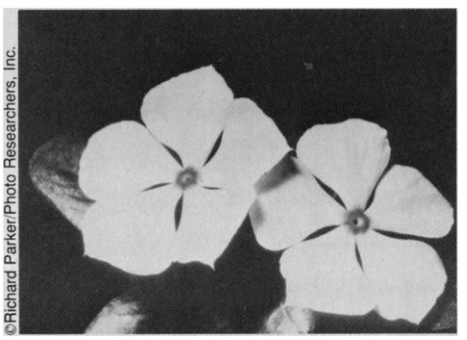
Combing the Earth for Cures to Cancer, AIDS

The cancer institute is looking for drug candidates in the heart of the rain forest and the belly of the sponge



Anticancer agent. *NIH wants to find more drug sources like the rosy periwinkle.*

THE little sea squirt *Tridemnun solidum* leads an obscure but tenacious existence, filtering its nourishment from the sea as it clings to rocks in shallow marine habitats, where a colony of the animals is said to resemble a glistening green crust.

What is remarkable, though, about this species of tunicate is not its color or consistency, but a compound that is extracted from it called didemnin B, a drug which last August entered clinical trials against a litany of human cancers.

A rejuvenated Natural Products Branch of the National Cancer Institute in Bethesda, Maryland, hopes the world holds many more surprises like the sea squirt. To find them, the institute has launched an ambitious $8-million program to support collectors who will spend the next 5 years combing the planet for possible drug candidates.

What lies ahead is the tremendous diversity of the rain forests and oceans, where the collectors will gather not only plants, but marine invertebrates, microorganisms, blue-green algae, and fungi. A laboratory to screen 10,000 substances a year against 100 cancer cell lines and the AIDS virus is now being organized in Frederick, Maryland.

Using natural products to manufacture drugs is, of course, an ancient and well-established practice that has yielded such familiar products as morphine, digitalis, penicillin, and aspirin. What is new about the cancer institute's latest drug-development program is the vigor and scope of the undertaking. The institute has even contracted with a small company called SeaPharm, Inc., of Princeton, New Jersey, to use submarines to collect marine invertebrates from depths reaching 900 meters.

In the past, the natural products branch screened plants obtained primarily from the temperate regions, a relatively barren habitat compared to the tropics. Also, material was often sent in willy-nilly by collectors, some of whom simply labeled their submissions "genus species unknown," which unfortunately made their gestures "barely better than worthless," says Richard Donovick of the natural products office. More problems included materials that were sometimes dried to such an extent that many of the active compounds were lost. Finally, extracts of plant and animal matter were tested for toxicity against murine leukemia, a screening technique that does much to gauge how well a toxin kills rapidly dividing cells but gives scant information about how effective the compound will be at controlling specific slow-growing tumors.

Such problems were in part the reason why the cancer institute's natural products branch went on the skids in the early 1980s. Its recent turnabout can be explained in several ways. Certainly, money devoted to AIDS research is one reason, as is the development of cell lines to test the extracts against specific cancers.

Moreover, a sense of urgency underlies the project, says Gordon Cragg of the natural products office. The rain forests, and the species they nuture, are rapidly disappearing. There is a feeling that if the jungles and reefs are not methodically scoured for drug sources now, it could soon be too late.

In some areas of the tropics, such as the Amazon valley, only 1% of the flora has been tested for any kind of bioactivity, reports Michael Balick of the New York Botanical Garden, one of three institutes under contract with the natural products office to collect and identify flora in the tropics.

Says Balick: "The problem is that rates of extinction are escalating so quickly that if one were to find a plant that displayed interesting bioactivity, it's quite possible to go back and find its habitat destroyed. It is a race against time."

Since it is almost impossible to predict what organisms might harbor substances that are effective in treating cancer, the natural products branch is casting a wide net. Interesting compounds seem as likely to come from the roots of the Mayapple plant as from microorganisms living in the gut of a sponge. Gregory Patterson of the University of Hawaii at Manoa, for instance, found a species of blue-green alga living in a fountain on campus that produced novel compounds that were active against types of leukemia in culture. On contract with the cancer institute, Patterson and colleagues will collect, cultivate, and prepare extracts of 1000 strains of blue-green algae over the next 5 years. Another group at the University of Connecticut at Storrs is doing a similar thing for fungi.

Collecting materials for the cancer institute is no walk in the park. Foreign governments can be suspicious of scientists coming to look for new and perhaps valuable medicines, says Djaja Doel Soejarto of the University of Illinois at Chicago, whose group is responsible for collecting plants in Southeast Asia. "The host country often wants to know, quite simply, 'What do we get out of it?' And I think that is a fair question." So Soejarto tries to involve individual researchers and herbariums from the host country and to explain to government officials that, should a plant prove promising, the country could cultivate it or petition a drug company to set up manufacturing. Says Soejarto: "If the plant is endemic, the country has a monopoly."

Other difficulties arise. The institute needs relatively fresh samples. For marine invertebrates, that means freezing. For plants, that means dry samples, but not too dry. "And this is not so easy to do in the jungle during the rainy season," adds Soejarto. The institute also requires bulk—about a kilogram for each sample of plant and marine material.

If a plant displays anticancer activity, it may take thousands of kilograms of raw material to get a hundred grams of a specific compound. For example, the institute has contracted for 30,000 kilograms of bark from the Pacific yew *Taxus brevifolia* because a compound isolated from the tree, called taxol, is in early clinical trials. According to Cragg, that amount of bark equals about 10,000 trees, or enough to cause an environmental skirmish in the Pacific Northwest where the tree is found.

The reason for all the dead trees is that many of these natural products are not easy to synthesize. Either the yield is too low or the process is not economically feasible to perform on a large scale. For instance, re-

searchers have been trying to synthesize taxol for the past 15 years.

The institute also wants collectors to keep detailed field notes. An area of great interest is how the plants and animals are used by local people. Consider the case of the rosy periwinkle *Catharanthus roseus*, of Madagascar, which native doctors prescribed for diabetes. In the United States, powerful anticancer agents isolated from the periwinkle—vinblastine and vincristine—are today used to treat various forms of leukemia.

Balick of the New York Botanical Garden just returned from the interior of Belize, where he worked with a well-known *curandero*, or healer, who uses herbal remedies to treat illness. As the forests disappear, however, so do sources such as Balick's medicine man. "These people are encyclopedias of local flora, and they're not being replaced," says Balick.

Indeed, the collecting program has pointed toward how important taxonomy is, a field of the natural sciences that in recent years has received little funding or attention. Says Mark Plotkin, director of plant conservation at the World Wildlife Fund in Washington: "As long as people think that the genetic engineers can cure everything, the world will think it doesn't need taxonomists anymore. But there is no biological diversity without the taxonomist to tell the stuff apart." ■ WILLIAM BOOTH

Briefing:

Foreigners in Science

Foreign-born scientists and engineers educated in the United States promise to become an ever larger part of the U.S. work force, according to the latest report from the National Science Foundation.* Eighty-five percent of graduate students with permanent visas indicate plans to stay in the United States, and the proportion of those with temporary visas who intend to stay has risen from less than one-third in 1972 to more than one-half in 1985.

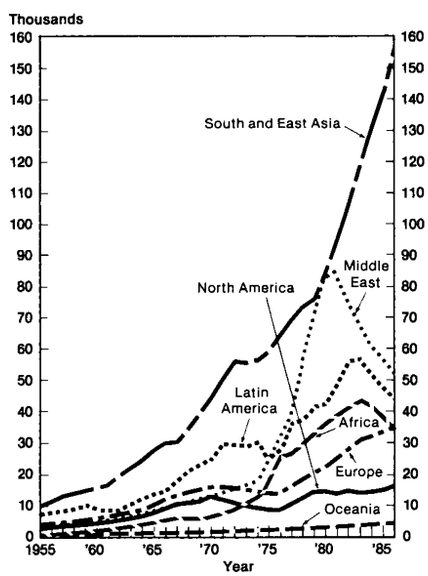
"From all indications, the growth trends in foreign involvement in U.S. science and engineering show no signs of abating" says the report. Foreign students comprise more than one-fourth of full-time graduate students in science and engineering, and their enrollment is increasing by 7% a year. At the same time, there has been a proportionate decrease in enrollment by Americans—for example, the number of science doctorates awarded to men dropped from 8.5 to 3.5 per thousand between 1970 and 1985, while the ratio for women rose only from 1.1 to 1.7.

The number of students from South and East Asia has grown precipitously and they now comprise over 40% of all foreign students. The number of Middle Easterners has dropped sharply since 1980, along with declines in world oil prices.

Engineering continues to be the dominant foreign interest, with more than one-half of engineering doctorates going to foreign citizens since 1981. The report says that if the number of foreign students in engineering doctorate programs increases by 2% a year, they will outnumber Americans by 3 to 2 by 1995. Among science fields, computer sciences show the greatest increases in foreign enrollment, averaging 21% a year during 1979–85.

The report says that although the U.S. hosts the largest number of foreign students of any country, it ranks only 15th in the percentage of foreigners in the student population. Among major industrialized nations, the only ones that rank lower are Japan and the Soviet Union. ■ C.H.

Chart 2. Foreign students in the United States by region of origin



NOTE: Geographic regions described here differ from those used by other data sources.
SOURCE: Institute of International Education; appendix table B-2

**Foreign Citizens in U.S. Science and Engineering: History, Status, and Outlook.*

Hopes and Fears at NSF

The National Science Foundation seems to be doing better in principle than in practice in achieving the doubling of the agency's budget over 5 years approved by President Reagan. Without disclosing any figures, NSF director Erich Bloch told the National Science Board on 21 August that the foundation's budget proposal for the 1989 fiscal year, which begins on 1 October 1988, exactly follows the plan set up by the Office of Management and Budget to achieve the goal. Bloch's mention of what he called a "second installment" toward a doubling suggests OMB's blessing. At the same meeting, however, Bloch acknowledged difficulties in landing the first installment—funding in the fiscal year 1988 budget now before Congress. With Congress searching for savings in the science budget (*Science*, 3 July, p. 22), he indicated that NSF faces a formidable task in convincing the legislators to fund the full $1.89 billion requested for the agency. ■ J.W.

Comings and Goings

Anthony J. Calio has announced his resignation as administrator of the National Oceanic and Atmospheric Administration. He will take a post as senior vice president for managment and operations of the Planning Research Corporation, a provider of computer and other technology-based services for industry and government.

Although the International Institute for Applied Systems Analysis (IIASA) lost the U.S. government contribution to its budget, the East-West research organization has appointed another American, **Robert Henry Pry**, as director. Pry has held high-level R&D management posts with General Electric and other U.S. companies. He succeeds **Thomas H. Lee**, who is returning to his professorship at MIT after his 3-year term at IIASA.

Astronomer **Sidney C. Wolff** has been named director of the National Optical Astronomy Observatories (NOAO) in Tucson. She moves up from the post of director of Kitt Peak National Observatory. NOAO manages Kitt Peak in Arizona and two other major observatories—Cerro Tololo in Chile and the National Solar Observatory, which has telescopes at Sacramento Peak, New Mexico, and Kitt Peak—and oversees a development program that includes work on the National New Technology Telescope. NOAO is operated by the Association of Universities for Research in Astronomy under contract to the National Science Foundation. Wolff succeeds **John T. Jefferies,** who remains at NOAO as a senior researcher. ■ J.W.