Chemical Prospecting: Hope For Vanishing Ecosystems?

As the United Nations Conference on Environment and Development draws near, negotiators attempting to craft an international treaty to preserve the world's plant and animal species are struggling with a major obstacle: how to make such conservation worthwhile to the developing countries that harbor much of the world's biodiversity. But while government negotiations inch along, a dollars-for-diversity scheme is already up and running in Costa Rica that may serve as a model for biodiversity preservation worldwide.

In an unprecedented move, the pharmaceutical giant Merck is paying Costa Rica's National Institute of Biodiversity (INBio) $1 million over the next 2 years for the opportunity to search for blockbuster drugs—a cure for AIDS, say, or Alzheimer's disease, or high blood pressure—in the country's diverse tropical forests. Should Merck succeed, in what everyone involved concedes is a crap shoot, it will pay INBio a share of the royalties as well. All that should provide one of the strongest incentives yet for Costa Rica to leave its forests standing.

The Merck-INBio deal, announced last November, is part of a resurgence of interest in natural products research among major pharmaceutical companies (see box). But two things set it apart from the plethora of other chemical prospecting deals. One is the $1 million Merck has provided up front—a sizable sum, considering that Costa Rica's national budget is just $1 billion a year, the same as Merck's R&D budget. The other unusual feature is that 10% of the upfront money, and 50% of any royalties, goes directly into conservation. "The potential for conservation is terrific," says Walter Reid, a biodiversity expert and vice president at the World Resources Institute, an environmental think tank in Washington, D.C. "If it is possible for a country to make money and channel it back to conservation, the dynamic will change. Countries will encourage not timber but medicinal plant exploration."

Use it or lose it. The arrangement is also winning fans in the developing world. Though it kicked off a heated debate in Costa Rica, where critics have blasted INBio for selling off the country's resources too cheaply, other species-rich countries, including Mexico, Indonesia, Nepal, and Nicaragua, are flocking to Costa Rica for advice in setting up their own INBios. And INBio itself has several new suitors—other pharmaceutical companies and the National Cancer Institute (NCI)—intrigued by the Merck model.

The new deal is a natural outgrowth of Costa Rica's "use it or lose it" school of conservation, pioneered in large part by tropical biologist Daniel Janzen of the University of Pennsylvania and plant virologist Rodrigo Gamez of the University of Costa Rica. Together, they came up with the idea for INBio, a nonprofit research and conservation organization. Their premise: that the only way to save biodiversity in a country facing growing development pressures is to find nondestructive ways to use it. The idea found a convert in former Costa Rican president and Nobel Peace Prize–winner Oscar Arias, and INBio was established in 1989 with Gamez as its first director.

MERCK

Chemical prospecting. Gerald Bills of Merck *(left)* and Rodrigo Gamez of INBio discuss a specimen of fungus.

INBio immediately set out to do a complete inventory of the nation's species—this tiny country is estimated to hold 5% to 7% of the world's biodiversity—an ambitious goal that could take a decade and cost $50 million. "You've got to know what is in your greenhouse if you put it up for sale," explains Janzen. To speed the process, Janzen came up with the idea of training parataxonomists—bus drivers, teachers, housewives, students—in the art of collecting and identifying species. More than 30 parataxonomists have been trained so far and are now at work cataloging Costa Rica's flora and fauna and, as of a couple of weeks ago, collecting samples for Merck.

To Thomas Eisner, a chemical ecologist at Cornell University, INBio looked like an ideal partner for a pharmaceutical firm seeking new compounds, because of both its scientific expertise and its strong ties to the Costa Rican government. A firm believer in the notion that nature can teach chemists a few tricks about how to design drugs, Eisner has long been an advocate of chemical prospecting, as he calls it, and in the past few years an increasing number of pharmaceutical companies and the NCI have come around to his view. But so far, says Tim Swanson, an economist at Cambridge University in England, "pharmaceutical companies have been able to have their cake and eat it too," reaping the bounty of the tropical forests while paying nothing in return. The classic example is vincristine, a multimillion-dollar cancer drug developed from the Madagascar rosy periwinkle. "Not a cent went back to Madagascar," says Eisner.

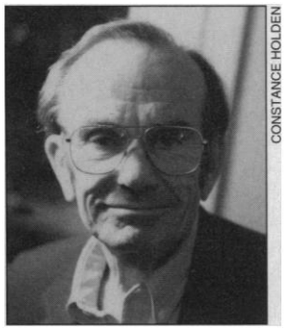
That pattern is changing as many pharmaceutical companies, often prodded by their botanists, are drafting royalty arrangements to ensure that a share of any benefits goes back to the source country. But such arrangements don't offer much immediate incentive for conservation, since the returns—if they ever come—are 10, 20, maybe 30 years away. "You can't operate in conservation with a promissory note," says Eisner. So Eisner came up with the idea of getting industry to pay upfront simply for the right to look.

With money from the MacArthur Foundation, Eisner put together a small conference in October 1990 to explore the possibility. Gamez came from INBio, as did Paul Anderson, a former Cornell postdoc and now vice president for medicinal chemistry at Merck. And the rest, as they say, is history.

Within about a year, Merck and INBio had signed a contract, setting up what both parties call a true research collaboration. Under the agreement, details of which have not been divulged, Merck gets right of first refusal to develop drugs based on samples of Costa Rican plants, insects, or microbes. Soil samples go directly to Merck's laboratory in Madrid. For plants and, soon, insects, INBio gives Merck a list, from which the company chooses a limited number. INBio then collects samples, freezes them, and, in collaboration with the University of Costa Rica, prepares chemical extracts. The extracts are sent to Merck's laboratories, where technicians run them through perhaps 50 or 100 bioassays, looking for activity against receptors or enzymes implicated in a variety of diseases.

Merck does not expect to find an active drug in these extracts, says Lynn Caporale, a biochemist who oversees Merck's outside collaborations, "though I would love that to happen." Rather, she and her colleagues are looking for promising compounds that could then be modified by Merck chemists. The odds, she admits, are stacked against them.

The rule of thumb in chemical screening is that just one sample out of 10,000 actually leads to a marketable product. Says George Albers-Schonberg, head of natural products screening at Merck: "Some people think that out of the rain forest we will quickly find half a dozen chemicals. That is totally unrealistic. We may find something in the next half-year, or it may be 3 or 4 years before we find anything." If and when the search yields paydirt, Merck will pay INBio an unspecified amount of royalties, thought to range between 1% and 3%, which INBio will split with the Ministry of Natural Resources.

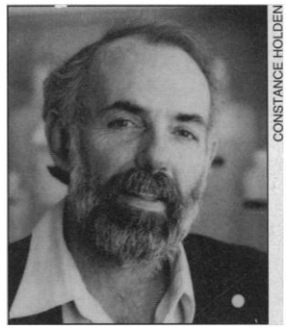

CONSTANCE HOLDEN

Thomas Eisner

Ultimately, INBio hopes to expand its role from merely collecting samples for Merck to carrying out some—if not all—of the drug discovery and development process in Costa Rica. And arguably the most important elements of the Merck deal, say its fans, are provisions for the technology transfer that will allow Costa Rica to build up its scientific infrastructure. In addition to the $1 million "prospecting fee," Merck donated $135,000 in equipment to INBio for chemical extraction and sent two of its key natural product chemists to set up the lab and train Costa Rican scientists. Costa Rican scientists are also spending time at Merck.

The skills INBio develops through the Merck deal should strengthen its position in negotiations with other companies. INBio is angling to perform more of the steps—perhaps even the screening itself—in Costa Rica. "The idea is to create alternatives for economic development, and alternatives for jobs," says Anna Sittenfeld, a microbiologist who heads biodiversity prospecting at INBio. "Then there will be less pressure against the land that is now protected." She notes that these benefits will accrue even if the prospectors fail to find a billion-dollar drug in the rain forest.

To Merck, the financial risk the company is taking in its drug discovery effort is a sufficient answer to one of the major complaints of the Costa Rican critics: that, once again, a multinational corporation is buying up the country's most valuable resource for a song. INBio, too, chalks up most of the criticism to misunderstanding. When the deal was first announced last November, critics were appalled that a private organization could sell the country's genetic resources. Many thought INBio was somehow profiting directly from the deal, rather than raising money for Costa Rica's conservation, says Sittenfeld. In fact, INBio has already turned over the first installment of Merck's upfront money to the Ministry of Natural Resources, which is using it to support a marine park at Coco Island.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Daniel Janzen

But even fans of the Merck-INBio deal, like Reid at the World Resources Institute, caution that although the model seems to be working well in Costa Rica, with its stable democracy and commitment to conservation, it is unclear how well it will transfer to other countries. "In other institutions, in other countries, I can see it leading to one more round of resource degradation that doesn't improve the quality of life or conservation." Elsewhere, says Reid, money earmarked for conservation could easily be siphoned off for some other use. Indeed, Reid is sufficiently concerned that he has just started a 9-month project, in collaboration with INBio, the Rainforest Alliance, and the African Center for Technology Studies, to develop guidelines for future prospecting deals. Any successful program, Reid says, must return a portion of the money to conservation and to the indigenous peoples who harbor medicinal knowledge.

Such deals could also work against conservation, say Michael Balick of the New York Botanical Garden, Albers-Schonberg of Merck, and others, if the lure of big bucks leads countries to abandon other strategies for preserving biodiversity, such as ecotourism, harvesting nuts and other renewable forest products, and simply setting aside the land. "It would be a shame if a lot of people in the developing world were to pin their hopes on the purported returns from a magic plant," says Balick. "If they base their hopes exclusively on economic grounds, it is hard to argue for conservation when that fails. And then the forest is in danger."

–Leslie Roberts

The Drug Industry Goes Green

When biotechnology and molecular biology exploded in the 1970s, they promised to make obsolete the kind of chemical prospecting that Merck is embarking on in the forests of Costa Rica (see main story). A molecular understanding of disease, coupled with the ability to engineer proteins, would open the way to synthesizing new, stunningly precise drugs from scratch. Many of the drug companies that had looked for their leads to microbes and other natural sources scaled back or dropped such screening efforts, which had come to look hopelessly old-fashioned. But now the very techniques that presaged the demise of natural products screening have led to its resurgence, as drug developers flock to the tropics in search of their next wonder drugs.

This back-to-nature movement has swept up not only Merck but also the National Cancer Institute, which is looking at such exotic sources as medicinal plants from China, Korea, and Samoa and marine organisms from the Red Sea; SmithKline Beecham, which is investigating plants from Ghana, Malaysia, and Costa Rica, marine organisms from the tropics, and microbes from all over; and many other companies. Driving the movement is the realization that biotechnology still can't compete with nature in coming up with clever compounds. "We are still not at the point scientifically where we can routinely design drugs from first principles without any clues," says Lynn Caporale, director of scientific evaluation at Merck.

Meanwhile, biotech does provide powerful tools for sorting through what nature (and synthetic chemists) has to offer: new bioassays that make it possible to screen tens of thousands of compounds a year for a fraction of the effort of testing compounds in whole animals or in classic microbial plate assays. Instead, companies now look for activity against an enzyme or receptor believed to be involved in, say, hypertension or AIDS. "Twenty-five years ago we had essentially one assay," says George Albers-Schonberg, head of the natural products screening effort at Merck. "Now we have 50 to 100 at a given time."

By and large, these new-age chemists don't expect to find a blockbuster drug ready and waiting in a plant or microbial extract—though there are precedents, such as penicillin or, more recently, Merck's cholesterol-lowering drug Mevacor. Instead, they are seeking clues that will serve as a starting point for drug design. Most of what nature provides needs to be modified, explains Albers-Schonberg, to make it less toxic, more powerful, or more easily absorbed. And that, he cautions, will take time. Even high-tech chemical prospecting, it seems, requires patience.

–L.R.