From the waters of Newfoundland to the South Pacific, ASU's Dr. G. Robert Pettit will go to any depth to learn the secrets of the oceans and find a cure for cancer — including fighting off sharks, pirates and poisonous snakes.

by Lori K. Baker

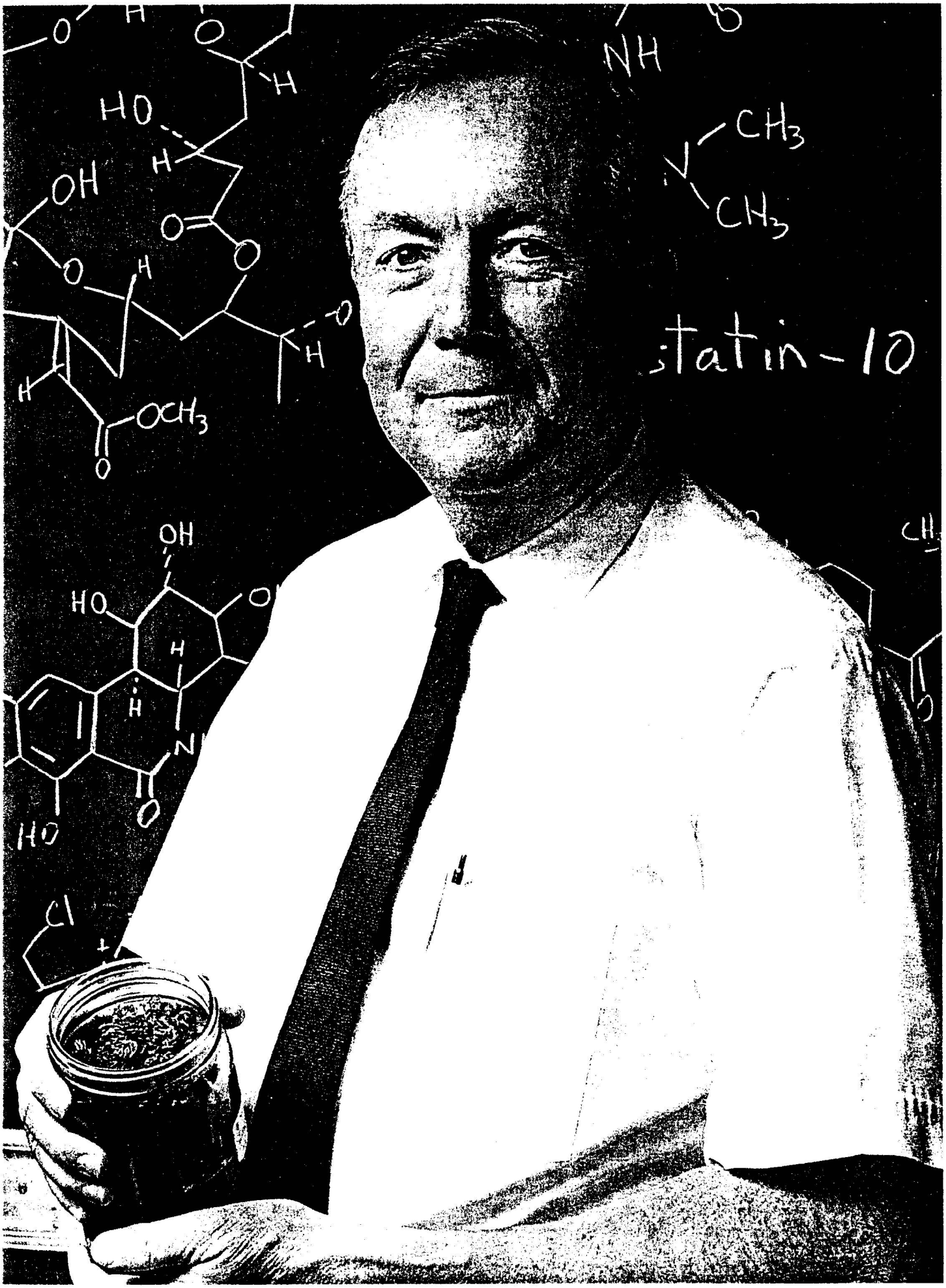
Under Study

G. Robert Pettit's bold search for a cancer cure reads like a plot plucked out of *Medicine Man*, the 1992 action adventure starring Sean Connery. Like the fictional Dr. Robert Campbell played by Connery, Arizona State University's Cancer Research Institute (CRI) director is known as a brilliant, but unorthodox, scientist hot on the trail of an amazing discovery. While Connery's character braves the dangers of the tropical rain forests in search of a cancer cure, Pettit's courageous quest leads him to remote regions of the ocean, the Earth's final frontier. There, shark attacks, poisonous sea snakes and modern-day pirates often pose a threat to Pettit and his team of scuba-diving scientists. But they're willing to take the risk. From the rugged Newfoundland coastline to the balmy shores of the South Pacific, they gather sponges, sea mats (colonies of tiny marine animals that mimic plants), slow-moving sea hares and other marine invertebrates. Back in the lab, some of these exotic creatures display breathtaking powers: they possess chemical compounds that kill cancer cells.

Tapping into the power of the world's vast underwater drugstore has made ASU's CRI one of the world's most prolific sources of promising new anti-cancer leads. Says Gordon Cragg, chief of the natural products branch of the U.S. National Cancer Institute (NCI): "It's a rare occurrence for one research group to discover so many anti-cancer drugs that are advancing through clinical trials." Six of CRI's drugs have wound their way through a maze of safety studies and are now being tested with small groups of cancer patients in very controlled clinical trials.

One such clinical trial of bryostatin 1, isolated from a marine pest known as "false coral," produced dramatic results. At the University of Manchester in England, three ovarian cancer patients — considered terminal — were given bryostatin 1 in combination with tamoxifen, an anti-estrogen medication. Four years later, all three have recovered. Pettit describes the results as "really exciting." Now in clinical trials in more than 40 medical centers in the United States, England and Canada, it's also being tested against lymphomas and kidney cancer. The unique drug also appears to boost the body's immune system while knocking out cancer cells, thus overcoming one of the most devastating side effects of chemotherapy.

Other promising CRI drugs currently in human trials include dolastatin 10, the most active low-dose



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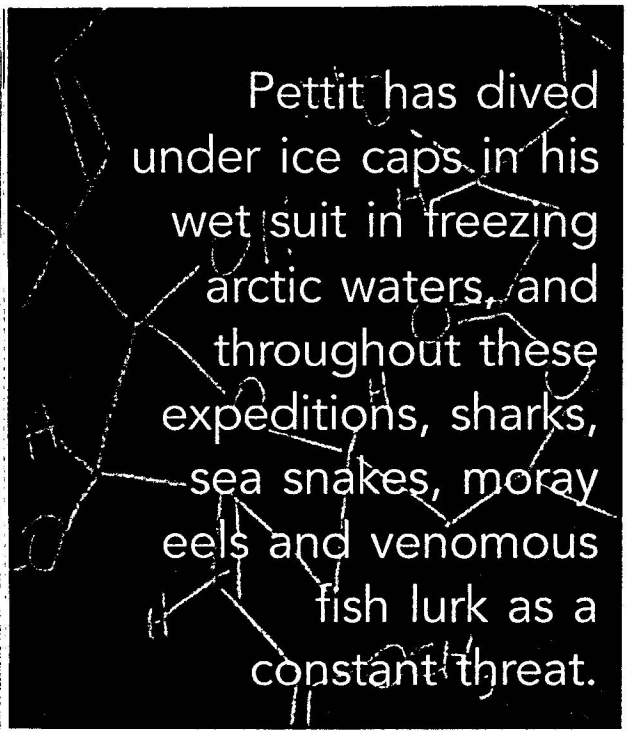

anti-cancer drug ever tested by the NCI. A compound derived from the Indian Ocean "sea hare," it's garnered 90 percent cure rates in treating certain types of human cancer transplanted in laboratory animals. For example, just a few milligrams of the potent substance wiped out all traces of melanoma in laboratory mice.

Isolated from red and black sponges also found in the Indian Ocean, spongistatin 1 is one of the most powerful compounds ever tested by the NCI, and may well become a major drug targeting chemo-resistant breast, ovarian and prostate cancers.

Discovered in the bark of the African bush willow, combretastatin A-4 has been described as "remarkable" by the *Journal of Cancer Research*. Licensed to the Swedish company OXiGENE, the drug cuts off the blood supply to cancerous tumors in about 90 percent of the solid tumor cancers tested, without destroying surrounding tissue. *Time* magazine's May 18, 1998, cover story declared it one of the promising anti-angiogenesis drugs on the horizon. And one of Britain's top pharmacologists, Tom Connors, recently predicted that combretastatin "might well develop into one of the most interesting anti-cancer drugs of the decade." Clinical trials began this fall in five medical centers in the United States and Britain.

Pettit's lifelong quest began in his youth, when he roamed the Atlantic shores near his Long Branch, New Jersey, family home. "One of the things that struck me at the time was that I didn't come across any marine invertebrate that looked like it had cancer," Pettit told a KAET-TV reporter. He'd seen the devastating impact of cancer at age 15, when he worked as an assistant to a pathologist at the Monmouth Medical Center in New Jersey. "It just seemed that people were dying all over the place and there was nothing that could be done about it, absolutely nothing," Pettit told a *Tribune* reporter. "I really developed a sensitivity to death and illness. I felt that I could do something about it."

His first step was graduating from Washington State University in 1952 with a bachelor's degree in chemistry. He finished his graduate education with a doctorate in organic chemistry in 1956 at Wayne State University, where he studied under Carl Djerassi. (Three decades later, Pettit would follow Djerassi, the discoverer of oral contraceptives, as a Chemical Pioneer Award winner. Only 100 chemists, including several Nobel Prize winners, have received this award from the American Institute of Chemists.) He joined the ASU faculty in 1965, and founded the Cancer Research Institute nine years later.

In his early studies of marine invertebrates, Pettit made the surprising discovery that they lacked antibodies — the backbone of the human immune system — but were far from defenseless. "The marine invertebrates in many cases have formed defensive substances based on about 3.8 billion years of evolutionary chemistry, carrying out trillions and trillions of biosynthetic organic reactions and devising ever-more complex molecules that have an ability to ward off predators," says Pettit. Thus began his 40-year quest to tap into that power, making him a pioneer in the search for anti-cancer drugs in the sea. "The oceans have given us substances that we chemists would not have thought of — and we might not have been able to design — for perhaps several more hundreds of years," he says.

Unlocking the life-saving secrets of the oceans can be adventurous and, at times, dangerous. Pettit and his scuba-diving scientists have plucked marine life from the sunken hulks of warships at the bottom of the Truk lagoon and other island waterways of Micronesia, from reefs in the Coral Sea, from inlets along the coast of northern Australia, and from waters throughout the Indian Ocean. Pettit has dived under ice caps in his wet suit in freezing arctic waters, and throughout these expeditions, sharks, sea snakes, moray eels and venomous fish lurk as a constant threat.

Along with dangers have come a few pleasant surprises, like Pettit's chance encounter with a famous Russian scientist on a remote, almost deserted island in the Republic of Seychelles, several hundred miles off the east coast of Africa. Pettit, his son, Robert, and two institute professional scuba divers were there collecting specimens. "It was toward the end of the day," Pettit told an *ASU Research* reporter. "We looked out and saw this beautiful 250-foot white ship that anchored about a half-mile off our camp." Pettit hopped into an outboard-powered rowboat and sped out for a closer look. He knew the vessel must be a Soviet scientific ship when he saw the name *Academik Oparin* painted on the bow. Alexander Oparin was a famous Russian chemist. As Pettit drew closer, the ship launched a small dive boat. He asked to speak with the deck officer. "I told him who I was, which probably was very unconvincing because I was soaking wet, wearing my old, battered military fatigues, and I had no ID except my ASU ID card, which I carry in a plastic envelope in my pocket. I found out later that the officer had radioed the captain to explain that he had a 'fisherman claiming to be a professor' who wanted to come aboard." After boarding the *Oparin*, one of the ship's officers ushered Pettit into a cabin, where he met Georgy Elyakov, a world-respected professor of organic chemistry. That chance encounter led to a joint Russian-American expedition in 1989. While aboard the *Oparin*, a giant, seagoing laboratory, ASU scientists gathered specimens from waters near the American-owned islands of Palmyra and Jarvis, near American Samoa, and in waters off northern Australia. ASU microbiologists took several thousand cultures and learned new techniques from some of the world's best marine microbiologists and chemists.

While finding the right specimens takes courage and an adventurous spirit, unlocking their secrets takes scientific brilliance and sheer tenacity. Under the direction of Pettit is a team of more than 55 botanists, cancer cell biologists, organic chemists, natural products chemists, microbiologists, marine zoologists and support staff. Over the years, CRI has examined — molecule by molecule — a vast number of organisms: about 8,000 marine, 3,500 plant and 1,000 insect species. Isolating cancer killers can be a daunting task, considering each exotic marine specimen they probe may contain several thousand compounds, only one or two of which attack cancer cells. Still, the ASU group has a remarkable track record:

it currently has in hand more than 400 organisms with known anti-cancer fighting drug poential.

What's CRI's secret? According to Cragg, Pettit is "a very gifted researcher" who possesses both an intimate knowledge of marine life needed to acquire sea specimens and a brilliance in chemistry that allows him to unlock their anti-cancer drug potential. But colleagues who know him best say his success rests on much more than raw talent. They use adjectives such as "tenacious," "tireless," "totally dedicated" and "determined" to describe him. Adds Gary S. Krahenbuhl, dean of ASU's College of Liberal Arts and Sciences: "He's an incurable optimist, and he shows incredible persistence in trying to solve a very complex problem. Another secret to his success is he's a non-conformist. Most cancer researchers are hoping to unravel the riddle of cancer. Instead, he looks in nature for organisms that never get the disease. Because people have been so fascinated by his work, and so many believe in it, he's been very successful in attracting non-public support — almost no state money goes into his research. That's allowed him to assemble a very large research group and keep it going."

After decades of toil and remarkable breakthroughs, he's landed some of science's most prestigious awards. This year, he won the Ernest Guenther Award in the Chemistry of Natural Products from the American Chemical Society at a standing-room-only ceremony in Dallas. Past recipients of the award include three Nobel laureates in chemistry as well as many nominees for the Nobel Prize. In 1989, Pettit was awarded the NCI's Outstanding Investigator Grant (OIG), worth more than $4 million over seven years. The OIG is a fiercely competitive grant that supports investigators with an outstanding cancer research track record spanning at least five years. Pettit's is the first such grant ever awarded to an Arizona scientist, and the first to a research chemist devoted to the discovery of new anti-cancer drugs. He's also an elected fellow of the American Institute of Chemists and the author of more than 400 referenced scientific papers and two six-volume reference texts.

Despite all his accomplishments, Pettit is quick to point out "there are no guarantees in this field. We continue searching, collecting, extracting, isolating and testing," he told an *ASU Research* reporter. "We have plenty of work yet to do." Indeed, there's still a long road ahead for many of his drugs. After tests in laboratory mice — where science actually excels in curing cancer — studies must show the medications work in humans, a far trickier species, without terrible side effects. Normally, that's a five- or six-stage process that can last 10 years or more. And for every five drugs that do go into clinical testing in humans, only one is eventually approved by the FDA.

That means Pettit and his team must remain in their lock-step race against time, while cancer kills approximately 600,000 Americans each year. It's estimated the total medical costs and economic losses in the United States this year from cancer will be well over $100 billion. That translates into combined medical and economic losses in Arizona of more than $1 billion per year. Meanwhile, the cost in personal suffering is incalculable.

Sidney M. Rosen, a lawyer and partner of Rosen, Ocampo & Fontes in Phoenix, has experienced that pain firsthand. The president and founder of the Phoenix-based International Foundation for Anticancer Drug Discovery (IFADD) lost his 55-year-old wife, Babette, to an aggressive form of throat and neck cancer in March 1996. Throughout his wife's courageous four-and-a-half-year fight for her life, Rosen immersed himself in the latest in cancer research. That's when he discovered Pettit and ASU's CRI, which he describes as "unequivocally the best-kept scientific secret in the state of Arizona." Because CRI is a research — not a treatment — center, it couldn't help Babette. Still, Rosen became convinced CRI was on the brink of discovering an arsenal of new weapons in the war against cancer, and he wanted to help. In February 1997, he launched IFADD to help fund anti-cancer drug discovery programs, with CRI as the primary beneficiary. Its first fund-raiser in 1997, the Herb Drinkwater Cancer Research Benefit, named for the former Scottsdale mayor, raised more than $300,000 for CRI and the Mayo Clinic Scottsdale, where proceeds were earmarked for clinical trials of two CRI drugs. In June 1997, IFADD spearheaded an effort in the state Legislature that resulted in a $10 million appropriation for cancer researchers statewide, creating an "Arizona Anticancer Drug Discovery Program." The goal is to trim at least 10 years off the time it takes to bring promising agents to clinical trials. The funds will benefit CRI, the Arizona Cancer Center in Tucson, the University of Arizona's College of Medicine, NAU, Mayo Clinic Scottsdale, Barrow Neurological Institute, Samaritan Health System and others.

The group's next fund-raiser is a tribute dinner honoring Pettit at 6 p.m. on November 18 at the Arizona Biltmore. An upbeat and festive celebration of Pettit's more than 40 years of productive cancer research, all proceeds from the dinner will be used to fund IFADD's agenda to enhance and accelerate anti-cancer drug discovery. Guest speakers will be Robert Peter Gale, M.D., Ph.D., a world-renowned oncologist and the 1986 coordinator of medical relief efforts at the Chernobyl nuclear disaster, and Michael R. Boyd, M.D., Ph.D., who heads NCI's Laboratory of Drug Discovery.

Says IFADD executive director Marcia K. Horn: "Our foundation is utterly convinced that if there's a major advance coming in cancer treatments, it will likely emanate from ASU's CRI under the direction of Dr. Pettit. This world-renowned institute may be the best-kept scientific secret in Arizona, but IFADD is planning to change all that."

Details on how to purchase tickets to the Dr. G. Robert Pettit Tribute Dinner on November 18 are available by calling IFADD at 861-3777. Dinner tickets are $250 per person, or $2,500 per table of 10. Because IFADD is a 501 (c)(3) tax-exempt organization, tickets and contributions are tax-deductible. PM