Medicine from the Rain Forest

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On a steamy day in 1987, a team of botanists from Harvard University's Arnold Arboretum, based in Massachusetts, U.S.A., trekked through the swampy forest of Sarawak, the Malaysian state in northern Borneo. On assignment from the National Cancer Institute (NCI), a U.S. government agency in Bethesda, Maryland, they were looking for plants that might eventually yield medicines for the world's deadliest diseases.

One of the botanists passed by an ordinary-looking, scrawny tree. "I almost didn't collect it," he would recall later. Fortuitously, he and his colleagues did collect leaves, bark and branches from the tree (scientific name: *Calophyllum lanigerum*). It turned out to contain the substance calanolide A, which may prove important in fighting AIDS. Later, the NCI sent a team from the University of Illinois at Chicago, U.S.A., to collect more samples.

The result is that calanolide A has been synthesized as a drug by MediChem Pharmaceuticals in Lemont, Illinois, in partnership with the government of Sarawak. It is now being tested by the NCI on human beings as a potential treatment for HIV, the virus that causes AIDS, in combination with other drugs to prolong the lives of AIDS sufferers.

On the drug development path

"Since 1986 the NCI has collected more than 50,000 species of plants around the world, but nothing yet has reached the stage of actual drug development," says Dr. Gordon Cragg, chief of the natural products branch of the NCI. "Calanolide A is probably our best lead that's come out thus far."

In 1984, Paul Cox, an ethnobotanist–he studies how indigenous people use plants–began working in Samoa. His mother had died of breast cancer, and Cox wanted to contribute to the fight against the disease. He ended up spending several years there with his wife and four young children. "I vowed I would do whatever I could to fight the disease that killed my mother," he writes in "Nafanua: Saving the Samoan Rain Forest" (W.H. Freeman, 1999).

Cox, now director of the National Tropical Botanical Garden in Kauai,

Hawaii, U.S.A., at first was excited when he found several plant compounds used by native Samoans to treat breast lumps. Unfortunately, subsequent testing at the NCI produced no solid leads. He may have failed in his quest to find a treatment for breast cancer, but along the way he did find *Homalanthus nutans*, a rain forest tree whose bark the Samoans used to treat hepatitis. A molecule derived from the tree, prostratin, was tested at the NCI and appeared also to inhibit the growth of HIV. Says Cox: "It's now of intense interest as a potential combination therapy for AIDS because... it protects healthy cells from being invaded." The NCI is accepting bids from pharmaceutical firms to develop the drug.

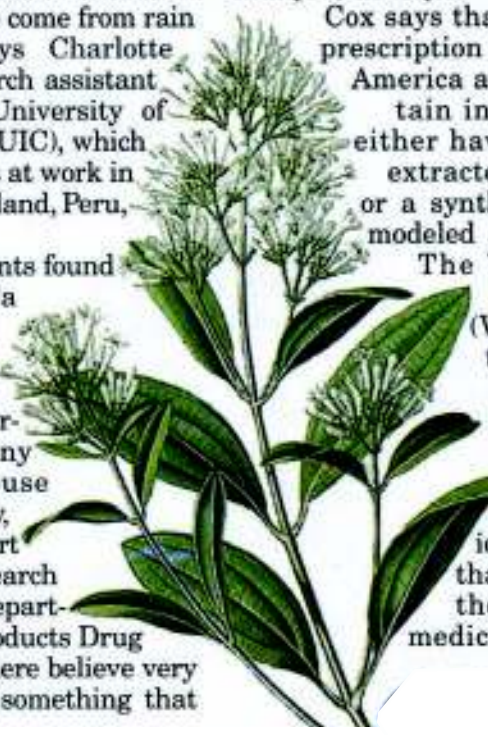
No longer 'voodoo'

Collecting rain forest plants and screening them for potential medicinal properties are now accepted practices. "People no longer think it's some sort of voodoo because a bunch of drugs have come from rain forest plants," says Charlotte Gyllenhaal, a research assistant professor at the University of Illinois at Chicago (UIC), which also has researchers at work in Laos, Vietnam, Thailand, Peru, Brazil and Uganda.

Research into plants found in rain forests is "a substantial area of endeavor" these days at Merck & Co., Inc., the pharmaceutical company based in Whitehouse Station, New Jersey, U.S.A., says Dr. Robert Borris, a senior research fellow in Merck's Department of Natural Products Drug Discovery. "People here believe very firmly that this is something that will pay off," he says. "Our research program covers the entire gamut of disease-based biological activities. If a disease is around, we're interested. That's one of the benefits of working for a major pharmaceutical company. Our department provides the chemical leads that hopefully will be developed into new drugs. Natural products to us are very interesting in that nature provides us with a tremendous diversity of chemical structures, and certainly a wider variety than a chemist would generate in a reasonable period of time."

Jim Miller, associate curator and head of the applied research department at Missouri Botanical Garden in St. Louis, Missouri, U.S.A., which works in locales from Vietnam to Panama, says that in the mid-1980s there began to be a concern about an increasing threat in the rain forests from rapidly expanding human populations. "The danger was that we'd let the world's chemical library disappear before we had to a chance to study it," he says.

Cox says that 25 percent of prescription drugs in North America and Europe contain ingredients that either have a compound extracted from a plant or a synthetic compound modeled after the plant. The World Health Organization (WHO) estimates that 85 percent of the world's inhabitants depend directly on plants as medicines. Countries that have adopted these traditional medicines as part of



their primary health care systems include Thailand, Mexico, Nigeria and China.

"The rain forest contains the highest diversity of species per hectare," says Gyllenhaal. "So by going to a rain forest you can increase the efficiency of collection just by getting lots of different species. The downside is that some of these compounds are so complicated, that it's not possible to manufacture them synthetically." As a result, she says, natural disasters and local political and social upheavals could create supply problems.

The process of transforming a jungle plant into a modern drug is costly and long. In the United States, the Food and Drug Administration (FDA) must give approval. Experts estimate that, from the time a plant is identified in the rain forest to the time a drug hits the market, it could cost anywhere from $300 million to $500 million and take anywhere from eight to 15 years. One drug might be developed out of every 5,000 to 10,000 plants tested, according to Norman Farnsworth, director of the Program for Collaborative Research in the Pharmaceutical Sciences at the College of Pharmacy at UIC.

The potential, though, remains great, since less than one-half of one percent of the world's estimated 250,000 species of flowering plants have been carefully studied to determine their potential therapeutic value, says Michael Balick, director of the Institute of Economic Botany at the New York Botanical Garden in the Bronx, New York, U.S.A.

In some cases, plants are collected randomly. In other cases, they are discovered with the help of local shamans, healers or others with traditional knowledge that may be centuries old. Balick worked for 10 years with a Mayan healer in Belize, who died three years ago at age 103. "Rainforest Remedies" (Lotus Press, 1998), which Balick wrote with Rosita Arvigo, discusses 100 healing plants of Belize, ranging from amaranth (a remedy for anemia) to yama bush (fever and flu).

A long history in medicine

Plants have long been a medicinal source. Quinine, used against malaria, was discovered by Spanish invaders in Peru in the bark of a rain forest tree later identified as the Cinchona. In 1785, William Withering in England proposed that foxglove (Latin name: *Digitalis*) could be an important medicine for dropsy, an ailment caused by inadequate pumping action of the heart. Digoxin and digitoxin, two important heart medicines, are still extracted from the foxglove plant.

"This is a very tricky game," concedes Balick, who is co-author with Cox of "Plants, People, and Culture" (Scientific American Library, 1997). "The odds are just phenomenally against you. That's not to say the work shouldn't be done, and that's not to say that drugs haven't been discovered."

Among the breakthroughs have been Taxol, a Bristol-Myers Squibb drug for treating ovarian cancer that came from the yew tree in the temperate rain forests of the U.S.

Northwest and British Columbia. In the rain forest, there have been discoveries that Miller of the Missouri Botanical Garden says approach "Holy Grail" status. "Vinchristine, which comes from the Madagascar rosy periwinkle, is one of the real success stories," he says. "It's very effective in treating childhood leukemia."

The danger, of course, is that many species will become lost if the world's rain forests continue to be destroyed. In Samoa, for instance, recent studies show that more than 80 percent of the lowland rain forest has already been logged. "I don't deny that saving our rain forests is a serious problem," Cox says. "But there's a clear solution: We just have to turn off the bulldozers and chain saws."

Mark Blumenthal, founder of the American Botanical Council based in Austin, Texas, U.S.A., and an adjunct professor of medicinal chemistry at the University of Texas in Austin, is also optimistic, but adds a caveat: "Just as important as saving the plants and animals, we need to do better in saving the cultures, which are actually disappearing at a faster rate than the plant life." Cragg agrees. "Knowledge is also being lost, and indigenous peoples are turning to modern medicine."

As for the future, there seems to be considerable hope. "Everywhere I go, attitudes are improving," says Cox. "Twenty years ago, nobody gave a hoot. But the president of Brazil just won [an election] based on an environmental campaign. So I'm guardedly optimistic. And if we can just hang on, 20 or 30 years from now, no one will dream of cutting down the rain forest. I mean, it'd be like machine-gunning whales."

Meanwhile, for Balick and Cox and the other "new explorers," it's back to the rain forest. And perhaps, just around the bend, there awaits a new, promising cure for another dreaded disease. ○

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Sharing the rain forest riches

Under the treaty that came out of the Convention on Biological Diversity in Brazil in the early 1990s, each signatory nation has sovereignty over all biodiversity rights within its boundaries. No plant sample that might result in the discovery of a pharmaceutical compound can be removed without the country's permission. "There are also guidelines that resource-rich countries can strike collaborations with pharmaceutical companies and other parties," says Tuah Ramo-Jameson Jenta, treasurer of Sarawak MediChem Pharmaceuticals in Lemont, Illinois, U.S.A., who holds a doctorate in physical chemistry. "These allow for benefit-sharing and equitable partnerships. If, for example, a royalty stream would emerge from calanolide A [see main story], 50 percent would filter back into Sarawak's state treasury."

Jim Miller, associate curator and head of applied research at Missouri Botanical Garden, says his employer was ahead of the curve. "In fact, in 1990, we signed our first agreement with the government of Madagascar, which guaranteed that we would share the profits and would support their scientists and scientific institutions. Ten years ago when I would tell an American pharmaceutical company that in order to get access to Country X, we're going to have to guarantee them a percentage of the profits, I'd often get a, 'We are? Why would we want to do that?' Today, they start in on that before I even bring it up."

"The goal is for the funds to trickle down to the villagers," adds Charlotte Gyllenhaal of the University of Illinois at Chicago. "We're working on a general trust fund here that will cover a number of different programs in our College of Pharmacy. We try to direct these funds to better conservation efforts, health improvement and local economic development, particularly in rural areas where people have been stewards of the rain forest for many years.

"A lot of the concern, too, is that scientists in developing countries need to be brought into the process of drug development. We have a scientist from Vietnam here at the moment who will potentially have a chance to get his name on a drug patent–which would then directly channel money back to his institution. And his training here will enhance Vietnam's ability to work on its own drug discovery programs, so it doesn't have to rely exclusively on scientists from the U.S. and Europe."

Testing for (possible) success

The process of collecting and testing rain forest plants for possible medicinal use begins when scientists get written permission from the particular government and village and establish rapport with the people, making sure everything is done with their consent. It may also involve talking to local healers about how they use particular plants.

The scientist then collects and identifies the plant, shipping back to the laboratory a flat, pressed specimen (known as the voucher specimen) and dried bulk specimens. These are soaked in an extract of ethyl alcohol or other solvent that ends up looking like what ethnobotanist Paul Cox calls "Nescafe — little freeze-dried crystals" and what professor Charlotte Gyllenhaal describes as "goo" ("admittedly, not a very scientific term").

Jim Miller of the Missouri Botanical Garden points out that large pharmaceutical companies like Bristol-Myers Squibb now have the capacity to evaluate 50,000 to 100,000 plant samples a week. Explains Cox: "A little robotic arm will take that plant sample and put it in a solution with thousands of other chemicals they're testing. It's put in a tiny glass plate with little wells in it, and there's a computer-controlled camera looking for color change. Maybe one out of 10,000 of those wells suddenly turns red, and if that happens to be my plant, that means we've hit it."

The next step is taking different extracts of the plant to discover which molecule is causing that activity, resulting in a "lead compound."

"Once we get that," says Cox, "it's sort of in the hands of God and Pfizer and Merck. Then they have to start this arduous research path, which at the end hopefully will spit out a drug of value to sick people."

In order to be approved by the U.S. Food and Drug Administration, tests first have to be made to determine whether the extract in the plant kills normal cells. "If there's a lot of toxicity, you just throw it out," says Gyllenhaal. "If not, it goes to animal testing to see if it works in a living system."

From there, the compound goes into human trials. In Phase I, it is determined if it can be formulated so that a sufficient dosage can be tolerated by the body. In Phase II, it's given to human beings and monitored to see if it actually works. Phase III are full-scale trials in combination with other drugs. If eventually successful, it can go on the market.

— *C.T.*