



### Back to Roots

*Drug companies forage for new treatments*

From cocaine to quinine, about one quarter of U.S. prescription drugs contain at least one compound derived from plants. Yet in recent years plants lost their cachet at the big pharmaceutical firms as new ideas came from microbes or variants gleaned from huge data bases of synthetic chemicals. Now drug companies are emphasizing their roots. Botanists are once again avidly scouring the world's fields and forests to locate plant sources for new drugs. "Synthetics haven't proven to be the panacea," observes Mark J. Plotkin of Conservation International, a Washington, D.C.-based group that is working to stop destruction of tropical forests. "There's still no cure for AIDS or the common cold."

The lure is twofold: a "green" public relations boon and the prospect of discovering the next taxol, a treatment for ovarian cancer that was originally extracted from the bark of the relatively rare Pacific yew tree. Botanists estimate that 10 percent or less of the more than 250,000 flowering plant species have been surveyed for pharmacological activity. But the task of finding an active molecule in a haystack is being eased by devices that can quickly search through tens of thousands of samples.

One molecule in 10,000 may get to market through random screening. Automated methods that rely on enzymes and other chemical tags can enable a company to test as many as 150,000 samples annually, hundreds of times more than was possible by testing chemicals in laboratory animals. "Once you get to that level, you're bound to find something," says Alan L. Harvey, director of the Strathclyde Institute for Drug Research at the University of Strathclyde in Scotland.

Among those looking is Monsanto, which has contracted with the Missouri Botanical Garden to supply the company with several thousand plants from both the U.S. and tropical countries. Merck & Co. has an arrangement with the New York Botanical Garden's Institute of Economic Botany for receiving plants from around the world. Biotics, a small start-up company in England



**TRADITIONAL MEDICINALS** bring new ideas for Shaman Pharmaceuticals, a San Carlos, Calif., firm that interviews healers in Latin America, Africa and Asia.

based at the University of Sussex, embodies another approach—that of a "science broker." It has supplied Glaxo and SmithKline Beecham and others with samples and chemical extracts from plants gathered from the tropics.

Many of the plant-screening programs are so recent that the leads they have gathered remain shrouded in the secrecy that cloaks drug development programs. But the wraps have come off a few of the results. SmithKline, for example, is pushing a cancer treatment called topotecan through clinical trials. An enzymatic assay revealed this compound, which comes from a Chinese tree, *Campotheca accuminata*. The active principal is derived from a chemical extracted from a tree that the National Cancer Institute (NCI) tagged for potential anticancer activity about 20 years ago.

The NCI has been a locus for searching for new drugs from plants. It mounted what may be the world's most extensive plant-testing program in 1986, replacing a 20-year screening project launched in 1960. Although the earlier

effort (which relied on mice as screening agents) produced taxol, it was scrapped in 1980 because it had not turned up enough leads. The effectiveness of taxol against ovarian cancer was not detected until the late 1980s.

So far the NCI's revived effort has collected 23,000 samples from 7,000 species in tropical areas and has identified three compounds that seem to work against AIDS in a laboratory dish. All three compounds have entered preclinical testing for toxicity.

One "hit" is an extract from a creeping vine that inhabits the canopies of rain forests in Cameroon. This member of the *Ancistrocladus* genus inhibits the replication of the AIDS virus. The plant was found in an attempt to search across the broadest possible taxonomic spectrum. It had no known medical use and still lacks a species name. "There are very few people on the planet who have ever seen this plant," says James S. Miller, a botanist from the Missouri Botanical Garden. More recently a University of Illinois team working for the



STEVEN FERRY/Merck

**COSTA RICAN FLORA** attracts botanists who conduct basic research and who hope to find plants that may yield new drugs.

NCI discovered a Malaysian tree, *Calophyllum lanigerum*, with potent anti-AIDS properties. Calanolide A, a compound from the tree, seems to work against an AZT-resistant form of the AIDS virus.

Another potential anti-AIDS drug was discovered in a plant in Samoa. Paul A. Cox, a Brigham Young University professor of botany, collected *Homalanthus nutans* on the recommendation of women healers there. The NCI extracted prostratin from the plant, a chemical that seems to protect immune cells from being destroyed by the AIDS virus. In Samoa, *H. nutans* was used as a treatment for yellow fever and other viral illnesses. "You have accumulation of knowledge in the culture that resembles human bioassay data," Cox says.

Indeed, several entrepreneurial companies are turning to traditional medicine to narrow their search for new drugs. Their idea, like Cox's, is to test materials that have shown pharmacological activity for hundreds of years and that are probably relatively nontoxic. Chemex Pharmaceuticals in Fort Lee, N.J., recently won approval from the Food and Drug Administration to market a treatment for precancerous skin

lesions. Called Actinex, the drug is derived from the creosote bush, which has a long history of medicinal use. Two companies founded within the past five years—Xenova in Slough, England, and Pharmagenesis in Palo Alto, Calif.—are combing through the traditional Chinese pharmacopoeia for promising leads.

Another company, Shaman Pharmaceuticals, was founded by a former venture capitalist, Lisa A. Conte, who wanted to combine drug development with an effort to preserve rain-forest flora. Conte's firm, based in San Carlos, Calif., sends teams of botanists and physicians to Latin America, Africa and Asia to search for plants that work against viruses, fungi or diabetes or that may become sedatives or analgesics.

Plants sent back to Shaman for testing must have been used in three geographically distinct areas. Conte claims that of the 200 that have passed this preliminary probe, more than half show activity against a targeted malady, as compared with less than 1 percent for mass screening.

In only 16 months Shaman has moved an antiviral drug for childhood flu caused by the respiratory syncytial virus from rural healers and urban botanicas in South

and Central America into FDA testing in humans. By showing medical photographs to healers in Peru and Ecuador, Shaman's botanists also turned up an antiviral agent that works against drug-resistant herpes infections. "What Shaman is doing is using thousands of years of human clinical trials," says William L. Current, a senior research scientist with Eli Lilly's infectious disease group. Last October Lilly made a \$4-million equity investment in Shaman and also struck an agreement to collaborate with the firm for four years in developing drugs that work against fungal diseases.

Gone are the days when a company could create drugs from plants that originate in developing countries without negotiating to pay royalties, as Lilly did during the 1960s with the rosy periwinkle. Extracts from the periwinkle produce vincristine and vinblastine, drugs used primarily against childhood leukemia and Hodgkin's disease, respectively. Shaman has pledged to pass up endangered plants and is committed to furnishing royalties from drug revenues to both the government and the native communities from which a plant is harvested, a policy that Lilly supports. Shaman will make these payments through

the Healing Forest Conservancy, a foundation the company set up to promote rain-forest conservation.

More unusual is Merck's agreement to pay \$1 million over a two-year period directly to Costa Rica's National Institute of Biodiversity (INBio) for collecting plants, insects and microbes. It also pledged to pay royalties for any leads that turn into pharmaceuticals. A portion of both the initial expenditure and any eventual royalties will help preserve wild areas in Costa Rica. Merck's collaboration with a nonprofit institute in a country whose gross national product is less than the drugmaker's annual revenues has generated intense interest in other nations between the tropics of Cancer and Capricorn.

INBio, which signed the accord with Merck in 1991, is now helping Indonesia to set up a similar institute devoted to biodiversity. Some public-interest groups have criticized the Merck-INBio agreement because of what they perceive to be a lack of accountability. "A nongovernmental organization doesn't have the right to sell genetic material to the rest of the world," says Jason W. Clay of Cultural Survival, an organization in Cambridge, Mass., that tries to find uses for indigenous materials, such as nuts for Ben & Jerry's Rainforest Crunch ice cream. INBio emphasizes that it was established three years ago by a governmental decree. A Merck official pointed out that others are not precluded from looking for natural samples in Costa Rica.

A five-year program set up last June by the National Institutes of Health, the National Science Foundation and the U.S. Agency for International Development aims to promote biodiversity and establish new economic ties with the developing world. The program, with \$1.5 million in annual funding, will set up consortia of universities, nonprofit institutes and industry to catalogue plants and other organisms, with the goal of isolating compounds that have pharmaceutical value.

Some environmentalists are rooting for the drug companies. "It is my hope and my expectation that people are going to find something pretty soon that is marketable," says Michael J. Balick, director of the Institute of Economic Botany at the New York Botanical Garden. This, he thinks, may lead to a "greater appreciation of the true value of these resources." Even if that happens, time may be running out for the rain forest. According to Cornell University professor of biology Thomas Eisner, "the looking for new chemicals is going slower than the rate at which species are becoming extinct." —Gary Stix