1995

The chemical prospectors

Aquaculture Department, Southeast Asian Fisheries Development Center

Southeast Asian Fisheries Development Center, Aquaculture Department (1995). The chemical prospectors. Aqua Farm News, 13(5), 2-4.

http://hdl.handle.net/10862/2480

The Chemical Prospectors

With little new ground gained in the war against cancer, no cure in sight for AIDS, and the looming threat of resistance to current antibiotics, modern researchers have become as intrigued by new natural pharmaceuticals as 15th-century explorers were by spices. Collectors search for specimens around the world, in remote jungles, coral reefs, marshes, and the depths of the ocean. And although it costs twice as much to get a specimen from the sea as it does to collect a terrestrial item, the effort is proving worthwhile. Today most natural compounds that show promise as anti-cancer drugs come from the sea. These include six compounds that have reached clinical or late-preclinical trials in the United States and Canada.

Marine chemists say they have only just begun to tap the chemical diversity of the sea. "Man has been interacting with plants on land for some 3000 years," says chemist William Fenical of the Scripps Institution of Oceanography. "In the ocean there are an incredible number of organisms - and we don't know their potential."

And it is not just the U.S. researchers who are looking to the oceans. The Japanese government is starting to emphasize marine natural products, and Japan has become the world leader in the use of submersibles for collecting deep-water organisms. So far, Japanese researchers haven't found anything that has reached the clinical trial stage. Also, they don't have a massive screening effort like the US National Cancer Institute (NCI). But Japanese scientists have isolated a number of potential anti-cancer and antibiotic compounds especially from deep-sea bacteria, and used crystallography or other techniques to determine their chemical structures which are often strange and unique.

Toxic defense

One reason sea creatures are particularly promising sources of anti-cancer compounds, speculates NCI chemist David Newman, is that natural selection has forced them to develop elaborate chemical arsenals. The sea is full of sitting targets: soft-bodied, stationary, brightly colored creatures that seem to say "eat me", he says. To avoid that fate, those creatures rely on powerful toxins. And toxicity is the reason cancer drugs work - the goal is to poison tumor cells more than healthy cells.

Collectors look for soft bodies and other signs of helplessness. Most of the samples come from the warm tropics, and although it's likely that those regions hold more biodiversity, a simpler explanation is that divers like the tropics, as Newman says. "I've gone diving off England. And it's bloody cold..."

Research has been given a boost by the development of screening techniques based on the tools of molecular biology. These screens generally look for a compound's effects on a specific chemical "target" -- usually an enzyme responsible for the growth of cancer cells. The speed of the molecular screens has revolutionized the search for drugs from natural products, says Crews. "You can screen thousands of things each day now."

Using this new technology, Crews, in collaboration with reseachers from Syntex in California, has identified two possible cancer-fighting compounds from sponges. One is a class of compounds called **bastadins** that interfere with the growth of leukemic cells and ovarian tumors; the other is a compound called **jasplakinolide**, which disrupts cell division in cultured renal and prostate cancer cells. Jasplakinolide has a serious drawback as a potential therapeutic agent. It is so toxic that it killed all the lab animals exposed to it. The hope, however, is that chemists will be able to alter the compound's structure to produce a milder derivative that retains enough toxicity to deal with tumor cells.

Researchers at Smith Kline Beecham are also using fast assays to plow through thousands of organisms they pluck from coral reefs, estuaries, marine lakes, and even wrecked ships, says Brad Carte, a marine products chemist. "We look for anti-cancer drugs, anti-inflammatory, antivirals, anything you can think of." They test extracts to see if they inhibit a target enzyme called a topoisomerase, enzymes that, by changing the topology of DNA, are important in the proliferation of cancer cells. They've used this to identify promising small molecules from several sponges from the Philippines and Japan, one of which has shrunk tumors in mice.

The company has also screened for chemicals that bind to an enzyme called protein kinase, which is essential for cell division and signal transduction -- the transfer of information from outside chemicals, such as growth factors and hormones, into cells. A drug acting against protein kinase might inhibit cancer growth or inflammation. Paul Scheuer of the University of Hawaii and his colleagues have identified protein kinase inhibitors from a sponge and a tunicate. And while NCI has found just one compound that has any effect on HIV, University of Chicago researchers have seen sponge extracts that inhibit HIV protease, an enzyme necessary for viral replication.

Microbial prospecting

While most researchers have been testing extracts from large organisms, others, including microbiologist Deborah Steinberg of American

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Cyanamid, have been thinking small. They are scouring the seas for microorganisms with potentially useful properties. She and her colleagues collect microbes from around the world and use a variety of molecular screens and tested them for signs of antibiotic, anti-cancer, or anti-viral properties, as well as potential for cardiovascular and central nervous system drugs. They test thousands per day right on the collection ship and have already found a number of leads. One is **bioxalomycin** -- a compound isolated from shoreline bacteria that shows antibacterial properties.

Scripps's Fenical is now working with Bristol-Myers Squibb to screen marine microbes for both anti-cancer and anti-inflammatory agents. Though his team searches water and sand, he's actually found the most interesting samples on the bodies of other organisms. "We look on the surfaces of plants and animals," he says, "in the tissues of fish and the digestive tracts of shrimp."

Indeed, some of the toxins associated with macroscopic animals come from microbes that live in or on their bodies. Take **tetrodotoxin**, a deadly substance that concentrates in the puffer fish -- and occasionally kills daredevil gourmets who indulge in this high-risk delicacy. Japanese biochemists Takeshi Yasumoto of Tohoko Uni-

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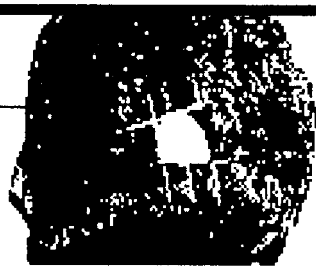

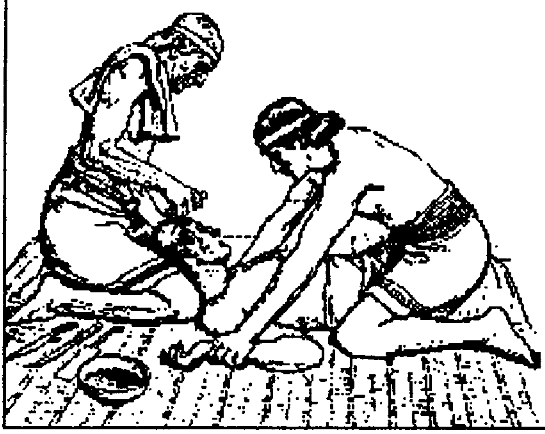

Ouch! That hurts!

Quite a long time ago, surgeons remove a section of bone from the skull to relieve pressure on the brain. First, the patient's head was shaved and the skin slit and drawn back, exposing the bone. Then a small surgical saw was used to remove the section, which was replaced when the drainage was completed. The hole remaining in the skull indicates that the patient died.

Surgeries in the 21st century are much less painful with the discovery of anaesthesia. Preventive drugs have also been discovered from both land-based and aquatic organisms. More bioactive compounds especially from aquatic organisms are being studied by scientists.

Reference: **Great People of the Bible and How They Lived.** 1974. The Reader's Digest Association, Inc. New York. p. 202.

versity and Michlo Murata of the University of Tokyo recently discovered that tetrodotoxin comes from a type of unicellular marine bacteria living in the fish's internal organs.

Fenical has found that many marine creatures and their eggs are covered with bacteria that protect their hosts from disease: "If you put organisms in polluted seawater and destroy the surface bacteria, the animals die because they get infected with pathogens." That finding, he says, argues for seeking new antibiotics in such protective microbes. Already, he has interesting leads, including a powerful anti-fungal compound, called **istatin**, isolated from bacteria that protect shrimp eggs, and two possible antibiotics, **salinamide A and B**, in bacteria living on the body of a jellyfish found in Florida.

Supply and demand

If a useful drug does turn up, researchers could quickly face a problem: demand may outstrip supply. Crews and other researchers are trying to prevent that by developing techniques for farming marine organisms. It can be a challenging task, however, for some creatures -- sponges, for example -- are notoriously difficult to cultivate, says Crews. One group, headed by marine chemists Murray Munroe and John Blunt at the University of Canterbury in New Zealand, has managed to start the first sponge farm, growing the sponge that produces halochondrin -- one of the six marine-based compounds that are moving toward clinical trials.

Microbes should be easier to grow, but even here, the strangeness of the marine world presents a challenge. "You have to reinvent microbiology," says Fenical. Terrestrial bacteria are often grown in protein compounds or glucose. But "there's no glucose in the sea." So to grow marine microbes, he says, "we've developed about 25 media based on all kinds of concoctions - fish meals and powders, special oils, and crab shells. ... You have to think about what's out there."

Chemical prospecting among marine organisms is still in its early stages. But with several compounds showing promise in the lab and a handful moving toward clinical trials, researchers like Fenical are confident that it is just a matter of time before they hit pay dirt. And, when that happens, the big drug companies will follow. "Within the next 5 years companies will look into the ocean as they've never done before," he says.

Excerpted from **Science** Vol. 266. November 25, 1994.