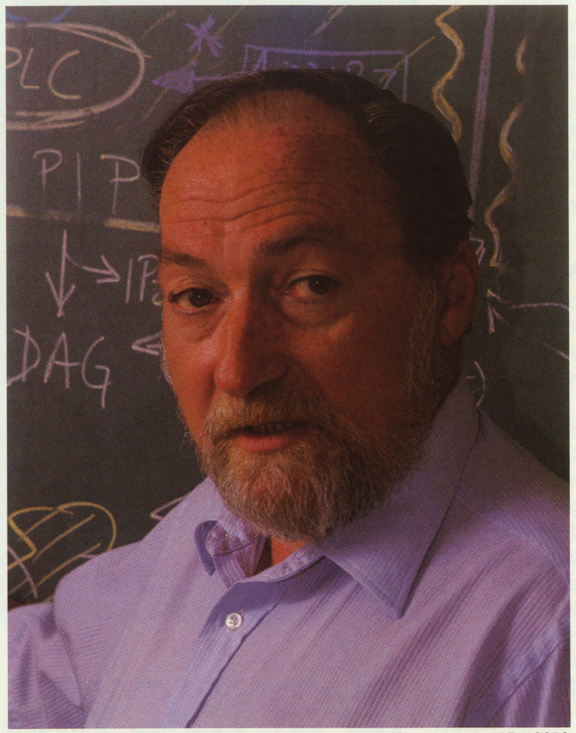
DRUGS FROM THE SEA



DR. ROBERT JACOBS

By Hillary Hauser

Photography by Steve Malone

The pharmacist of the future may dish out potions from the sea to cure the ills of mankind — soft corals for ulcers, brown algae for cancer, and Pacific sponges for arthritis.

While pharmacology is, in reality, not as simple as this sounds, university researchers are making significant discoveries that may establish an important connection between the underwater world and the dry land of medicine.

Dr. Robert Jacobs, an associate professor of pharmacology at the University of California, Santa Barbara, began his marine research at the institution in 1975. The marine pharmacology program began in 1977, when the Marine Science Institute at UCSB received Sea Grant funding to investigate pharmaceutical remedies from the sea. Jacobs' lab is housed in a modest, tin-roofed shed next to the biology building on the campus, marked simply with a sign that says "mycology."

What is going on inside, however, is much more that the study of fungus. Of 400 chemical compounds extracted by Jacobs' team of researchers from sea animals and plants, 25 have proven promising — and three have reached advanced research stages. One substance is being examined by the National Cancer Institute.

One compound investigated by Jacobs' researchers, called lophotoxin, is isolated from a type of soft gorgonian coral collected from the Mexican Pacific. Lophotoxin causes paralysis similar to that which occurs in diseases like myasthenia gravis; by isolating the substance and identifying its mechanism, the scientists hope to come up with an antidote.

"Chances are that the chemical can be used as a scientific probe to study the system," Jacobs explained. "For example, the communication between the nerve and the muscle."

Stypoldione, which comes from the brown alga (*Stypopodium zonale*), is being examined by the researchers for its ability to inhibit cell division, first in sea urchins and then in mammals. The National Cancer Institute is testing its potential use for man.

Another substance, manoalide, is from the sponge *Luffariella variabilis* found in the deep seas around Guam. It may have pain-killing and anti-inflammatory properties that can also inhibit tumor growth. Among the substances studied by Jacobs and his researchers, manoalide is the most promising — the closest to the final testing process and possible availability to the public.

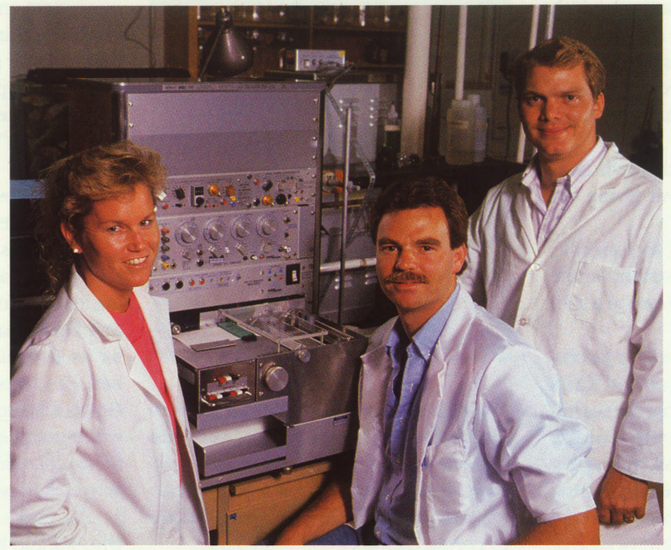
Jacobs said that when his researchers go on diving/collecting trips there are clues they watch for, clues that hint of the pharmaceutical potentials of sea animals or plants.

"One of the things we look for is lack of predation," he said. "We look at the things that the fish are not eating. For example, if we come across a bed of sea fans that are not chewed on, but where there are lots of fish, we assume the corals are secreting something to protect themselves, some chemical defense."

In the earlier days of drugs-from-the-sea research (six years ago), the researchers would collect the marine organism, grind it up, and put it in a fish tank on the boat. If it killed the fish they took the material and extracted it with an organic solvent.

Today, scientists work from more sophisticated research ships, where researchers can subject the sea animal or plant to thin-layer chromatography. The chromatography tests tell if the substance is antibacterial. This process tells a researcher immediately if there are possibilities in the sample, without subjecting it to the fish test. Researchers aboard ship also inject the substance into sea urchin eggs, which reveal if the substance will inhibit cell division (a major factor in determining the effectiveness of the substance on cancer).

If it is determined that the chemical has an unusual property, then a large collection is made and frozen. Samples are sent to the Smithsonian Institution for verification or identification, then forwarded to Scripps Institution of Oceanography in La Jolla, California, to be studied for chemical structure. If the Scripps scientists find that the chemical structure has "very unusual features," the work will continue on the substance.



Researchers working on pharmacology from the sea are Krista Grace, Ed Luedke (sitting) and Peer Jacobson.

"We run a little risk because we may come up with something pedestrian," Jacobs said. He pointed out that if, for example, an organism yields a set of histamine-like molecules or hormones, the further study of these compounds would be of no interest because "those things we already know."

If, however, the chemical or molecular mechanism of the substance proves new or interesting, the samples come back to Santa Barbara — to Jacobs' laboratory, where they undergo a series of studies to determine their biological applications.

Toxins are tested on nerves and muscles of rats or frogs, and substances suspected of having an effect on cell division are tested on sea urchin eggs.

Pointing to a saltwater tank of urchins, Jacobs said that potassium chloride is put into the tank to induce the urchins to sperm, and that the resulting eggs are collected for experimentation. As the eggs start to divide, the chemical in question is injected into them, to see if it blocks cell division.

Jacobs said any substance which continues to prove unusual is made available to other scientists to study.

"It's a way of introducing something new to science," he explained. "One of the goals of Sea Grant is to introduce something new to the scientific community. We're not in the business of developing drugs — that's not our department."

He explained disdain for sensationalism about his work. Any hint on magic cures emerging from the lab, he said, starts his "phone ringing off the hook" — both from the media and from people looking for solutions to their problems. The procedure of isolating a new type of drug from a sea animal or plant, he explained, is very slow and very expensive.

"In this business, you're faced with having to be very, very patient," he said. "It's like growing trees. In this business there are already too many false promises." He said sensationalism about an unproven drug can divert enormous resources away from research on legitimate remedies, because drug companies have a certain amount of money for development of drugs, and they logically prioritize what they spend.

Another danger in moving a product too rapidly is the possibility of overlooking dangerous side effects ("Look at what happened with thalidomide," Jacobs said).

In developing drugs, the intent of research is not to produce them from the

marine organism itself. Rather, researchers identify the chemical structure and reproduce it synthetically, using the marine organism as a model. In other words, they look at nature and as Robert Frost has said, they take a hint.

Jacobs said some chemical substances in marine life are too difficult to synthesize, in which case the pharmaceutical product is derived from the organism itself.

"No one's tried to synthesize cod liver oil," Jacobs joked.

He talked about calcitone, which is used to treat bone disease and which comes directly from fish. Another substance, prostaglandin, comes directly from soft coral and is being studied for potential use in ulcer therapy and a "morning after" pill for women.

Pharmacological researchers talk carefully about their work, never giving out vital information.

"We can't say anything too specific, because there is a big investment on the part of a drug company to develop a substance," Jacob said.

Three researchers working in Jacobs' lab, Ed Luedke, Peer Jacobson and Krista Grace, said that pharmacy from the sea has grown rapidly in the past ten years. Luedke, a graduate student at UCSB, has spent the last three and a half years studying pseudopterosins, a natural product derived from a Caribbean sea whip (a type of soft coral). The pseudopterosins, Luedke said, are showing promise for their anti-inflammatory and analgesic properties, which are useful in controlling swelling and pain in humans. At present the pseudopterosins are being tested on mice and human blood cells, and several drug companies have expressed interest in the compound.

"Most current drugs on the market have been developed from nature, from plants," Luedke said. "A lot of drugs started from the leaves of plants; antibiotics came from mold, aspirin from the bark of the willow tree."

An inhibitor to AIDS and other forms of cancer, he said, may well come from sponges.

Drugs reproduced by synthetically copying the chemical structure of marine products may provide in humans an earlier attack on what is called the "inflammatory cascade," Luedke said.

When a person suffers any sort of trauma, pain or inflammation, the body begins to manufacture hundreds of different substances, "some good, some bad, some inflammatory, some carcinogenic," said Peer Jacobson, a graduate student who has been studying under Jacobs for seven months. "The idea is to get in earlier on the cascade effects, before these things start to happen."

Krista Grace working with sea urchins in Dr. Jacobs' lab. Urchin eggs are able to be observed as they divide; marine pharmacologists test substances on the eggs to see if cell division is inhibited (a major factor in curing cancer).

Of all the marine substances studied so far, manoalide (named for the Manoa Valley in Hawaii) is proving the most hopeful in this regard. In testing this substance on human enzymes, Jacobson has learned that it acts earlier in the inflammatory cascade, blocking negative chain reactions in the body at the outset and thereby preventing "all the bad stuff."

Before Jacobson's work, manoalide had been tested only on bee venom. In working with human enzymes, Jacobson has been able to observe the effects of manoalides on the human cardiovascular system.

Jacobs said manoalide has also proven highly effective in blocking the formation of a very potent tumor promotor in the body, called PMA (phorbol myristate acetate). Standing before a blackboard full of scientific scribbles illustrating the inflammation cascade process in the body, Jacobs explained how manoalide blocks PMA at the very outset of the chain-reaction process.

If manoalide proves safe to use, it can be easily synthesized, Jacobs said. Already the clinical trials on the substances are complete, and toxicity studies are underway. The Food and Drug Administration may pass final judgement on manoalide some time in 1989.

"It's a very, very powerful drug," he said. "That's why it has to be thoroughly tested — its effect on the heart, the nervous system and so forth. However, if you want something new, and in cancer we're desperate for something new — we have to look at the process, chemical and molecular, and see if there is a way to block that process," Jacobs said. "Manoalide is hopeful."

The discovery of manoalide's properties was made in Jacobs' UCSB lab.

There has been such significant increase in research activity and corresponding interest on the part of drug companies that Jacob's lab has a full-time manager for its screening program of marine natural products. The manager is Krista Grace, who supervises graduate students working in the lab, follows up on research being done on marine compounds found active, and serves as liaison between Jacobs and outside graduate students who want to bring their projects into the lab.

Jacobs said the sea is still a largely untapped resource because scuba diving as a tool for collecting is a relatively recent innovation. His research team is one of the few in the world, although he said the Japanese have been very active in studying sea animals for their pharmaceutical benefits.

Interest in the U.S. is rising. Jacobs is presenting his findings to a National Institute of Health workshop on October 18-19, 1988 in Bethesda, Maryland.

Jacobs said the sea is unique among research areas because the marine species have evolved along with man into their own specialized forms, and because there is a uniformity of species populations in the sea. Also, there is a diversity of life in the ocean "we don't see anywhere else."

"The ocean — there's a little warehouse of stuff out there," Jacobs said.