

Ethnobotany and the identification of therapeutic agents from the rainforest

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Abstract. Many rainforest plant species, including trees and herbaceous plants, are employed as medicines by indigenous people. In much of the American tropics, locally harvested herbal medicines are used for a significant portion of the primary health care, in both rural and urban areas. An experienced *curandero* or herbal healer is familiar with those species with marked biological activity, which are often classified as 'powerful plants'. Examples are given from studies in progress since 1987 in Belize, Central America.

The Institute of Economic Botany of The New York Botanical Garden is collaborating with the National Cancer Institute in Bethesda, Maryland (USA) in the search for higher plants with anti-AIDS and anticancer activity. Several strategies are cited for identification of promising leads from among the *circa* 110 000 species of higher plants that are present in the neotropics, the focus of this search. Recommendations are offered for the design of future efforts to identify plant leads for pharmaceutical testing.

1990 Bioactive compounds from plants. Wiley, Chichester (Ciba Foundation Symposium 154) p 22-39

Of the 250 000 species of higher plants known to exist on earth, only a relative handful have been thoroughly studied for all aspects of their potential therapeutic value in medicine. Yet the plant kingdom has yielded 25% or more of the drugs used in prescription medicines today (Farnsworth 1988). This paper is focused on the unstudied portion of the plant kingdom, particularly on strategies for increasing the efficiency of the search for new therapeutic agents, given the rate at which natural vegetation, especially in the tropics, is being destroyed.

The New York Botanical Garden Institute of Economic Botany (IEB) began its research programme in 1981. One focus of this programme is the search for plant species with new applications in agriculture, industry and medicine. In October 1986, the National Cancer Institute (NCI) awarded the IEB a contract to collect 1500 plant samples from the neotropics annually for its anticancer

and anti-AIDS screening programmes. Because the number of species of higher plants in the neotropics is estimated to be 110 000, we decided to test several approaches to determine which system of collection could generate the largest proportion of leads or 'hits' in the *in vitro* screens. By early 1990, IEB scientists or collaborating scientists from other institutions had collected plants in twelve countries as well as in the Commonwealth of Puerto Rico (Fig. 1).

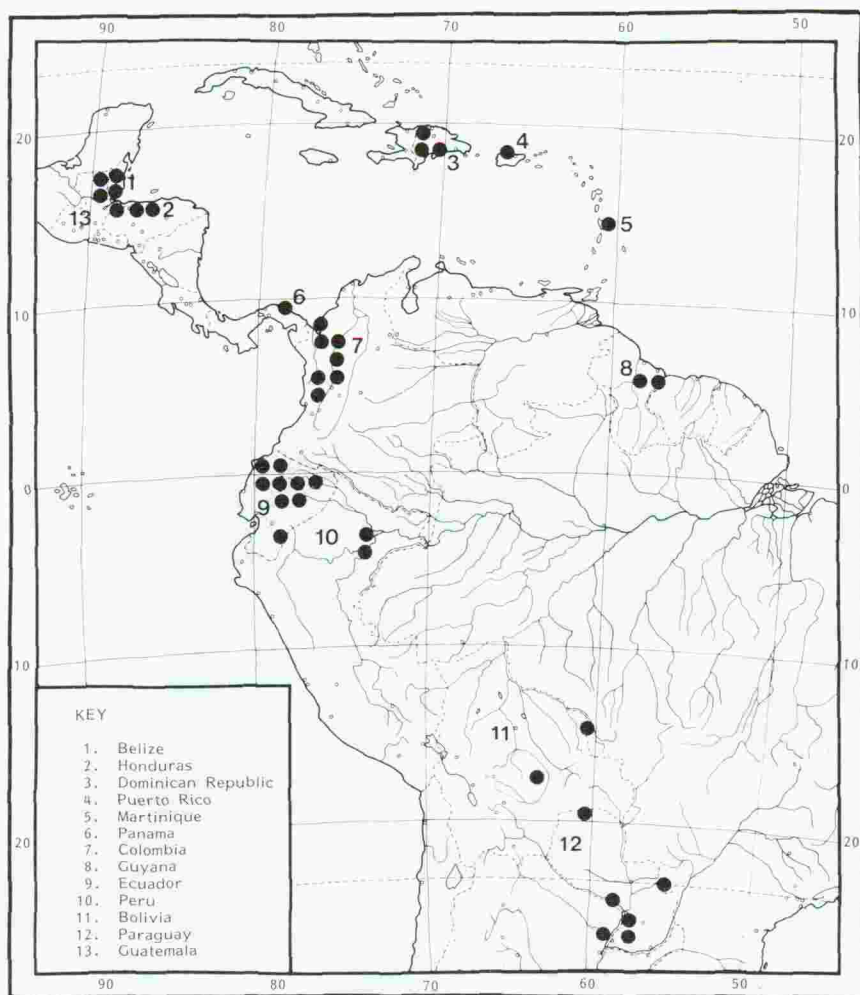


FIG. 1. Collection sites from 1986-1990 for the National Cancer Institute-sponsored plant collection programme.

Collection strategies

The random method

This method, as shown in Fig. 2, involves the complete collection of plants found in an area of tropical forest. In most cases, only plant species in fruit or flower are collected, as determination of sterile specimens can be time consuming, difficult, or occasionally impossible. Large numbers of species can be collected in this way, depending on the season and the number of fertile plants present in the area.

Targeted plant families

The second strategy is to target for collection those plant families known to be rich in biologically active compounds, such as alkaloids, glycosides, steroids or flavonoids. Fig. 3 illustrates an area of tropical forest but in this example plants from four botanical families are the focus of the collection because they are known to produce biologically active compounds: Apocynaceae, Euphorbiaceae, Menispermaceae and Solanaceae. Naturally, there are many other families rich in biologically active compounds.

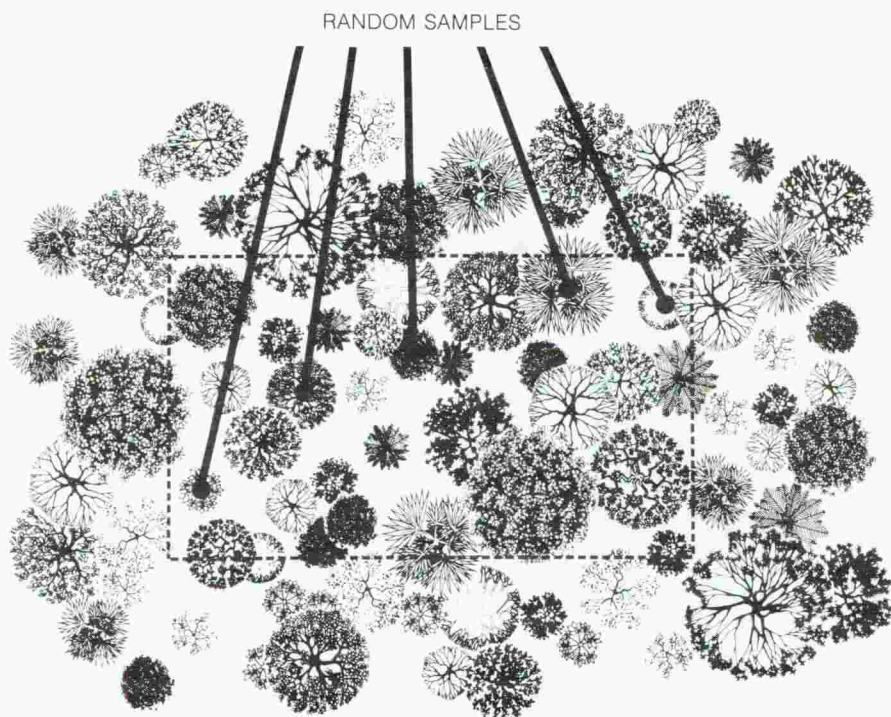


FIG. 2. Strategy for random collection in tropical forest. Diagrammatic aerial view of forest showing marked plot where plant species are collected.

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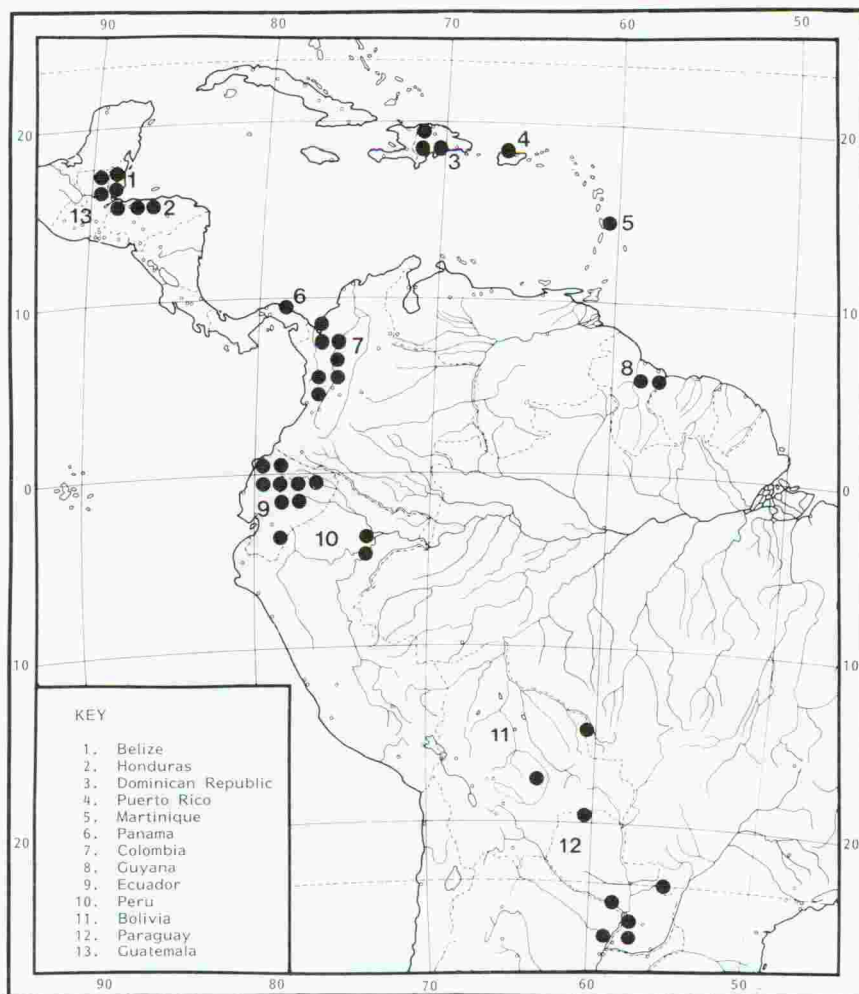


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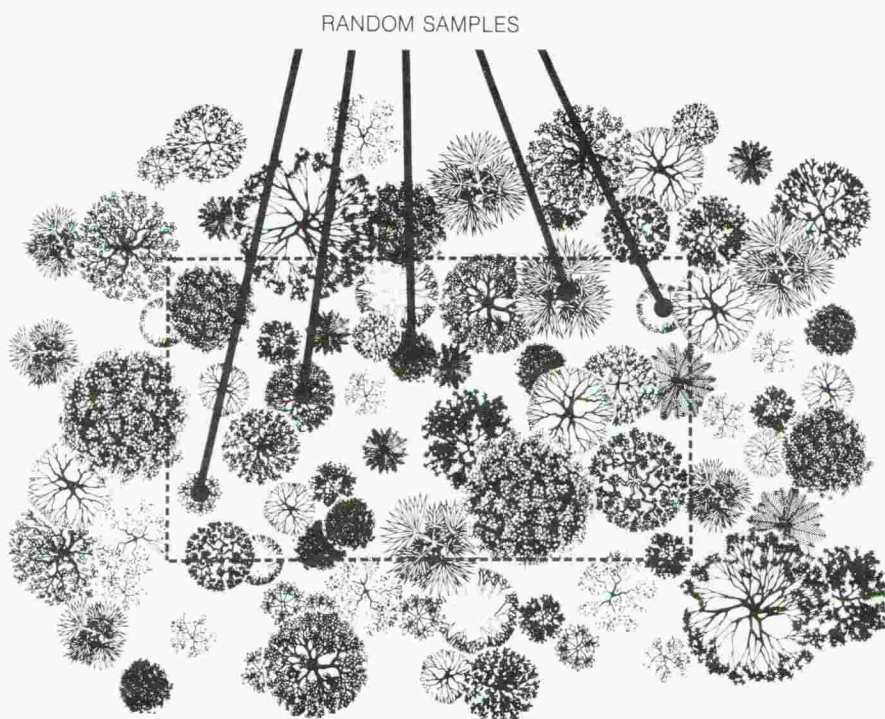


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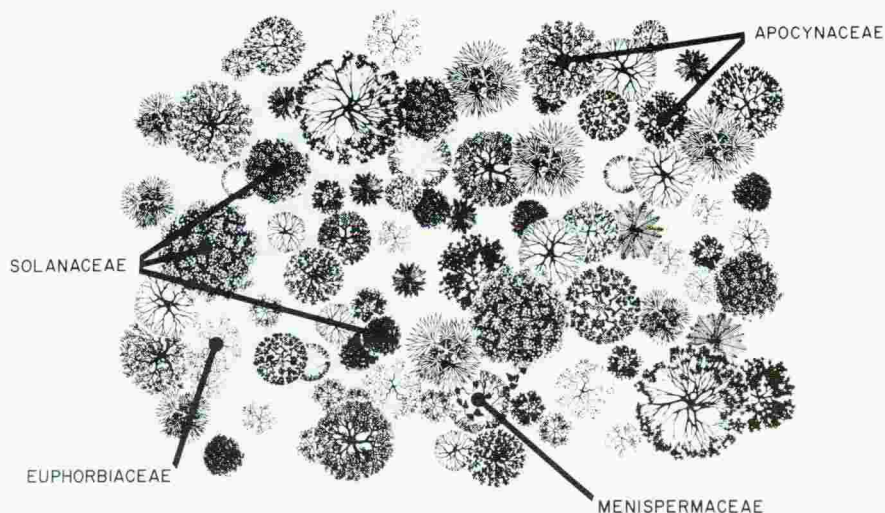


FIG. 3. Strategy for plant collection in tropical forest by plant family on the basis of known presence of bioactive compounds in certain families.

The ethnobotanical approach

This approach employs local people's knowledge about the medicinal uses of the plants and their environment. These people, working with an ethnobotanist, select the species of plants that are used medicinally in the area. Fig. 4 depicts an aerial view of the same area of tropical forest as Fig. 3 in which four genera of plants are used for medicinal purposes: *Bursera*, *Protium*, *Simaruba* and *Strychnos*. This strategy is the most difficult and intellectually challenging one, as it involves identifying people who are knowledgeable about the medicinal uses of their flora, and securing their cooperation in identifying the species they use or know.

It is the ethnobotanical strategy that I will focus on in this paper. Most of my work for the NCI programme involves the ethnobotanical strategy, primarily working in Belize. The co-principal investigator on this project, Dr Douglas C. Daly, has carried out both random collections and ethnobotanical studies in Bolivia, Colombia, Ecuador, Martinique and Peru. Plants from other areas illustrated in Fig. 1 have been collected using the random approach by 23 collaborating botanists.

In July 1987, I travelled to Belize at the invitation of Dr Rosita Arvigo, a nature-cure physician and doctor of naprapathy (a traditional medicine regimen, using manipulation, diet and massage). An accomplished Western herbalist, Dr Arvigo had been studying with an elderly Maya *curandero* or herbal healer, Don Eligio Panti, for four years. Dr Arvigo wanted to collaborate with an ethnobotanist, to document the Maya pharmacopoeia, as utilized by

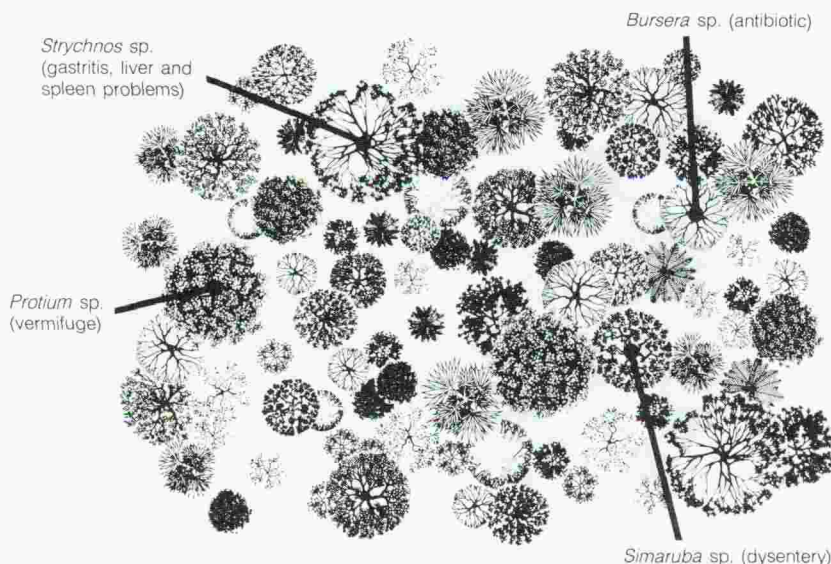


FIG. 4. Strategy for collection in tropical forest based on ethnobotanical uses, in this case for medicines. Examples of useful plants taken from studies with the Maya in Belize.

Don Eligio Panti. After a few days with Don Eligio, and further discussions with Dr Arvigo, I recognized the opportunity to document botanically the *materia medica* of this *curandero* and agreed to return to Belize to work with Dr Arvigo, Dr Gregory Shropshire and Don Eligio Panti. This collaboration developed into the 'Belize Ethnobotany Project', a country-wide survey of the plants used by herbal healers, bushmen and other people knowledgeable about the uses of the native Belizean flora. Belize is a small country with some 180 000 people, but it is culturally diverse and the population includes Mopan Maya, Kekchí Maya, Mennonite, Ladino, Creole, Garifuna and North American groups. All of these people use plants to varying degrees, and comparative ethnobotanical studies are underway.

Traditionally, the major focus of ethnobotany has involved the preparation of lists of plants used by people. In the last few decades, an interdisciplinary approach has developed and ethnobotanists have joined with social scientists and researchers from other fields to gather information concerning useful plants (e.g. Berlin et al 1974, Davis & Yost 1983, Denevan & Padoch 1987, Vickers & Plowman 1984). These interesting collaborations have generated new perspectives on the study of the relationship between plants and people.

The ethno-directed sampling hypothesis

The ethnobotanical approach to collecting plants, as defined above, involves recognition of the activity as a process involving two components. The first

component is the *cultural pre-screen* by local people of plants in their environment. This is usually thought of as a trial and error process occurring over hundreds or thousands of years. Another perspective, which is the one held by some of the *curanderos* we work with in Belize, is that the selection of useful plants is at least partially directed by supernatural forces. The second component is the *ethnobotanical filter*, in which the information about specific plant usage is acquired and introduced into the body of scientific knowledge through the ethnobotanical research. The *ethnobotanical filter* scans all the plants present in a region and captures those species of pharmacological use in order to, in the present case, provide samples to a drug development screening programme. The ethno-directed sampling hypothesis therefore maintains that the combination of indigenous knowledge about medicinal plants and the ethnobotanist's collection and documentation of this knowledge will yield a higher number of biologically active compounds for the screening programme on a per sample basis as compared to a group of plants collected at random. This will result in a higher probability of producing useful therapies from a group of medicinal plants. The pharmacological literature contains many references to the value of ethnobotany and indigenous knowledge in the development of therapeutic agents from plants (Cox et al 1989, Elisabetsky 1986, Farnsworth 1984, Svendsen & Scheffer 1982), although there are, to the best of my knowledge, no actual investigations carried out with a random collection as a control group. Later in this paper I shall discuss the data that we have received from the NCI's study in relation to the ethno-directed sampling hypothesis.

The *in vitro* anti-HIV screen

The first priority for the plants collected in the NCI sponsored programme is screening against the human immunodeficiency virus (HIV), the causative agent of AIDS. Plants are air or heat dried (below 65 °C) in the field and packaged in 0.5–1.0 kg samples, which are sent to The Frederick Cancer Research Facility Natural Products Repository in Frederick, Maryland for extraction and study. Voucher (herbarium) collections are made in the field and accompany the bulk samples to the US for distribution and study by botanists. Duplicate specimens are deposited in herbaria in the country where the plant was collected.

The dried plant samples are stored at –20 °C for a minimum of 48 hours immediately after arrival at the NCI. This period of freezing is a requirement of the US Department of Agriculture as a precaution to reduce risk of release of alien pests.

Each sample is labelled, either in the field or on arrival at the repository, with a bar-code label designating a unique NCI collection number. After freezing, samples are logged into a raw materials database and sent to the Natural Products Extraction Laboratory for grinding and extraction. A small portion

of each sample is removed and kept as a voucher. The rest of the sample is then ground and extracted by slow percolation at room temperature with dichloromethane/methanol (1:1 mixture), followed by a methanol wash. The combined extract and wash are concentrated *in vacuo* and finally dried under high vacuum to give an organic extract. After the methanol wash, the residual plant material is extracted by percolation at room temperature with distilled water; lyophilization of the percolate gives the water extract. All extracts are returned to the natural products repository for storage at -20°C until requested for testing.

In the *in vitro* anti-HIV screen, human T lymphoblastic cells infected with the AIDS virus are incubated for six days with varying concentrations of the extract (Weislow et al 1989). Untreated infected cells do not proliferate and die rapidly. Infected cells treated with extracts containing effective antiviral agents will proliferate and survive at moderate extract concentrations, whereas high concentrations of extracts generally will kill the cells. The degree of activity is measured by the level of protection provided by extracts at sub-toxic concentrations. Extracts are formulated for testing by dissolving in dimethyl sulphoxide and dilution with cell culture medium to a maximum concentration of 250 $\mu\text{g}/\text{ml}$.

Random versus ethnobotanical collection

To test the ethno-directed sampling hypothesis, two groups of plants were collected and sent to the NCI for screening against HIV. The random collection included plants from Honduras and Belize. The ethnobotanical collection was composed of species identified by Don Eligio Panti as 'powerful plants'. The 'powerful plants', according to Don Eligio, are species with substantial therapeutic value which are frequently used in his practice for a variety of purposes. The results from screening the two samples are presented in Table 1. It should be emphasized that these results are preliminary, and that data from only a small number of samples are available for analysis. However, these data have been analysed using the Fisher exact probability test, a methodology useful for handling data from small sample sizes (Siegel 1956). The results of this test show that $P=0.101$; while providing no firm proof, this is a strong indication that the null hypothesis (that there is no relationship between ethnobotanical

TABLE 1 Preliminary testing of plants in an *in vitro* anti-HIV screen

	<i>Collection method</i>	
	<i>Random collections</i>	<i>Ethnobotanical collections</i>
Total species tested	18	20
Per cent (number) active	6% (1)	25% (5)

collections and active compounds) should be rejected. Therefore, although the results from these two data sets do not conclusively prove the ethno-directed sampling hypothesis, they do support its validity. We expect that at the end of the five-year collection period, information on 7500 plant samples will be available, representing a minimum of 2000–4000 species, which can then be classified according to medicinal and non-medicinal uses and further analysed for their effectiveness in the anticancer and anti-AIDS screens. At that time we will also be able to detect trends by plant family, as discussed in the second collection strategy.

The conservation imperative and medicinal plants

Each year large areas of rainforest are destroyed through conversion to agricultural land or for other purposes. These habitats contain plant and animal species that are found nowhere else on earth. Most conservation activity focuses on the rainforest as an important and biologically rich habitat, and as a potential source of new products, such as medicines that could be introduced into commercial use. Rarely is the perspective taken that the forests contain a wealth of medicinal plants currently used by local people. It is estimated that up to 80% of the world's population uses plant medicines as an important component of primary health care (Farnsworth et al 1985) and certainly our fieldwork in Belize and elsewhere in Latin America supports this assertion. Therefore, since adequate hospitals and Western-trained doctors are not found in much of the tropics, the destruction of the rainforest will also destroy the primary health care network involving plants and traditional healers. Although no census has ever been taken, it is likely that there are thousands, if not tens of thousands, of traditional healers practising throughout the neotropics. Very often these people are elderly and, because of the forces of acculturation present in their society, many have no apprentices to carry on their work. One effect of deforestation is to reduce dramatically the supply of medicinal plants available to the traditional healer. Fig. 5 gives an idea of the situation facing Don Eligio Panti in the collection of plants he uses in his medicinal practice. In 1940, in an early stage of Don Eligio's practice, he walked for ten minutes from his house to the secondary forest site where he collected medicinal plants used to treat his patients. In 1984, when he began working with Dr Arvigo, it took them thirty minutes to reach a site that had sufficient quantities of these same species. In 1988, when I accompanied Dr Arvigo and Don Eligio Panti to the nearest collection site, it took us seventy-five minutes to reach an area where the plants could be found. Clearly, the added time and effort involved in the collection of medicinal plants is an increased burden for the traditional healer, therefore reducing his or her effectiveness in offering primary health care services to the community. Thus, in addition to building a case for conservation activities based on the *potential* use of the forest as a source of medicinal plants for our society,

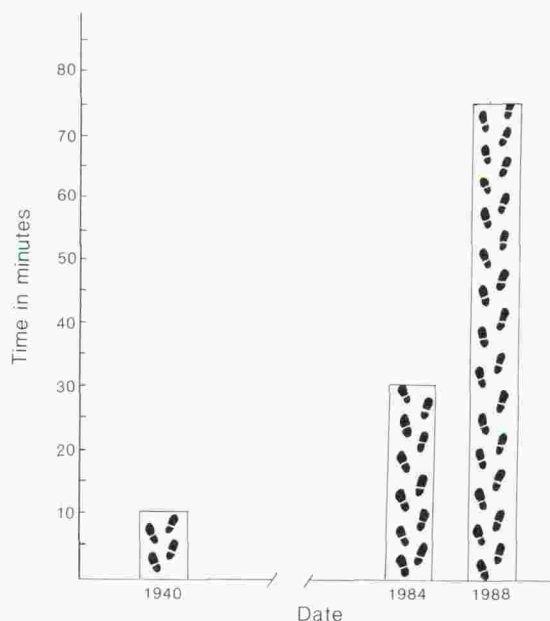


FIG. 5. Time required for Don Eligio Panti to reach secondary forest site for medicinal plant collecting. Note substantial increase from 1984 to 1988, indicating high level of forest destruction in the San Antonio region of Belize.

there is also great strength in the contention that conservation of these species is essential to the survival of the existing health care network in many tropical countries involving traditional medicine. Otherwise, as effective therapies are identified and developed from tropical forest plants over the next 5–10 years, the original habitats in which the species are found may no longer exist, and the plants so desperately needed as a supply of raw material will have become extinct.

Conclusion

As tropical forests are destroyed and tribal peoples acculturated, our ability to discover new pharmaceutical agents and bring them into everyday use is being seriously compromised. The lull in natural products research over the last few decades combined with the reduction in global plant biodiversity has resulted in an urgent race against time. Given the relatively small number of scientists qualified to address this problem, it is clear that choices in the allocation of time and resources must be made. The ethno-directed sampling methodology allows the researcher to obtain a higher number of leads in a pool of plant samples as compared to a group of plants selected at random. The broader utilization of this methodology could streamline the discovery and development of drugs from natural products.

Acknowledgements

I would like to acknowledge the input of Drs Elaine Elisabetsky and Douglas C. Daly in developing the terminology for the ethno-directed sampling hypothesis and to thank Dr Gordon Cragg for the very clear explanation of the screening programme carried out by the NCI. Dr Elaine Elisabetsky and Wil de Jong kindly provided help with the statistical analysis and Dr Charlotte Gyllenhaal provided bibliographic assistance. Drs Brian Boom, Elaine Elisabetsky and Douglas Daly offered comments on an earlier version of this paper. Bobbi Angell and Carol Gracie prepared the graphics presented in this paper. The fieldwork in Belize and Honduras was sponsored by the National Cancer Institute, the Metropolitan Life Foundation, and the US Agency for International Development. I am most grateful to the Philecology Trust for support of my research. Active collaboration of the Belize Forestry Department and Ix Chel Tropical Research Center, San Ignacio, Belize and the Fundacion Hondurena de Investigacion Agricola, San Pedro Sula, Honduras is acknowledged. Finally, thanks are due Dr Rosita Arvigo, Don Eligio Panti and Dr Gregory Shropshire for their interest in and continued collaboration on the Belize Ethnobotany Project. It is Don Eligio Panti's fondest wish that we will find a way to build a bridge between the medicinal plant knowledge of the ancient Maya and the therapeutic needs of Western medicine and contemporary society, and we are working toward this. This small contribution is dedicated to those thousands of traditional healers in the neotropics who, for the most part, toil under the most difficult circumstances and in the face of an onslaught of 'modern' culture.

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DISCUSSION

Hall: Do you have a trained Western physician participating in your studies? A large proportion of people who come to Western doctors (I think some of my friends would say 60–70% of their patients) basically come for reassurance. So it's hard to tell which treatments are cures and which are not cures.

Balick: I have just led a scientific tour to Belize. In the group were two doctors, two nurses and five other lay people who wanted an experience in the rainforest and wished to help in the NCI plant collection programme. Some of these people were initially quite sceptical. At the end of the tour they admitted that they came wanting to see that a healer was prescribing a certain plant for something like melanoma and claiming to cure the disease—and they were going to disprove it. But they had realized that this was not the point; many patients come to herbal healers for help with primary health care. The Western-style hospitals are often too far away and too expensive for local people. Many of these people live to a ripe old age using traditional medical systems.

I would also say that these healers do not claim to cure all cancers or AIDS or some of the diseases that many of the MDs would try to pin them down on. They are curing diseases that are much more important to the people of the country—diarrhoea, malaria, fevers, dehydration, things that cause many deaths in Third World countries.

Kuč: I think it would be absolutely imperative to have medical doctors on the plant and information-gathering expeditions. It would be interesting and important to compare the diagnoses of the healers and the Western-trained medics, granted that the latter would not have the facilities they were accustomed to in making their diagnoses. The people that come to the healer mention a particular ailment. The healer then gives them, as I understand it, a particular drug for that illness. It would be very important to have documentation of what the healer was giving for particular ailments and what the medical doctor diagnosed. When the plant material is brought back to the West, one can relate the testing of that material to a particular illness. That might be more useful than the current approach where there are preconceptions of what you are looking for—a cure for AIDS, a cure for cancer—regardless of what the healer has in mind when giving the treatment.

Balick: That's a very good point. The patient interviews that I do take very careful note of the complaints, of the herbs administered and the quantity administered. We are also working with local Belizian doctors, so-called Western trained doctors and nurses.

I would like to find some MDs who would be willing to come with me. The conditions are not always very pleasant; some of the Western people I meet in the field do nothing but complain. There is a real opportunity here for people who are willing to get out of their own environment for a while, enter another environment and get some interesting data.

Cox: In my own research in the South Pacific we've had MDs participating. We find that MDs sometimes lack the anthropological ability to relate well to the people. I have had some MDs who have done very well, others who have experienced severe 'culture shock' and climbed back on the plane in two days. I find that sometimes physicians are culturally biased, so if people don't wear suits and ties and talk English and act in a Western manner, they are very uncomfortable in dealing with that other person, not only as a source of information but as a potential colleague.

My experience in the South Pacific, particularly in Samoa, is that the MDs I have taken down have been very impressed with what the people have been doing. The problem is trying to relate a specific remedy to a specific Western disease. Indigenous peoples do not use disease terms like we do; there is not a one-to-one correspondence between their disease classifications and ours. For example, where Michael Balick works a prominent disease is *susto*, which really does not translate into Western terms. And yet we have this sort of thing in European countries. In England there is something called gripe that babies have (they seem a little grumpy); the treatment is to give substances rich in ethanol to the baby. In Sweden, broken heart, loss of a romantic partner, actually causes disease and is recognized as an illness.

It takes a very special sort of MD to be able to undergo the sort of rigours of field work that Michael and I experience in our work. We welcome MDs who can approach other cultures with an open mind.

It is important to see our work as ethnopharmacologists in relation to the long-term needs of science. Everybody is interested right now in AIDS; they want substances that show anti-HIV activity. Obviously we should respond to that, but if we do our work properly we will not just respond to HIV, which in ten years may not be an issue, but we will address the drug needs of the 22nd century. A hundred years from now traditional antibiotics may no longer be efficacious and we may need new sources, new types of antibiotics. If Michael does his work correctly and I do mine correctly, our work will continue to provide a font of natural products for diseases and needs that we haven't even realized yet.

Balick: Let me give an example of a negative interaction between the MD and the healer. A medical person whom I met in the field once complained that the healer's shirt was dirty and therefore he wouldn't take him seriously as a health professional. Something as insulting, in a cultural way, as a statement like that could absolutely destroy years of work building a relationship with a healer. You have to balance the sort of suspicion and the arrogance of our own systems with the goal of the project which is to document the customs of the healers, understand it and utilize it before these people die.

Hall: You are making major claims that if we don't go out and do these analyses then things will be lost forever. Yet when we really look at the range of plants that you are analysing, I think the answer is that a large number of

your patients, as I mentioned with Western patients, are concerned with emotional diseases. The fact is that someone sitting in the middle of the Bronx or in the middle of Chicago with no forest or plants around can be 'cured' by a good psychologist. So if the healer gives the patient something and tells them it's good, then it can cure people. I agree that in terms of human treatment that's important, but it doesn't relate to the search for bioactive compounds. I think the distinction hasn't been made of changes in emotional feelings. We certainly recognize that many plants, including tobacco, have major effects on people's emotions. Most of the discussion of these issues has been focused on diseases and we are sitting waiting for new cures.

Certainly the antihelminthic and antipyretic activities are effective. Dr Cox commented that there is no Western equivalent to some of these diseases; that's very worrisome because we need a precise focus on what we are talking about; otherwise we have no idea whether there is a specific compound that will deal with the aetiological agent. I am concerned that you may be getting a very large database but it won't contain the vital information about the purpose of a particular drug.

Balick: There is a notion that if something is not of physical origin it is not really a problem. I have a bias after living and working for fifteen years in environments where diseases are known to be caused by factors other than physical (e.g. infectious organisms). For example, I have seen someone go into convulsions after having their picture taken. They very strongly believed that their soul was being captured by the camera. It was a movie camera pointed at a person by a tourist without asking first. The person had to be hospitalized, they had to be treated by Western doctors, they had to be given valium and oxygen and a lot of other things and they were not released until three days later.

It is very hard for me to answer that kind of criticism because it assumes that these diseases or conditions do not exist unless they have been previously described by Western doctors. They do exist and that's where there is a very dangerous cultural gap between these two disciplines (ethnopharmacology and Western medicine). The only way we can bridge that gap is for you to come with me into the forest. Our surveys show that a significant number of patients come with problems caused by things like *susto*. Do you know what *susto* is? If something scared you and you went into a panic or a jaguar crossed your path, you could get physically ill from that. You would show symptoms of *susto*, which might manifest itself as a total lack of energy or 'spirit'.

The cultural heritage of a patient is very important. Perhaps we have to shed some of the burdens that we carry as scientists into the field and begin to consider things from other people's perspective, for example what are the disease concepts in a particular culture.

I witnessed a treatment for snake bite under the supervision of an MD in 1978 with the Guahibo Indians of the Llanos of Columbia. A man was brought into the hospital two days after being bitten by a very poisonous snake. He was in a state of toxic delirium, he had blood coming through the skin and

blood in his urine. This patient was in the hospital and his condition was carefully monitored and documented. He was dying, he was given sufficient antivenom serum by a Western-trained MD to neutralize 200 mg of venom. It did nothing. A Guahibo *curandero* was there. He explained that the man did not understand what the needle was that the MD was putting into him. The *curandero* said 'You are not addressing his culture, you are not treating the spiritual side of his condition. Let me heal him, he's going to die, he has a couple of hours left, let me try.' The Western doctor was very open minded, having grown up and worked in Indian cultures, so he let the *curandero* treat the man. The *curandero* gave the patient a smoke-blowing treatment. He blew smoke and put water on the extremities of the patient. The patient was semi-conscious and was somewhat aware that this was happening. The results were amazing, the patient started to recover immediately: the symptoms started turning around, the heart beat changed, the blood, all of that started to improve. The doctor said that in the treatment of many snake bites he had never seen the patient's condition change for the positive so quickly. We wrote a paper together on this experience (Zethelius & Balick 1982). The great lesson is that if you don't treat the spirit, for people not accustomed to Western medicine, you are only going to be half as effective as you might be.

Elisabetsky: I would suggest that we are being too narrow by trying to find a single rule to deal with traditional information. Even in Western medicine, we treat each case individually. We have different pharmacokinetics, different dose ranges, routes of administration and so on. Now we are trying to find one rule to cover information from different cultures, each with their own traditional medical system.

We are trying to find plant species that are sources of cross-culturally effective drugs, so it does make sense to look for plants that are used in different cultures. What is being questioned here is the pattern of use. For instance, *Jatropha curcas* is used by 105 different cultures for 112 different purposes. That might be a sign of general toxicity rather than specific pharmacological activity. On the other hand the same disease can be expressed by different people in different manners. One people may use a plant to treat sneezing and another people may use it for itching, but we are talking about antihistamine activity in both cases. A plant may be used to treat allergy or inflammation and we can be talking about anti-platelet activating factor activity. So it is crucial to analyse the symptoms. We might not care to know that it's caused by susto but an epileptic fit can be described and interpreted as epilepsy. So even if MDs cannot go to the field (I had the same experience as Mike and Paul, it's very difficult to find an MD who is culturally prepared to respect a traditional healer), it's crucial to collect this information on symptoms and then work systematically.

Fowler: Am I right in thinking that a number of plants are used by different tribes and have different pharmacological effects in those tribes? In other words, the same species is used for different medicinal purposes.

Balick: No, one of the interesting things about studying five cultures and working with different healers in these cultures is that you also find examples of plants that are used to treat the same disease in different cultures. Remember that in the NCI programme, one of the cultural groups under study came from India, one came from Africa. Then there are other plants that have different uses in the various cultures.

Fowler: So to what extent are you picking up these variations because of a difference in the population physiology? And how would that relate to Western European or North American populations. We have a medicinal/clinical effect which may bear no relation to the Western situation, if there is a difference in the genotype of the human species.

Balick: In the case of parasites, in the case of stomach ache, eating bad food and feeling very sick, I don't have the medical training to say if there's a genetic difference between one group of people that gets *Entamoeba histolytica* and has one reaction and another that does not.

Farnsworth: I am intrigued by your finding that the plants selected on the basis of their use in traditional medicine have a hit rate against HIV considerably higher than that of randomly selected plants—I find this extraordinary. I believe your selections from traditional medicine were too small or they represented a specific plant family which ultimately will be shown to contain a certain widespread class of chemical compounds that will have biased your data.

Chapuis et al (1988) tested 200 extracts, prepared from 75 medicinal plant species used in Panama, Africa and Mauritius, for cytotoxicity. Fifteen of the 75 species showed activity in the single assay employed. The authors stated that pre-selection of plants on the basis of medicinal use might be a useful criterion for the identification of new bioactive compounds. There was no comparison of their pre-selected sample with a randomly collected sample. From these results, I find it difficult to rationalize the relationships between use in traditional medicine, cytotoxicity and new chemical compounds!

Balick: I don't know of any data sets that have compared random collections to targeted ones. Ours was a very preliminary attempt to examine the data we have from the NCI and present it. It is preliminary; I agree that 38 species is a small number. But those plants were from different families, from a diverse botanical spectrum. At present our analysis shows that this data set is borderline with regard to statistical significance. We will have a much larger data set three or four years from now when we have the other 7000 species analysed on our computers.

Of the 250 plants in the Mayan pharmacopoeia that we have identified, the ones that pop up over and over and over again in the healing process are the group that we refer to as 'powerful plants'. They run along certain curative lines, for example some are antihelminthics. By looking at the powerful plants that have very effective bioactivity, we can select species that will give higher numbers of hits in the screens.

Fleet: Would your HIV screen distinguish between general cytotoxicity and a specific antiviral effect? In this particular piece of work, you might just be looking at a set of plants that contain cytotoxic materials.

Balick: What I am suggesting is that by using this system we can maximize the number of leads that are found in the screens in a shorter time than with the random collections. I think we have shown that in a preliminary way. I cannot predict how many useful compounds are going to come out of this programme, if any. I view my job as the person in the field attempting to maximize the efficiency of your laboratory's time by delivering plants that will result in as many leads as possible.

I want to clarify the concept of the 'powerful plant'. I am not saying that if we are looking for a hepatitis cure we should go and look at all the healers who are treating hepatitis and then take only those plants back. I am suggesting that we look at the plants with the greatest amount of biological activity as identified by their frequent use by healers, and take those species back to the laboratory. That's how I got the anti-HIV data. I was not trying to bias the healer in any way, I simply observed and selected the most 'powerful plants' and provided them to the lab scientists. The result, admittedly very preliminary, is a fourfold increase over the random collections.

Bowers: I like the concept of the powerful plant very much. Certain plants produce a few chemicals in relatively high concentrations. If these chemicals do have some effect in biological systems, they will be more readily discovered than a chemical in the extract of a plant which may contain thousands of compounds but at only low concentrations.

An interesting example is the use of *Piper* species. Several years ago I was in Hawaii and I went to the botanical garden. With their permission I collected some leaves, took them back and put them into our tests against insects, fungi or nematodes. One of these plants contained a number of compounds which had very good nematocidal activity and also antifungal activity. These were allypyrocatechol, its diacetate, chavicol, chavibetol and chavibetol acetate. Two of those were previously unreported. The plant was *Piper betle*. In the literature I found that people in South East Asia chew the leaves of this plant after eating a meal. There were no claims about curing disease or a relationship with medicine, only that it was refreshing somehow. One report from the Philippines said that the leaves were sometimes wrapped around powdered lime and chewed after a meal. I made the calcium salts of those compounds and they were one hundred times more active against nematodes and fungi in the more soluble form (Evans et al 1984).

About that time I got a New Year's greeting card from Professor Sharma at the National Chemical Laboratory in Poona. This card was reproduced from an Indian painting of about 1750 AD. The fine print which explained the picture was a poem taken from this very old painting. The poem went 'clad in delicate fabrics of yellow, red and orange hue, the divine lovers seated on a low throne

are enjoying the taste of betel leaf. (It was implied that this was *Piper betle*.) The handmaiden in the lower left corner is preparing betel from a gilded box. The sign of ecstasy on the lovers' faces is in tune with the hush of eventide that pervades the setting.' This was a very curious circumstance. Here is a plant the leaves of which have entered into the common use of people in many parts of Asia, just a cultural use, not a medicinal one. Yet there is sufficient of these compounds in one or two leaves to be effective against stomach nematodes and opportunistic fungi that might contaminate food. Chewing the leaves would be beneficial to health. So here is a link between cultural practice, presumably to refresh one's taste, and a clear medicinal utility associated with this sophisticated group of plants.

I looked in other species of *Piper* and found compounds that interfered with insect growth in various specific ways without being particularly toxic. Chemically, it is a very interesting genus. So I very much support the concept of powerful plants. These compounds are present in the plants at high enough concentrations that they can be detected in many assays.

McDonald: It is still worrying that maybe what you have there is a group of plants containing compounds that are relatively non-specific in their biological action, for example compounds that uncouple oxidative phosphorylation and interfere with respiration. In screening synthetic chemicals for biological activity one does come across these sorts of agents, which give an effect but are taken out of our current protocols for selecting compounds for clinical testing because of that very property. This is worrying in two ways: one is that perhaps from your natural sources these compounds will be less useful to medicine; the other is that modern pharmaceutical practice rejects compounds at an early stage which might be useful in medicine.

Cox: I would like to take up Norman Farnsworth's challenge. He asks why we should expect to find plants from Belize that are active against HIV? This virus wasn't found in Belize before about five years ago. There's no reason to believe that the people had that as a traditional pre-European contact disease category. There's no reason to believe that the people had specific remedies for HIV, so his challenge is quite cogent. Why should Michael Balick expect a higher rate of anti-HIV activity in plants derived from the healers in Belize than in plants collected at random?

To me an analogous situation would be the search for a bioactive molecule useful in treating another specific disease. Would we be more likely to find a useful substance by going through a pharmacy, pulling out all the drugs in the pharmacy and testing them, or by going through Chemical Abstracts and pulling out molecules at random? We know that the drugs in the pharmacy show bioactivity in human systems. Furthermore, we know that certain crucial problems of toxicity are unlikely to arise from these compounds; for example, they are unlikely to be mitochondrial poisons. Michael is generating plants that contain compounds that are bioactive in human systems. The belief is that by

looking at those compounds we are more likely to find useful bioactivity than by just going randomly through the forest collecting plants that have no evidence of bioactivity. I believe that this explains why Michael would find a higher anti-HIV hit rate in plants derived from medicinal usage.

Balick: In addition, it's interesting that all of these plants are consumed orally. There are no arrow poisons that we found effective, for example. I think that gives you a lead on some of the cytotoxic effects.

I think we will have the answer in about five years. We will have thousands of collections, we will have thousands of bits of information. I have no cancer data, even though the first plants were collected two and a half years ago. I agree that these are very preliminary data, it is a small data set, but it's the only one around.

Rickards: Dr Balick, is there any information on the chemical analysis of the plants you have identified, particularly those you call 'powerful plants'?

Balick: I use the NAPRALERT system and I asked Norman Farnsworth for a series of print-outs—some of the powerful plants are discussed in the print-outs. For some of the plants there is quite a lot of information available, for others there is none.

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