of the platform. Two-foot swells washed up and down its waterline, revealing the topmost layer of what the scientists were seeking: a wrinkled crust of barnacles six inches thick. A crewman tied the *Spree* to the structure with a heavy rope. A diver, Sam Salvo, plunged overboard and fastened a bright yellow safety line to one leg about 20 feet down. Rainey had high hopes. "There are so many microbes out here," he said from the aft deck. "Half of what they bring back will be new to science."

PEOPLE HAVE LONG exploited potent chemicals made by marine creatures. In imperial Rome, historians speculate, Nero's mother, Agrippina the Younger, paved the way for her son's reign by lacing hapless relatives' food with a poison extracted from a shell-less mollusk known as the sea hare. On the Hawaiian island of Maui, native warriors dipped spears in a lethal tidal-pool coral; enemies succumbed if they were so much as nicked.

Scientists have pursued such historical clues with some success. They have isolated a series of powerful toxins from *Dolabella auricularia*—the sea hare that was most likely the source of the poison that dispatched Nero's rivals. Today, researchers, including a group at Arizona State University, are investigating the compounds, called dolastatins, for their potential anticancer properties. Chemists have also discovered a perhaps even more toxic compound, palytoxin, from the soft coral *Palythoa toxica*, likely the organism used to deadly effect by Hawaiian warriors. Researchers at Harvard, Northwestern and Rockefeller universities are trying to determine this compound's potential.

The work done over the years in medicinal botany has been a major spur for marine bioprospecting. More than 100 important drugs originate either as direct extracts or synthetic redesigns of plant molecules, including aspirin (from willow bark), digitalis (from the flowering herb foxglove), morphine (from opium poppies) and the antimalarial drug quinine (from the bark of the cinchona tree).

Researchers largely overlooked the oceans as a source of pharmaceuticals until the advent of scuba technology, first tested in 1943. Among the pioneers of marine bioprospecting was Paul Scheuer, an organic chemist and a refugee from Nazi Germany who ended up at the University of Hawaii at Manoa in 1950. He began to collect, identify and study an astonishing array of organisms—in particular, soft, sessile creatures. What intrigued Scheuer and others was that although such creatures possessed no obvious defense mechanism against predators—no teeth, claws, flippers to effect escape, or even a tough skin—they thrived. Scheuer and others assumed that the organisms had potent chemical defenses that might prove useful to people, so they began searching for the compounds using tried-and-true methods of biochemistry: grinding up specimens, dissolving the materials in various solvents, then testing the resulting extracts for a range of properties, including an ability to kill bacteria, to react with nerve cells or to attack malignant cells.

By the 1970s, the U.S. National Cancer Institute (NCI) and other research centers had begun to fund expeditions around the globe to collect marine samples. So far, the NCI has screened tens of thousands of marine extracts, and the institute continues to receive roughly 1,000 organisms from the field each year. David Newman, a chemist with the NCI's natural products program, says the massive canvassing is necessary because only one out of every several thousand sub-

KEVIN KRAJICK, a freelance writer who lives in New York City, specializes in covering science and the environment. JEFFREY L. ROTMAN is based in Lawrenceville, New Jersey.

stances shows any promise. "You might expect to make a better return by playing Powerball," says Newman. "But with drugs, when you hit it, you hit it big."

The arduous process of identifying and testing marine compounds is about to greatly accelerate, some scientists say. Automated chemical probes will seek out interesting stretches of genetic material in a batch of seawater or ground-up sponge; then, the thinking goes, gene-copying techniques will enable researchers to produce an abundance of whatever compound the gene is responsible for. "Now we have more ways to find the gene clusters that produce these substances, and clone them so they can produce more," says Bill Gerwick, an Oregon State University marine biochemist who studies blue-green algae from the Caribbean and the South Pacific. Recently, molecular biologist Craig Venter, president of the Institute for Biological Energy Alternatives, began sequencing the DNA of every microbe in the Sargasso Sea, a region of the Atlantic Ocean.

Most "discoveries" don't pan out, either because test-tube results don't translate to real-world problems or beneficial compounds also may produce harmful side effects. As a result, perhaps only one or two out of every hundred compounds that reach the preclinical testing stage yields a potential pharmaceutical—after anywhere from 5 to 30 years. "Both the beauty and the downfall of these compounds is that they are exotic and complicated," says Chris Ireland, a University of Utah marine chemist.

A score of compounds derived from marine sources are being tested in clinical trials: one such compound, trabectedin, has been isolated from *Ecteinascidia turbinata*, a Mediterranean and Caribbean tunicate, whose colonies look like translucent orange grapes. A pharmaceutical company based in Spain, PharmaMar, is testing a drug, Yondelis, from this compound against several cancers. Another compound, contignasterol, is the source of a potential treatment for asthma being developed by a Canadian company, Inflazyme. The drug, based on a substance found in a Pacific sponge, *Petrosia contignata*, reportedly produces fewer side effects than current medications and can be swallowed instead of inhaled.

In the United States, a marine-derived drug that has been extensively tested for the treatment of chronic pain is Prialt. It is based on venom from a species of Pacific cone snail, whose poisonous harpoonlike stingers can paralyze and kill fish and humans. At least 30 people have died from cone-snail attacks. Biochemist Baldomero Olivera of the University of Utah, who grew up in the Philippines and collected cone-snail shells as a boy, conducted the research leading to the discovery of the drug. He and his colleagues extracted a peptide from the venom of *Conus magus* (the magician's cone). "I thought that if these snails were so powerful that they could paralyze the nervous system, smaller doses of the compounds from the venoms might have beneficial effects," Olivera said. "Cone snails are of exceptional interest because the molecules they make are very small and simple, easily reproducible." In January, the Irish pharmaceutical firm Élan announced that it had completed advanced trials on Prialt in the United States. The drug, acting on nerve pathways to block pain more effectively than traditional opiates, appears to be 1,000 times more potent than morphine—and, researchers say, lacks morphine's addictive potential and exhibits a reduced risk of mind-altering side effects. One research subject, a Missouri man in his 30s who had suffered from a rare soft-tissue cancer since he was 5, reported to scientists at the Research Medical Center in Kansas City that his pain had abated within days of receiving Prialt. About 2,000 people have received the drug on an experimental basis; Élan plans to submit the data to the FDA for review and possible approval of Prialt, with a decision expected as early as next year. Other researchers are investigating the potential of cone-snail venoms, the components of which may number up to 50,000, in the treatment of nervous system conditions such as epilepsy and stroke.

Two antiviral drugs already on the market might be said to have been inspired by marine product chemistry: Acyclovir, which treats herpes infections, and AZT, which fights the AIDS virus, HIV. Those drugs can be traced to nucleosidic compounds that chemist Werner Bergmann isolated from a Caribbean sponge, *Cryptotheca crypta*, in the 1950s. "These are arguably the first marine drugs," says David Newman.

Marine-derived products other than drugs are already on the market. For example, two essential fatty acids present in human breast milk are also manufactured by a marine microalga, *Cryptocodinium cohnii.* Infant-formula makers use the algae-derived substances in some products. An enzyme synthesized from microbes found in undersea hydrothermal vents has proved highly effective in decreasing underground oil viscosity—and therefore increasing oil-well yields. Already, automakers are using one compound, based on glues made by the common blue mussel, to improve the adherence of paint; sutureless wound closure and dental fixatives are other possible applications. New varieties of artificial bone grafts, produced from ground-up corals, possess a porosity that precisely mimics that of human bone tissue. A group of compounds with anti-inflammatory properties called pseudopterosins have been extracted from a Caribbean gorgonian (a soft coral) and are included in an antiwrinkle cream marketed by Estée Lauder.

With the field of marine products chemistry showing such promise, a new breed of hybrid scientist has emerged: scuba-diving chemists. They generally spend half their time shaking beakers in a lab, the other half scraping strange-looking things off underwater rocks. Jim McClintock, a University of Alabama at Birmingham marine-chemical ecologist, collects bottom-dwellers in the waters off Antarctica. A perhaps unexpected diversity of organisms thrives there, with more than 400 species of sponges alone. To explore that environment, McClintock and his co-investigators have to pry open sea ice eight to ten feet thick with chain saws, drills or even dynamite. They wear 100 pounds or so of diving gear, including special kinds of super-insulated diving suits, known as dry suits, and descend into deep, narrow holes—often with as little as a two-inch clearance in front of their noses. In this hermetic world, the water may appear pitch-black or gloriously illumined, depending on how much snow covers the ice overhead. Leopard seals, 1,000-pound predators that devour penguins and other seals, may demonstrate a hungry interest in the divers. McClintock recalls seeing a behemoth charging menacingly and surfacing through a crack in the ice to swipe at researchers topside. "I try to stay out of the food chain," he says. Back at the University of Alabama, McClintock's colleague, molecular biologist Eric Sorscher, screens Antarctic organisms for compounds; he has identified a few that may be tested for the treatment of cystic fibrosis. The Pennsylvania-based pharmaceutical firm Wyeth recently detected antibiotic and anticancer properties in extracts from Antarctic sponges and tunicates.

Tropical waters pose their own hazards. Bill Gerwick, who refers to the blue-green algae he studies as "pond scum," says that his specimens prefer the same cloudy bays favored by stinging jellyfish, saltwater crocodiles and sharks. His colleague, Phil Crews, a natural products chemist at the University of California at Santa Cruz, finds people more threatening. In New Guinea in 1999, villagers, fearing that the scientists were invading fishing grounds off their island, attacked Crews with spears and slingshots. Another time, a machine-gun-wielding gang of young Indonesian soldiers boarded Crews' research vessel and demanded money. "Basically," Crews says, "we came up with enough cash."

He has identified more than 800 compounds in tropical sponges. One promising source of cancer-fighting substances are the compounds called bengamides, after Fiji's Beqa (pronounced "Benga") Lagoon, where Crews collected the original specimens. Gerwick has isolated a substance he christened kalkitoxin, from an algae collected off the Caribbean island of Curaçao; he says it has potential as a treatment for some neurodegenerative disorders and possibly cancer, as well as pain control.

Technology is opening the deep sea to bioprospecting. In the past, biologists hoping to collect samples from waters as deep as 3,000 feet could do little more than sink trawl nets and hope for the best, says Amy Wright, an organic chemist at Harbor Branch Oceanographic Institution in Fort Pierce, Florida. But since 1984, Wright has collected from inside the Johnson-Sea-Link I and II, deep-water submersibles equipped with robotic claws and high-powered vacuums. They have enabled her to gather delicate sea fans and a host of other organisms intact, mainly from the Atlantic and the Caribbean. "It's always a surprise," she says. A compound from a Caribbean sponge, *Discodermia*, "is now in clinical trials for the treatment of pancreatic and other cancers."

The deep sea has turned up leads in the quest for oceanic pharmaceuticals. A San Diego-based biotechnology firm, Diversa, announced two years ago that its scientists had sequenced the genome of *Nanoarchaeum equitans*, an unusual organism collected from a seafloor vent north of Iceland. The organism, smaller and simpler and with less DNA than any known bacterium, is being studied as a possible minuscule, living factory for the production of marine chemicals. "We can use what we learn from Nanoarchaeota to figure out something very basic: which genes are essential and which we can do without," says Michiel Noordewier, a researcher at Diversa. "This is the smallest genome ever found."

SUDDENLY A SQUADRON of bluefish, converging in a feeding frenzy, thrashed out of the waves and began snapping at the swells' surfaces—a reminder of the astonishing variety of marine life around the Gulf of Mexico oil platforms. A few minutes later, the divers surfaced one at a time and clambered onto the deck—just in time. What looked like a shark fin had flashed in the water 100 feet off starboard. They hauled the specimen bag out of the water and onto a table.

What spilled out of the laundry-basket-size bag was mind-boggling. Amid a matrix of varicolored, agglutinated barnacles—their shells opening and closing, working overtime in the air—grew tiny tube worms; strands of telesto coral, branching like miniature caribou antlers; and hydroids, filter-feeding organisms resembling ferns. Juan López-Bautista, the expedition's algae expert, picked through the tangled mass with long tweezers, teasing out flywing-shaped specks of purple and green. Each tiny dot, he said, probably contains several algae species. Tiny crabs, brittle stars, shrimplike amphipods and delicate, green marine worms wriggled from the muddy gunk. Something bigger wriggled into view. Rainey quickly stepped back. A bright red bristleworm, a centipede-like creature spiked with poison-tipped spines poking out from its six-inch-long body, dropped onto the deck. "Don't touch that," he said. "It will hurt like hell. At the very least." He snared the bristleworm with long tweezers and gingerly placed it in a jar, saying: "We're going to grind up your gut and see what kind of microbes you have."

The research team failed to find one creature they had particularly sought: the bryozoan *Bugula neritina,* a tiny, tentacled aquatic organism that looks like a piece of moss the size of a quarter. It yields a compound currently being tested as a cancer drug; the compound originally was identified by George Pettit, an organic chemist at Arizona State University, who collected the bryozoans off western Florida. He found that compounds from the *Bugula* demonstrated anticancer properties, and in 1981 he isolated a compound he christened bryostatin. Lab tests have found that it attacks various malignancies. It is currently undergoing advanced human trials in the United States, Canada and the United Kingdom.

More than two decades after Pettit's discovery, scientists at Harvard and in Japan have synthesized small amounts of the complex molecule, which is in great demand. Researchers in California have discovered populations of *Bugula* growing on West Coast oil platforms. The team was hoping to find a *Bugula* source in the Gulf. But not today.

EARLY THE NEXT MORNING, as the day dawned clear, the *Spree* floated in a calm sea alongside 82-A, a big platform lying 27 miles out in clear blue water. We could see the divers 20 feet down. A Portuguese man-of-war floated by; schools of feeding fish, extending on all sides for perhaps half an acre, flashed at the surface. A four-foot-long barracuda cruised in to investigate. Then the divers began to resurface; within minutes, everyone had climbed aboard. The take this time was also dazzling—extravagant pink conchs, spiny pure-black sea urchins the size of half dollars, and mats of what the biologists call "scunge," gooey conglomerations of bacteria and algae.

The next platform, lying also in blue water, offered up bell-like corals, tiny purple-and-white octopuses and—at last—a few strands of seemingly unimpressive reddish mossy stuff, possibly the much-sought bryozoan *Bugula neritina*. "We'll have to wait until we get back to the lab," said Rainey. "A lot of these things look alike."

By the time we reached the fourth platform, we'd returned to silty waters opaque with Mississippi River mud, which may well also contain contaminants ranging from petroleum runoff and mercury from power-plant emissions to raw sewage. Perhaps most toxic to marine life is chemical fertilizer, washed from farms upriver. In fact, many environments where aquatic life once thrived have simply vanished; estuaries and bays along much of the coastal United States were long ago filled or otherwise destroyed. Ironically, oil platforms some distance from shore may constitute the last best hope for some marine organisms.

The *Spree* reached the last site, 23-EE, just as a strong wind rose out of the south. The crew secured the vessel to the rig, but the *Spree* would not stay put; the wind and an opposing north current battered us at our mooring. What to do? The divers said they could avoid being crushed by the tossing boat—but only if they could discern the vessel from below, which was unlikely. About 60 feet down, visibility would be nil. Yet nobody wanted to quit. "Well, what's the worst that could happen?" asked one diver. "We get lost, or die." Everyone laughed nervously.

"Well, if you get lost, I'll look for you," Captain Frank said. "For a couple of hours at least, depending on how much money you left in your wallet." More anxious laughter.

"What about the surface sample?" inquired Rainey.

"That is a no-go," said Mark Miller, one of the divers. Whitecapped four-foot swells dashed against the platform legs, which were studded with several inches of razor-sharp mussel shells.

"Let's abandon this," Rainey said. "It's not worth the risk." He may be a landlubber microbiologist, but he respected the power of the ocean. Whatever promising slime was down there, it would have to wait for another day.