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Biodiversity prospecting: *a new panacea* for development?

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Biodiversity has been touted by some as the developing countries' new competitive advantage because these countries have sovereignty over the majority of the world's biodiversity, the value of which is yet to be determined. Biodiversity prospecting is the examination of biological resources in search of active compounds for pharmaceutical development, agricultural and industrial use. In this article, five cases of biodiversity prospecting are described, their future prospects are analysed, and policy options for other institutions and countries interested in pursuing such prospecting are discussed. The market for essential oils (particularly for cosmetics), phytopharmaceuticals and herbal preparations, agricultural chemicals, and industrial enzymes is much greater and easier to get into than that for new compounds to be tested for possible pharmaceutical use. The long testing period for pharmaceuticals makes immediate returns unlikely, though there is long-term potential. Moreover, there are important spillover effects for other economic sectors, particularly agriculture and industry, because of the scientific capacity that has to be developed in order to add value in the various stages of the biodiversity prospecting and drug development process. Initial findings indicate that biodiversity prospecting can be beneficial for developing countries provided they already have or can establish the relevant scientific infrastructure, intellectual property laws, conservation areas, good negotiating skills, and the political will to collaborate both with each other and with industries in the developed countries.

I

Introduction

Biodiversity has been touted by some as the developing countries' new competitive advantage because they have sovereignty over the majority of the world's biodiversity, much of which is still unknown to science and the value of which is yet to be determined. Biodiversity prospecting –the exploration of biological resources in search of active compounds for pharmaceutical development, agriculture and industry– has captured the imagination of many scientists, policy makers and environmentalists. Interest has primarily been in medicinal plants and natural substances that have biological activity, because "rational drug design" using biochemistry and supercomputers has proven more complicated than it was once thought. Biodiversity prospecting, then, is seen as a way of preserving biodiversity because of its potential economic value in the drug discovery process.

Other reasons why biodiversity prospecting is in vogue include the fact that "more than 60 per cent of the world's people depend directly on plants for their medicines: the Chinese use more than 5,000 of the estimated 30,000 species of plants in their country for medicinal purposes. Moreover the great majority of Western medicines owe their existence to research on the natural products that organisms produce: for example, natural products played a role in the derivation of each of the top 20 pharmaceutical products sold in the United States in 1988" (Raven, 1994). Ten of the top twenty-five best selling drugs in the United Kingdom in 1993 were also derived from or inspired by natural sources (Ten Kate, 1995, p. 10). Arguments both for saving biodiversity because of its future potential and for searching through it using advanced scientific techniques cite estimates that "less than 10% of the estimated 250,000 flowering species in the world have been examined scientifically for their potential in medicine" (not to mention other forms of biodiversity) and that by the year 2050 one in four of the higher plants will probably have become extinct before their medicinal potential has been explored.[1]

Perhaps most important from the pharmaceutical perspective is something that was pointed out by Dr. Gordon Cragg, Chief of the U.S. National Cancer Institute's Natural Products Branch: "no chemists can 'dream up' the complex bioactive molecules produced by nature, but once the natural lead compounds have been discovered, then the chemists can proceed with synthetic modifications to improve on the natural lead."[2] Biodiversity prospecting is useful for the further development of natural leads, but even more importantly, for providing chemists with ideas that may form the basis of their computer-aided search for interesting chemical structures that may prove useful in drug development.

While continuing to use supercomputers for drug design, various pharmaceutical companies and research institutions have fostered agreements with scientists in developing countries for the collection and identification of samples from plants, microorganisms, insects and marine life. With very few exceptions, the source country provides samples to be sent abroad for screening for potential biological activity.

News of the first agreement between Merck (one of the world's largest pharmaceutical companies) and the Costa Rican National Institute of Biodiversity (INBio), that provides for the payment of US$ 1 million to INBio for biodiversity prospecting services over a two-year period, has led to debate and controversy as well as raising hopes and fears of similar possibilities throughout the Western Hemisphere. Unfortunately, much of the discussion of the Merck-INBio agreement by those not directly involved in it has been based on incomplete, erroneous or totally false information.

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[1] Akerele, cited in "*The Lancet*", 1994, p. 1514.

[2] Cited in Raven, 1994, p. 7.

In this paper, I will briefly describe some cases of biodiversity prospecting in Latin America –particularly the Merck-INBio accord– and analyse their future prospects. In the final section I will discuss policy options for other institutions and countries interested in pursuing biodiversity prospecting. The research for this article was based on an examination of much of the existing literature (published and unpublished), interviews and discussions with key actors in this field, and my work organizing the interdisciplinary symposium on Biodiversity, Biotechnology, and Sustainable Development in Health and Agriculture, organized by the Pan-American Health Organization (PAHO) and the Inter-American Institute for Agricultural Sciences (IICA), and editing the proceedings of that meeting (Feinsilver, ed., 1996).

II

Biodiversity prospecting experiences and models

Biodiversity prospecting has occurred since time immemorial, but the actual term is of recent vintage. Before publicity about the 1991 Merck-INBio contract, the Rio Summit in 1992, and the publication of *Biodiversity Prospecting* in 1993 by the World Resources Institute (WRI) *et. al.*, collectors of samples of biological resources either worked directly for institutions and companies in the developed countries, or sold their wares to them. Some of the worst offenders, from the developing countries' perspective, were the major botanical gardens, which worked directly with pharmaceutical and agricultural seed companies. The profits from the products developed from these resources also remained abroad, thus giving rise to the term "biopiracy".

Since the Rio Summit, however, many source countries have established or have made more stringent regulations on the collection and exportation of biological resources, in an effort both to exercise greater control and to capture some of the economic benefits realized. The creation of Costa Rica's National Institute of Biodiversity (INBio) was a milestone in biodiversity prospecting, because INBio provides direct returns to conservation from prospecting and seeks to be a model for others. The brief case descriptions that follow will give an idea of the possible benefits to source countries of different types of biodiversity prospecting arrangements.

1. Costa Rica's National Institute of Biodiversity (INBio)

INBio was established in 1989 by governmental decree as an autonomous, private, non-profit, public interest institution with the support and collaboration of the Ministry of Natural Resources, Energy and Mines (MINEREM) in order to prepare an inventory of Costa Rica's biodiversity and develop means for its conservation and sustainable use and development. This non-governmental institutional arrangement was designed to promote operational agility and flexibility and to facilitate the search for external sources of funding. INBio's great flexibility has enabled it to take advantage of funding from foundations and NGOs that would not have been available to it had it been a governmental agency.

On the other hand, INBio's non-governmental character has caused some concern, precisely because –although INBio is not directly under government control– it is managing the country's biodiversity information systems and collection of specimens and is perceived to be "selling" the country's biodiversity, although this is not the case. The fear is that the lack of direct accountability may not be in the country's best interest, despite the current management's public-mindedness. Moreover, there is considerable concern about what will happen in the future when INBio's management changes or when the opposition party comes to power again, thereby changing INBio's relationship with the government.[3] When Mexico established an INBio-like institution with direct assistance from INBio, it opted to make CONABIO (the National Commission for the Knowledge and Use of Biodiversity) a governmental agency charged with the preparation of an inventory and conservation but not, as yet, bioprospecting.[4]

[3] Interviews with scientists of various institutions in Costa Rica, August 1993.

[4] See CONABIO's information brochure.

Although biodiversity prospecting is the best known division and activity of INBio, it is only one of four interrelated divisions and activities of INBio, the others being: i) preparation of a biodiversity inventory, ii) biodiversity information management, and iii) biodiversity information dissemination. Biodiversity prospecting's role is to find novel sustainable uses for biodiversity so as to provide some of the financial resources needed to sustain the other divisions' activities, particularly the inventory, which is the basis of all of INBio's work for conservation.[5] A full discussion of all of INBio's activities is beyond the scope of this paper and is available elsewhere (Sittenfeld, 1993 and 1994; Aylward, Echeverría, Fendt and Barbier, 1993).

INBio's biodiversity prospecting activities are based on the comprehensive knowledge of certain important segments of Costa Rica's biodiversity that is available from its inventory and INBio's and Costa Rica's scientific capacity in related disciplines. INBio conducts "biodiversity prospecting for chemical compounds, genes, species, macro and micro-organisms in collaboration with local and international universities, research institutions and industries...[through] random, chemotaxonomic and ecologically guided sample collection and the collection of natural history, behavioural and ecochemistry data".[6] It also provides consulting services to other institutions in the field of biodiversity prospecting. In fact, one of INBio's most successful "products" is the idea of INBio-like institutions in other countries, with INBio, of course, as both the role model and external advisor and consultant (Juma, 1993, pp. 217-218; Chapela, 1996).

a) The Merck-INBio Agreement

The singular event that put INBio on the map globally was its contract with Merck, some of the details of which are proprietary and therefore not available. What is in the public domain, however, is that in September 1991 Merck and INBio signed an agreement whereby Merck would pay INBio US$ 1 million in advance for the "identification, collection and extraction of a limited number of plants and insects, and collection of material from which Merck cultures microorganisms" (Caporale and Dermody, 1996, p. 16). This limited quantity of samples, the exact number of which is unknown but estimated at about 2000, would be collected from Costa Rica's conservation areas over a two-year period (Aylward, Echeverría, Fendt and Barbier, 1993, p. 49). In exchange for exclusive access to those samples for two years for screening in the fields of health and agriculture, INBio was also given over US$ 180,000 worth of equipment both for the chemistry laboratories at the University of Costa Rica that would collaborate in this endeavour and for the development of INBio's own extraction capacity. Moreover, Merck agreed to provide training for four chemists either at its own laboratories or at other research centres and it sent "two key scientists to Costa Rica to set up and train Costa Rican scientists to run the laboratory..." (Sittenfeld, 1993). Merck also agreed "to advise INBio of confirmed and reproducible activity that has been identified in an INBio sample".[7]

Merck would own the patents to any inventions resulting from this collaboration, but would pay INBio royalties "on any human or animal pharmaceutical product or agricultural chemical compound which is isolated initially from or produced by a sample provided to Merck by INBio. The royalty obligation also applies to any products which are derivatives or analogs of such compounds".[8] The amount of royalties that INBio would receive if a product were developed on the basis of its collaboration with Merck is secret, but current industry practices suggest that it would be around 3% of the net profits.

On the basis of an estimated 2000 samples provided over two years, Bruce Aylward and colleagues estimated that the expected present value of those royalties would be around US$ 350,000 if a drug were developed, although it could rise to as much as US$ 1.5 million if the drug were one of the top ten in the market. They point out that this is not a significant amount when compared with the gains from training, technology transfer, and fees for samples (Aylward, Echeverría, Fendt and Barbier, 1993, p. 49). A more recent estimate as to what INBio might earn in royalties at a rate of 3% if a drug were de-

[5] Interview with Dr. Ana Sittenfeld, Costa Rica, 24 August 1993.

[6] Ana Sittenfeld, information on INBio for the "Bioprospecting Models" table prepared by Julie M. Feinsilver and Ignacio H. Chapela for Feinsilver, 1996; personal communication, 24 October 1994.

[7] "Summary of Terms of Collaboration Agreement between INBio and Merck & Co., Inc.", leaflet provided by Pedro León, representative of INBio at the International Academy of the Environment's Cuernavaca [Mexico] Round Table, 6-8 April 1994, p. 2.

[8] *Ibid*, p. 3.

veloped can be inferred from a statement by Michael Dreyfuss of the Sandoz company, in which he indicated that Sandoz (and one can assume most other transnational pharmaceutical companies) would not touch a compound, no matter how effective it were, if it were worth less than US$ 100 million in sales annually: it would just not be worth their while to develop for less.[9] If this were to hold true for Merck as well, then INBio would have even less chance of earning royalties.

In sum, the Merck-INBio accord provides INBio with an advance payment for samples, as well as technology transfer, human capital development, and potential royalties. In return, Merck receives exclusive access to certain samples from INBio, but only for the very specific purposes outlined in the contract and for its duration. This, however, does not mean that another institution, private company, or individual could not sell the same type of samples to another company, nor does it prohibit INBio itself from selling the Merck samples to another company as long as that company is not engaged in research on human or animal health or agriculture.[10] There is an exception, however: Merck may extend the period for exclusive evaluation of up to one percent of the total number of samples provided "so long as Merck acts diligently in the evaluation and commercialization of the sample".[11] This suggests that the expectation of finding a novel compound is one percent or less. In fact, senior Merck scientist Dr. George Albers-Schonberg said in 1991 that "in the last 25 years, Merck Sharp and Dohme has found only five compounds from natural sources that either directly or with some chemical modification have become marketable drugs" (Schweitzer and others, 1991, p. 1295).

The quantity of samples INBio supplies is relatively small, particularly if one considers that the pharmaceutical industry's high-throughput screening equipment requires at least 5000 samples a week to run efficiently: more than double what INBio would provide over a two-year period. This also suggests that INBio's potential contribution to Merck's drug discovery program is relatively insignificant, though its cost to Merck is also relatively insignificant: only US$ 500,000 per year out of a research budget of US$ 1.2 billion per year. Conversely, INBio's income from the Merck contract is not inconsequential, but it is dwarfed by INBio's other sources of endowment and funding, such as large foundation grants and, more importantly, "its access to US$ 4.6 million from reconverted external debt (debt-for-nature swaps)".[12]

What is unique about this arrangement are the advance payments and the fact that INBio has an agreement with the Ministry of Natural Resources, Energy, and Mines to pay 10% of the advance payment (US$ 100,000) and 50% of any royalties generated to the Ministry for support of the conservation areas. Because INBio makes its collections from those areas, it would be very shortsighted from a business perspective if it did not invest in their preservation and maintenance. Very important, but not unique to the contract, is the technology transfer and training of Costa Rican scientists.

What is the value of the INBio contract to Merck? Some argue that it has a purely public relations value. As a result of this contract, Merck has gained considerable publicity and commendation as an environmentally responsible company (Chapela, 1996). Merck renewed its contract with INBio for another two years in July 1994; although the main focus has shifted away from plants to insects, plants and microorganisms are still included. As of January 1996, no leads expected to be developed into drug candidates had resulted from this collaboration. The only scientific publications resulting from the first contract were two articles on microfungi on Costa Rican leaf litter, rather than anything on the main focus of the agreement: plants and insects (*ibid.*). An interesting point is that Merck, rather than INBio, cultures the microorganisms, so that INBio only supplies the raw material for what could be one of the most promising contributions of biodiversity to the drug discovery process.

Although very positive about the INBio-Merck collaboration, Caporale and Dermody (from Merck) point out that combinatorial chemistry can rapidly generate molecular diversity on an enormous scale through the "rapid synthesis and screening of thousands or even millions of compounds" (Caporale and Dermody, 1996). Pharmaceutical companies have

[9] Interview with Ignacio H. Chapela, Washington, D. C., 9 January 1995, citing oral presentation by Michael Dreyfuss of Sandoz Pharma, Ltd. at the Oaxaca Mycological Facility (Mexico), 16 December 1994.

[10] *Ibid.*

[11] Summary of Terms of INBio/Merck Agreement, p. 2.

[12] Data from INBio, 1992, cited in Chapela, 1996.

enormous chemical libraries from which they screen molecules for new leads. The screens, however, change quickly as scientific and technological advances occur (Chapela, 1996). Biodiversity, however, is still useful to the pharmaceutical industry in combination with combinatorial chemistry. For example, natural product leads, by suggesting new molecular structures that interact with the target, may provide a starting framework for subsequent optimization by combinatorial chemistry. In addition, combinatorial chemistry requires novel fragments to include in the synthetic mix, some of which may be difficult and/or time-consuming to prepare in the laboratory. Novel enzymes, derived from microorganisms, may provide one rapid route to these fragments, and this is another potential use of biodiversity (Caporale and Dermody, 1996).

As a sober reminder, the U.S. National Cancer Institute's general rule of thumb regarding natural products samples is that out of 10,000 samples tested, one activity may proceed to the next level of sophistication (preclinical pharmacology). Of every ten that get to preclinical pharmacology, one becomes an investigational new drug (IND). Of every ten investigational new drugs, only one or two get to the market. As a result, the odds of getting a drug to market from any given sample are 1 to 250,000.[13] These odds could be decreased if one screens for more than one assay type. For example, if one screens the same sample against five different types of cell lines, enzymes or animal models with a different biochemical mechanism for each type of screen, then the odds are reduced "not linearly, but probably to below 1 in 80,000 or so".[14] Clearly, this is not very encouraging, but insofar as INBio is concerned, its *raison d'etre* is not bioprospecting but the preparation of inventories and the conservation of biodiversity. Bioprospecting is, however, the means to achieve that end, and it has also gained considerable publicity for INBio.

b) INBio's prospects

INBio has reasonably good prospects of getting more contracts with both Merck and other companies in pharmaceuticals, agricultural chemicals and biodiversity information management systems, for a variety of reasons. First, INBio has a proven track record as a good and reliable partner. Second, INBio has a well-developed international public relations programme aimed at improving its financial position. This has resulted in the full support of its government, much of the international environmental community, and major donors.

The three areas of greatest potential commercial success for INBio, however, are not in bioprospecting but in the following three fields. The first of these is the promotion of INBio-type institutions elsewhere, with all of the related consulting and information management services that go with this; the second is the development of computerized biodiversity information systems with the U.S. company Intergraph, and the third is the development of a natural nematicide discovered by the British company BTG for use by the banana industry. The first potential success story, INBio itself as a product, is already having an impact as other countries, institutions, non-governmental organizations and international agencies seek advice and assistance, and as more consulting services are offered by INBio. Thus, INBio will have considerable influence over developments in the fields of biodiversity inventory, conservation, information management and dissemination, and biodiversity prospecting. This, in turn, will undoubtedly lead to greater funding for INBio.

The collaboration with Intergraph should produce marketable products in the near future, particularly as countries begin to prepare the type of inventories foreseen by the Convention on Biological Diversity. Finally, the nematicide project is extremely challenging in that the active compound is found in an endangered plant. If INBio succeeds in isolating the active compound (with the same efficacy) in leaves rather than seeds and can domesticate the plant, the economic returns should be substantial because the nematicide is non-toxic to humans and biodegradable. This should be a boon to the heavily polluting banana industry.

With regard to biodiversity prospecting, it is difficult to understand the scientific or economic rationale for the second Merck-INBio contract without access to the details of the agreement. The new contract focuses primarily, but not exclusively, on insects rather than plant samples. Lynn Caporale, of Merck, said that it was an opportunity for both parties to collaborate in an area of new scientific interest where little is known.[15] Merck's interest does

[13] Interview with Dr. David Newman, U.S. National Cancer Institute (NCI), Natural Products Branch, Frederick, MD, 1 November 1994.

[14] Personal communication from Dr. Gordon Cragg, Chief, NCI Natural Products Branch, 20 January 1995.

[15] Telephone interview with Lynn Caporale, 23 September 1994.

not appear to be easily justifiable on scientific grounds, because it is quite difficult to isolate a given activity in insects as it could be caused by any number of things unrelated to the insect's chemistry, such as changing geographic locations, food consumption patterns, etc. Caporale, however, believes that insects are "a unique resource".[16]

It may be asked: if the INBio-Merck deal is so good for the pharmaceutical industry, why aren't all of the major pharmaceutical companies jumping on the bandwagon and establishing similar relationships with host country institutions? A possible explanation is that most drug companies would rather keep their options open so as to be able to get samples (if they want them) from numerous geographical locations and various institutions and collecting agencies. Moreover, most would prefer not to pay money in advance for a long-term contract when they can merely pay for samples as they get them. Pharmaceutical and biotechnology companies may find that justifiably stricter rules for access to developing countries' biodiversity make their own countries more attractive as sources of samples. Pfizer, for example, recently made a deal with the New York Botanical Garden to provide samples from the U.S., where collection is easier.

Although INBio is not a model to be replicated exactly (Feinsilver and Chapela, 1996), much can be learned from it. Some important questions to ask are: What products has it generated? What products are in the pipeline? What is INBio's potential market share for any products it might develop? Is INBio economically sustainable, or can it only survive with grants and pro-bono technical assistance? Has it actually contributed to sustainable development, and if so, how? Who are the stakeholders and who benefits from INBio? What are the mechanisms for accountability to the Costa Rican Government? Can INBio's work provide any economic benefits for the non-scientific community? Is there any incompatibility between INBio's science-driven policies and its market-driven biodiversity prospecting, and if so, how can this be resolved?

2. The U.S. National Cancer Institute (NCI)

The National Cancer Institute's Natural Products Branch has a long history of screening natural products in search of new drugs to combat cancer and now AIDS as well. As an agency of the Federal Government, the NCI must seek pharmaceutical companies to license and produce any drugs it discovers. In its first phase, from 1960 to 1982, the NCI screened 114,000 plant extracts derived from 35,000 plant samples, mostly from temperate zones. In its second phase, beginning in 1986, the NCI has shifted its focus to plants from tropical and subtropical areas (Cragg and others, 1994a, p. 178).

Since 1986, the NCI has contracted with three U.S. institutions to collect plant samples in tropical and subtropical Africa and Madagascar, Central and South America, and Southeast Asia, and with one institution to collect marine samples.[17] In all cases, the contractors are U.S. institutions that have collaborative agreements with host-country institutions. The NCI is not working directly with any of the host country institutions on these contracts, but has other collaborative agreements with ten developing country institutions, primarily for research on those countries' medicinal plants.[18] When the current round of five-year collection contracts ends in August 1996, Dr. Cragg has predicted that the NCI will then eliminate the intermediaries and purchase samples (and extracts, where the capability exists) directly from source country institutions.[19]

The most notable success of the NCI's screening programme is, of course, Taxol, a major breakthrough in the treatment of ovarian cancer and advanced breast cancer. Taxol was originally derived from the bark of the Pacific Yew, but it is now produced semisynthetically (sustainably) from the needles and twigs of a Himalayan Yew (*The New York Times*, 1994). Three other plant-derived anti-cancer compounds are currently in the clinical trial phase. In the first phase of the NCI's screening programme, eight plant-derived anti-cancer agents made it to clinical trials, but these were terminated either because of unacceptable toxicity levels or lack of efficacy (Cragg and others, 1993a, p. 85). Although these agents might be worth retesting under new, more sen-

[16] *Ibid.*

[17] Missouri Botanical Garden, New York Botanical Garden, and the University of Illinois at Chicago, which has collaboration agreements with the Arnold Arboretum at Harvard University, and the Bishop Museum at Honolulu, Hawaii.

[18] "Natural Products Acquisition Program" of the Developmental Therapeutics Program, Division of Cancer Treatment, National Cancer Institute (computer printout, N.D.).

[19] Interview with Dr. Gordon Cragg, 28 December 1994.

sitive protocols, Dr. Cragg has said that it is unlikely that the NCI will do so, because it is very difficult to get clinicians to revisit these agents when they had previously demonstrated very high toxicity levels and because there are so many new prospects in the pipeline.[20] Beyond the NCI's own direct work, there are four plant-derived anti-cancer drugs in use today that, although not discovered through the NCI screening programme, were developed with considerable assistance from the NCI (*Ibid.*, p. 81).

The NCI's policy as regards the collection of samples is to obtain both medicinal plants and broader-based taxonomic collections (Cragg and others, 1994a, p. 188). Interestingly, none of the three plant-derived anticancer drugs discovered at the NCI was collected through ethnobotanical leads. With regard to anti-HIV activity, "As of August 1993, 21,881 extracts derived from over 10,500 samples [from 2320 medicinal plants] had been tested ..."; 18% of both the total number of samples and of those from medicinal plants showed activity. Upon further examination, it was found that 90% of this activity was due to ubiquitous polysaccharides or tannins, neither of which is under consideration for drug development, thereby resulting in the elimination of those samples from further tests (Cragg and others, 1994a, p. 178).

On a more positive note, license agreements have either been negotiated or are in the process of negotiation with Cameroon, New Zealand and Sarawak (Malaysia) for the further development of potential anti-HIV drugs from active principles found in plant and marine samples. MediChem has licensed Calanolide A and is working with Sarawak. Michellamine B has not yet been licensed, but the NCI is still working with Cameroon on it. The Government of New Zealand, as well as various New Zealand academic groups, are still collaborating with the NCI on the marine-derived Halichondrin B.[21]

What do the source countries get from their relationship with the NCI? First, they get payment for their samples from the collection contractor with whom the NCI has an agreement. Second, they receive the test results for their specimens, through the collection contractor. Third, the source country's national herbarium receives voucher specimens for samples collected. Fourth, selected source country scientists are invited to the NCI for training in isolation and screening techniques, at the NCI's expense. Fifth, cell lines and screening methodology for cancer and HIV are available for transfer to the source country if requested. Sixth, if a large quantity of raw materials is required for further testing, the source country would be the first country of choice for the supply thereof. Seventh, should a drug be developed, the source country would get a share of the royalties. The NCI's Letter of Collection stipulates that the source country will be informed of any positive screening results and will be compensated through profit-sharing by a drug company licensee of the Federal Government's patent, should a usable drug result (Cragg and others, 1994b, pp. 13-14). See figure 1 for source country benefits from the various types of collaboration mentioned here.

Finally, the NCI is considering the transfer of some extraction and initial screening to qualified source country institutions at some time in the future, probably after August 1996, when the current collection contracts end and thus free up resources for other types of arrangements.[22] This policy change probably results from recent source country demands, particularly those relating to efforts to increase their control over their biological resources (since the Rio Summit in 1992) and to develop their own scientific capacity. Some countries have banned collection by intermediaries and instead are developing collection and extraction capabilities and working towards having their own screening capacity.

Dr. Cragg foresees drug discovery being done in the source countries, with the NCI subsequently assisting them in drug development (from advanced animal toxicity studies on through human clinical trials), should a likely candidate be found. The Natural Products Branch of the NCI is committed to capacity-building in source countries and will thus help them to establish extraction, isolation and screening capabilities and will work with them to develop into drugs the active compounds they may discover.[23] On the other hand, no country –even if it so desired– could develop the scale of facilities that the NCI has, nor indeed would it make sense to do so. Clearly, what does make sense is some form of collaboration that would maximize both economic and scientific benefits for the source country.

[20] *Ibid.*

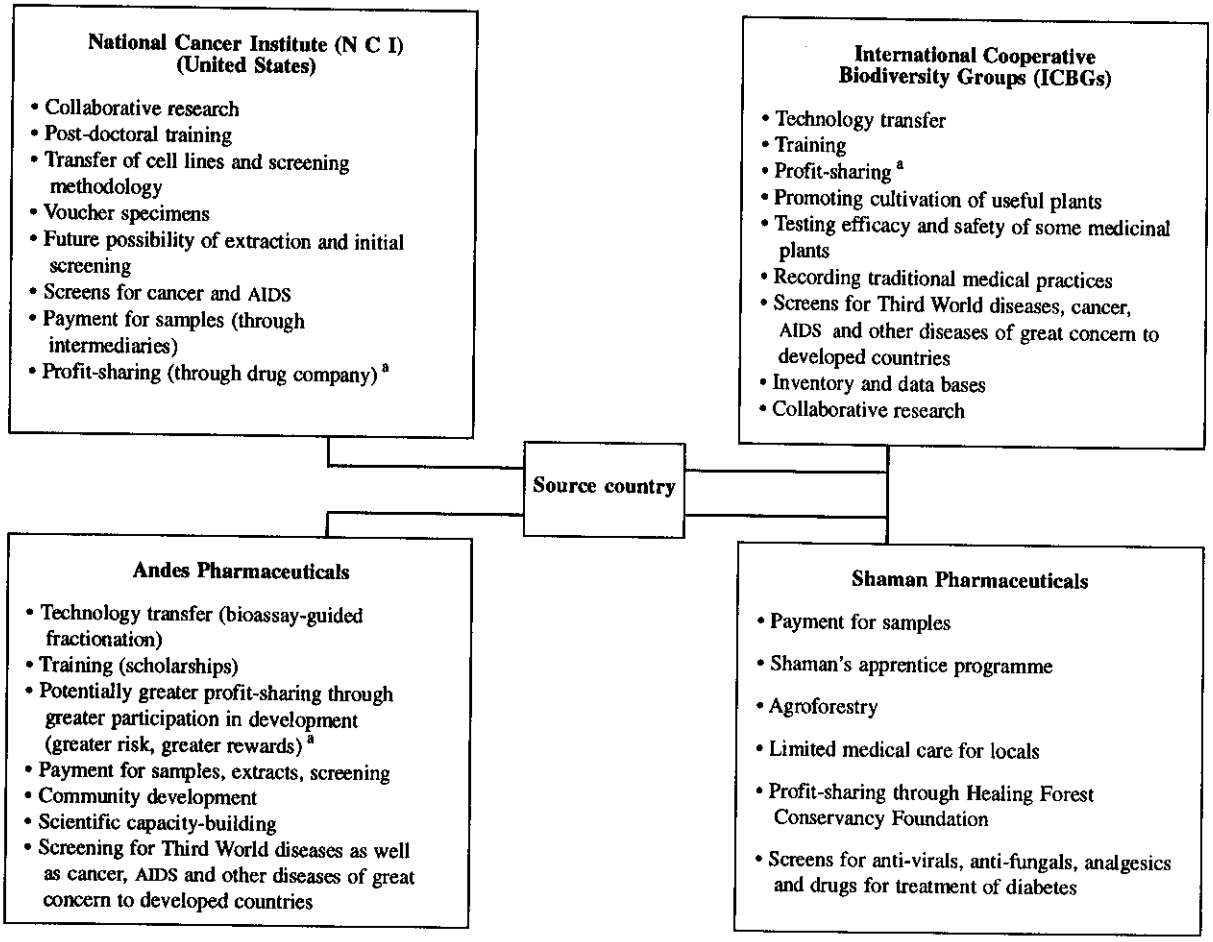
[21] Interview with Dr. David Newman, 29 January 1995.

[22] Interview with Dr. Gordon Cragg, 28 December 1994.

[23] *Ibid.*

FIGURE 1

Source country benefits from collaborations



Source: Prepared by Julie M. Feinsilver for *Biodiversity, Biotechnology and Sustainable Development in Health and Agriculture: Emerging Connections*, edited by Julie M. Feinsilver (Washington, D. C., Pan-American Health Organization, 1996).
[a] Profit-sharing if –and only if– a drug is developed.

a) The NCI's prospects

With its extraordinarily large collection of natural products extracts, large number of cancer and HIV cell lines, and long experience in natural product screening, the NCI has good prospects of discovering or facilitating the discovery and development of anti-cancer and anti-HIV drugs. This may be done in conjunction with pharmaceutical companies or source countries. It matters little to NCI how a drug is discovered: they are willing to work with anyone on the advanced stages of testing.[24]

On the other hand, the NCI receives only about 2000 samples per year from each of its three contractors: a small number by industry standards. With some exceptions, success has been elusive, although there are some promising candidates in the pipeline. Whether or not they get to the market remains to be seen.

Funding for the Natural Products Branch of the NCI may decrease in the near future because the interests of its new director lie in combinatorial chemistry rather than natural products drug discovery. Moreover, in a tight budget environment, if no new drugs are developed from this programme by the turn of the century, continued funding at current levels may well be in jeopardy.

[24] Interview with Dr. Gordon Cragg, 29 December 1994.

3. International Cooperative Biodiversity Groups (ICBGs)

The International Cooperative Biodiversity Groups are five U.S. government-funded research and development consortia engaged in "an integrated conservation and development program which addresses the interdependent issues of biodiversity conservation, sustained economic growth, and human health in terms of drug discovery for diseases of concern to both developing and developed countries" (Grifo, 1996). The five consortia funded by the National Institutes of Health, National Science Foundation and Agency for International Development (USAID) are composed of U.S. universities, U.S. drug companies, source country research institutions, local communities, and NGOs. Three consortia operate in single countries (Costa Rica, Peru and Suriname), while two work in multiple countries (Argentina, Chile and Mexico, and Cameroon and Nigeria). These consortia have each been awarded competitive grants of US$ 400,000 to US$ 475,000 annually for a five-year period beginning in 1994 to promote sustainable development and conservation through the search for new drugs from natural products. Moreover, the ICBGs will also document traditional medicine practices, provide training and transfer technology, prepare project-specific biodiversity inventories, develop methods for sustainable harvesting of economically promising potential drug sources, and provide funding for conservation (Grifo, 1996; USAID/NIH/NSF, 1993, pp. 1-2).

The development of this interagency effort began in 1991, but due to the recency of the awards, there is little public data on the ICBGs' progress. A preliminary report indicates that of the 2000 species of plants and insects screened, 120 had biological activity, but it is not yet clear how many of these are already known entities, so dereplication studies are being carried out. Twenty-five leads are being studied chemically for use against cancer, central nervous system disorders, malaria and viral diseases. Training has been provided to some 75 students and technicians from both the U.S. and the developing countries, and "significant infrastructural development [has taken place] in source-country institutions of at least 6 countries".[25]

The source countries benefit considerably from this type of collaborative arrangement because they gain technology transfer, various types of relevant training, sustainable development assistance, capacity building, conservation information systems, the preservation of indigenous knowledge, and last but not least, equitable compensation should a drug be developed from source country samples. More important, however, is source country collaboration from the outset of these projects as a full partner in both the design and execution of the projects. These benefits, unfortunately, are only available to a very few countries, due to funding limitations.

a) The ICBGs' prospects

Prospects for future funding of the ICBGs are not very bright unless there is a major drug discovery in the next four years: an event that is not very likely, because testing, product development and U.S. Food and Drug Administration (FDA) approval often take decades despite good intentions and efforts. With the Republicans in control of Congress and the goal of balancing the federal budget in seven years, the reality is that budget priorities are likely to be redirected elsewhere. Already there has been a decrease in funding in fiscal year 1996, compared with the previous year, as the U.S. Agency for International Development (USAID) reduced its contribution to the ICBGs from US$ 500,000 to US$ 150,000, and it will not fund the ICBGs at all in fiscal years 1997 and 1998.[26] Moreover, the director of the National Institutes of Health (NIH) is planning a reevaluation of all international programmes, and this could lead to decreased funding.

The lessons learned in establishing these north-south collaborative research consortia and the technology transfer and training included therein will be of great value, but they are unlikely to be replicable without major external funding. It is also highly unlikely that the pharmaceutical industry will put sufficient money into this project to keep it afloat, because according to some critics the ICBGs are a federal subsidy for U.S. pharmaceutical companies' drug discovery process. An indication that this is indeed a kind of subsidy is that, as of January 1996, the pharmaceutical company partners in the five consortia provided only a little over "US$ 300,000 in domestic screening investment, and over US$ 150,000 in advance payments, infrastructure and capacity-

[25] Joshua Rosenthal, personal communication of 31 January 1996, based on Rosenthal (forthcoming).

[26] *Ibid.*

building efforts in host countries".[27] This amounts to about US$ 45,000 per year per consortium: a paltry amount compared with the upwards of one billion dollars per year that major pharmaceutical companies spend on research and development. Thus, with little likelihood of the private sector funding these projects and with Congress and government agencies looking for ways to further cut the budget, it seems, unfortunately, that the future of the ICBGs may not be bright.

4. Shaman Pharmaceuticals, Inc.

Shaman Pharmaceuticals is a small, relatively young natural products pharmaceutical company (with no products on the market yet) that uses ethnobotanical collection methods in its search for active compounds. If a plant is used in a similar way in three or more different cultures it is sent to Shaman's California laboratories for isolation of the active principle and screening "against disease assays including viruses, fungi, analgesia or diabetes" (Zisson, 1993, p. 2). Shaman claims a hit rate of 50 percent, but they are known to define a hit very loosely and this claim is not borne out by any hard data. They were, however, able to bring two compounds to clinical trials after only two years of operations, but though this is impressive it does not necessarily mean that they will have two marketable products.

Shaman's lead compound is Provir (SP303), an anti-viral derived from Sangre de Drago (Dragon's Blood), the red latex of the ubiquitous *Croton lechleri* that is widely used in South America for gastrointestinal and respiratory diseases as well as a cure-all. Provir was in Phase II clinical trials for use against respiratory syncytial virus (RSV), but it was insufficiently active. It will go back to Phase II trials, but as a potential anti-diarrheal (*BioVenture View*, 1995b). Virend is a topical version of SP303 for use against oral and genital herpes simplex virus. The market is well covered by Zovirax, so Shaman is seeking entry into the market as a drug for strains resistant to it (Zisson, 1993, p. 6). Successful Phase II trials on AIDS patients have led Shaman to design Phase III trials for fast-track Food and Drug Administration (FDA) over-the-counter (OTC) approval. Shaman is seeking European and Japanese partners to develop and market Virend abroad (*Pharmaceutical Business News*, 1995). News of the successful clinical trials boosted Shaman's stock by 14% to US$ 7 (*The Wall Street Journal*, 1995, B11, p. 6).

Shaman's other lead compound, SP1100, is a family of anti-fungals which is claimed to have "a totally novel mechanism of action, apparently unrelated to the azoles and polyenes that comprise standard therapy today". Phase I trials were expected to begin in 1995, based on analogs developed after the original formulation was found to have "very low bioavailability and some systemic toxicity" (Zisson, 1993, pp. 8 and 9), but in mid-November 1994 the company announced that it would not file an IND (investigational new drug) for it "because it requires a large medicinal chemistry effort, which isn't the company's strength" (The Bernstein Report on BioBusiness, 1994, p. B1). Shaman will, instead, seek to license the compound for further development and will seek partners to take both Provir and Virend to Phase III clinical trials (*Ibid.*).

In the mid-November 1994 company restructuring, Shaman's focus appears to have changed from ethnobotanical collection to *in vivo* whole animal model testing. This reverses the accepted industry practice of doing *in vitro* tests first and then *in vivo* animal models, although Shaman argues that this saves time and, by implication, money. They will now concentrate on "areas where it's advantageous to use whole animal screens. SHMN [NASDAQ code for Shaman] is shrinking its anti-infectives program, eliminating antifungal screening and cutting back on antiviral screening" (*Ibid.*). Shaman's plan is to work on diseases of greater importance to the pharmaceutical industry from which it desires funding: diabetes, "central nervous system disorders, inflammatory diseases, and symptoms such as gastrointestinal and respiratory problems associated with infections" (*Ibid.*).

Unlike the previous bioprospecting models, Shaman is a profit-seeking company and thus has been funded by venture capital, licensing revenues, stock traded on the NASDAQ, and corporate partners. Its bottom line is, therefore, to make a profit, but it is claimed to be much more sensitive than others in its dealings with local communities and indigenous peoples (Chapela, 1996). Shaman Pharmaceuticals sends U.S. collectors to get information from traditional healers in the developing world in exchange for both the promise of future compensation should a drug be developed, and the delivery of some medical care for the collaborating communities as well as the provision of various types of goods and/or services that

[27] *Ibid.*

the communities tell the U.S. ethnobotanists they need. For example, at a recent meeting Shaman Vice-President Steven King mentioned providing PVC tubing to a community that had asked for it. He was roundly criticized for exchanging tubing for indigenous knowledge,[28] but it was explained that the PVC was intended as a confidence-building measure to improve rapport with the community and did not represent the total compensation that would be paid, should a product be developed.

In a recent Shaman patent application, no indigenous community was mentioned in the patent, although the information for the development of the product was ethnobotanical (*Ibid.*). In response to criticism of this patent application, King said that their application stated that the plant was widely known and used throughout South America. Moreover, he claimed that they were unable to pinpoint its origin to a specific community.[29] One of the functions of the Healing Forest Conservancy, a foundation established by Shaman Pharmaceuticals, is to provide mechanisms for benefit-sharing among the communities involved in their drug discovery process. Because there have not been any profits to share, questions as to which communities would be included have not been addressed. All communities that possess the same knowledge but were not asked for it by Shaman may contest the "rights" of those selected by Shaman to provide information, and thus benefit. Because U.S. patent law does not allow for the inclusion of indigenous peoples or communities in patents, these communities have no protection under law unless they have a separate side agreement (contract) with Shaman for a portion of future profits.

As a profit-seeking enterprise, Shaman does not provide training for source country scientists nor does it assist in scientific capacity-building nor technology transfer. Its collection model is more culturally sensitive than that of other for-profit collectors, but its very existence and success depend upon developing good rapport with indigenous healers so as to extract ethnobotanical information from them in order to develop drugs. It is therefore not surprising that Shaman launched the Shaman's Apprentice programme (a concept also adopted by some of the ICBGs following Shaman's lead) and the Healing Forest Conservancy to preserve and promote traditional medicine.

One of the criticisms of Shaman Pharmaceuticals is that its ability to raise funds has been tied less to any potential product development than "to the extraordinary media coverage of the loss of biodiversity and the institutions that are perceived as countering this loss" (*Ibid.*). As of September 1993, Shaman had a deficit of US$ 22.2 million, with an operating loss of US$ 13.3 million up to May 1993.[30] Shaman took a US$ 500,000 charge against earnings in the fourth quarter of 1994 to meet restructuring expenses (The Bernstein Report on BioBusiness, 1994, p. B1). This, however, is not uncommon in the biotechnology industry, with which Shaman seems to have more in common than the pharmaceutical industry.[31]

Shaman's restructuring is designed to save operating costs, make the company stand out in the crowd of biotech drug discovery companies seeking strategic alliances with pharmaceutical giants, and make the company viable in general. A company source said that they remain a natural products company and will continue their ethnobotanical approach to collection and maintain The Healing Forest Conservancy.[32]

a) Shaman's prospects

Shaman's prospects depend greatly on i) whether their lead compounds pass muster, and ii) whether they can continue to raise enough capital and make strategic alliances to keep on testing and developing their compounds. Eli Lilly's recent decision not to renew its contract with Shaman suggests a loss of confidence in the company and/or in their ethnobotanical approach to drug discovery (*The Wall Street Journal*, 1994, B7, p. 1). On the other hand, Shaman has recently negotiated a new partnership arrangement with Ono Pharmaceuticals of Japan whereby Ono provides research capital and Shaman provides new clinical entities in a project to develop an oral

[28] Comments made at the PAHO/IICA Biodiversity Symposium Follow-up Meeting, Washington, D. C., 22 October 1994.

[29] Interview with Dr. Steven King, Ph.D., Vice-President for Ethnobotany and Conservation, Shaman Pharmaceuticals, Inc., at Cuernavaca, Mexico, 8 April 1994.

[30] Chapela (1996) cites a 1994 "Financial Fact Sheet" of Shaman Pharmaceuticals, Inc.

[31] For Shaman's similarities with the biotech industry, see Chapela (1996), and on biotech industry losses see Burrill and Lee, Jr., 1993, p. VII.

[32] Personal communication from Martha, assistant to Steven King, 3 January 1995.

hypoglycemic agent to treat diabetes. If the project is successful, Ono will have exclusive manufacturing and marketing rights for Japan, South Korea and Taiwan (*Biotechnology Newswatch,* 1995). In a move away from ethnobotany, Shaman has licensed some patents and preclinical data from Bayer in an effort to develop antifungal agents. Shaman will pay Bayer royalties if a successful product is developed (*BioVenture View*, 1995a).

Sales for Aciclovir, the only FDA-approved genital herpes treatment, were greater than US$ 1.4 billion in 1994 (*AIDS Weekly*, 1995). Thus, if Virend successfully passes Phase III trials and the costs of production make the medicine commercially viable, then Shaman should be able to recuperate its operating losses, attract new strategic alliances and investment, and become profitable.

5. Andes Pharmaceuticals, Inc.

Andes Pharmaceuticals is a natural products drug discovery company dedicated to responsible biodiversity prospecting by setting up source country joint ventures to which it "transfers proprietary natural products drug discovery technology, expertise, and support in order to perform drug discovery activities within the source countries".[33] Under this arrangement, source countries are able to add greater value to their biodiversity, have greater control over its use and over product development, and develop their own scientific capacity. Andes establishes strategic alliances with source country universities, institutions, NGOs and the private sector.

In Colombia, for example, Andes has collaborative agreements with two universities and two NGOs, and has recently formed its first joint venture, BioAndes de Colombia, S.A., with a Colombian partner. Rather than merely using the host country population as a source of cheap labour, these in-country partners, including universities and NGOs, will have an equity stake in the joint venture. The assumption of greater risk leads to greater technology transfer and a greater share of any profits realized from the marketing of a drug, should one be discovered and developed.[34] Although drug discovery activities will take place in BioAndes' own laboratories, the company will utilize and help expand existing scientific capacity through collaboration with the source countries' universities and institutes.[35] The first bioassay results from the BioAndes pilot project are expected in late 1996.

The stated goals of Andes Pharmaceuticals are technology transfer to developing countries; conservation through sustainable economic activity; capacity-building in developing countries; equitable compensation of local/indigenous communities, and the creation of opportunities for source country entities/collaborators to share in profits.[36] Specific activities to be conducted by Andes Pharmaceuticals include ethnobotanically-guided and taxonomically-guided plant collections as well as random collection of plants, soil microbes, and fungi, with voucher samples deposited in source country and international herbaria; bioassay-guided fractionation and screening in joint venture research laboratories located in the source country; technology transfer (equipment, know-how, etc.) to appropriate source country collaborators (i.e., universities, institutions, etc.); capacity-building through appropriate source country partners/collaborators; technical training of local indigenous people as guides and parataxonomists and technical training of local scientists and students (both graduate and undergraduate) in areas related to bioprospecting; and information dissemination within the source country to promote traditional medicine and the publication of scientific papers for the international scientific community.[37]

Other companies, such as Shaman Pharmaceuticals, send samples back to the U.S. to be screened, but Andes Pharmaceuticals differentiates itself from them by having source country nationals do that work in their own country. This not only creates significant opportunities for transferring biotechnology to developing countries and furthering their scientific capacity, but also permits the source countries to add greater value to their biodiversity. Moreover, some bioassays will even be conducted in the field with simplified bioassay field kits that Andes is developing specifically for this purpose. These bioassays

[33] Interview with Edgar Asebey, President of Andes Pharmaceuticals, Washington, D.C., 1 February 1996.

[34] Asebey, 1996, and interview with Edgar Asebey, 30 December 1994.

[35] Interview with Edgar Asebey, Washington, D. C., 6 January 1995.

[36] Edgar Asebey, information on bioprospecting models, for inclusion in Feinsilver, ed., 1996.

[37] *Ibid.*

will use fresh rather than dried samples, which should lead to increased activity (Asebey, 1996). The greater the value added locally, the greater the proportion of benefits returned to the source country. Thus, Andes' approach may create an economic rationale for the conservation of biodiversity.

a) Prospects for Andes Pharmaceuticals

Andes' prospects for gaining substantial financing as well as access to source country resources in the immediate term look good because they have gained support from investors and scientific institutions in Latin America, Europe and the United States. Because Andes is committed to technology transfer and conservation in the source country, it has also gained the support of major international environmental organizations based both in Latin America and the United States. This will further legitimize Andes' activities and make fund raising easier.

With regard to drug discovery, Andes may have a good chance of succeeding in this respect too, because its screens are developed specifically for natural products, making them more efficient than those used more generally. Andes has an impressive group of scientists on its advisory board, some of whom worked with the United States NCI previously. In fact, the scientist who developed the NCI's anti-cancer screens is now the chief scientific officer at Andes.[38] Andes' drug discovery operations are based in the source country, where it has reliable access to some of the world's richest biodiversity and the ability to systematically screen it. Finally, Andes is currently negotiating strategic alliances with several U.S.-based biotechnology companies that have accepted the principles of the Biodiversity Convention so as to guarantee access to genetic resources.

The reality facing Andes, as well as the others, is that drug discovery is a long and arduous process with extremely high risk and little likelihood of rewards. Andes, however, is also keenly searching for drugs that are important to the developing countries (particularly the source country), and may thus have greater success than companies only seeking drugs for diseases of major concern to the developed countries.

III

Policy options for other institutions and countries

When most policymakers discuss the prospects of biodiversity prospecting, they mention the INBio-Merck agreement as an example of how potentially lucrative their countries' biodiversity might be. What they fail to realize, however, is that biodiversity prospecting may not be the best, most efficient, most cost-effective way to achieve their goals. Nonetheless, biodiversity prospecting does stimulate the development of scientific capacity in a variety of areas, and this scientific and educational effort has spillover effects in other economic sectors.

Biodiversity prospecting is only beneficial to developing countries if they receive sufficient technology and training to develop their own biotechnology capacity. This is necessary given the increasing scientific and technological gap between countries. Without minimal understanding of biotechnology, it will be difficult to decide what technology a country needs and what economic development, scientific, and environmental policies to adopt, and this will lead to yet further economic marginalization.[39]

Biodiversity prospecting is also useful if it is combined with other efforts to produce scientifically validated and standardized herbal remedies to meet the primary health care needs in the developing world, as well as some of the European countries, where phytopharmaceuticals and herbal remedies are common. A recent editorial in *The Lancet* (18 June 1994) suggests that there is an urgent need to screen

[38] Interview with Dr. David Newman, 29 January 1996.

[39] It could be argued that Cuba, although in dire economic straits, would have been much worse off in agriculture, industry and medicine in the current circumstances, had the revolutionary government not made heavy investments in science in general and biotechnology (biomedical, agricultural and industrial) in particular. For a discussion of Cuba's biotechnology development see Feinsilver, 1993 (chapter 5 on biotechnology) and Feinsilver, 1994, pp. 167-189.

plants for potential therapeutic benefit, and "priority should be given to tropical infectious and chronic diseases, for which current medications have severe drawbacks, and to the scientific appraisal of plant-based remedies that might be safer, cheaper and less toxic items for self-medication than existing prescribable medicines" (*The Lancet*, 1994, p. 1515). The same article suggested that research into "nutriceuticals" (food plants used as preventive medicine, i.e., antioxidants) could be important (*Ibid.*), although it recognized the difficulty in finding funding for these activities.

The probability of bringing a new drug to market based on bioprospecting is only between 1 in 80,000 and 1 in 250,000. With odds this great against success, why bother? First, there are important educational benefits in focusing on an array of scientific disciplines related not only to the environment, but also to genetic engineering and computer science. These include the preparation of a scientific workforce trained to deal with both current problems and those of the 21st century. Second, there are spillover effects for other economic areas in terms of both improved and better-directed scientific education and science and technology capacity-building. As is well known, scientific achievements in one field are often directly utilized or converted for use in other fields. Biotechnology development is one area where the techniques are standardized, but the actual use made of them varies widely from human medical research to agriculture to industrial applications. This is not to suggest that someone trained in one of those areas could work in another, but rather that many of the techniques are common to all the areas.

Policies regarding bioprospecting will be most successful if integrated into a larger plan for both economic development and environmental preservation (sustainable development). Coordination of institutions that might participate in various aspects of programmes established in this field is critical to avoid duplication of efforts and inefficient, and possibly ineffective, use of resources. Support at the highest levels of government is necessary for formulating government policy and overseeing programmes linking the various actors into a web of collaborative and mutually reinforcing institutional arrangements.

To meet the obligations of the Convention on Biological Diversity, countries will need to inventory their biodiversity. This inventory would then form the basis not only of preservation efforts, but also of sustainable development, and possibly bioprospecting endeavours. Even without an inventory, however, countries and institutions can still sell their services as collection agencies. Pharmaceutical companies do not need to know everything that is out there in order to carry out high- throughput screening, but they do need accurate identification of samples.

As a minimum, institutions and countries could develop reliable, high-quality collection and extraction capabilities. There must be sufficient guarantees that samples and extracts provided can be recollected without difficulty; supplied in larger quantities if needed; properly described, marked, and the data accurately computerized; and sent without contamination. The technology required is not terribly sophisticated, but training and considerable care are necessary. Furthermore, ethnobotanical knowledge should be surveyed, where possible, and accurately recorded. While these seem like simple steps, they are more complex than they appear.

Following the INBio model, trained biologists and taxonomists could oversee and educate parataxonomists. Frequent monitoring is important. Identification, description and data entry may take place anywhere and only require a laptop computer, a bar code encoder and scanner. Samples may be dried and packaged with minimal infrastructure. Extraction, on the other hand, requires a laboratory, a stable electricity supply, and proper storage facilities. One or more chemistry departments at area universities could establish extraction laboratories, preferably for use by a consortium of collectors either under the supervision of a university department or interdepartmental programme, an external research institution, an NGO, or in collaboration with the private sector. Subsidization of start-up costs would probably be necessary, but with prior market analysis it might be possible to find a company willing to negotiate a supply-for-equipment agreement for the initial stages of a contract

If at all possible, countries or institutions could also establish bioassay-guided fractionation, isolation, characterization and structural elucidation capacity, and screening facilities. Countries with sufficient scientific expertise could also attempt to synthesize active compounds, because "most natural product agents, once they have been purified from their native mixtures, do not make good pharmaceuticals....They may not formulate well; they may not be bioavailable; they may not have the appropriate

stability; they may have toxic side-effects as a single agent. Often an analogue programme is designed to overcome those issues, more than to get around a particular patent".[40]

The development or refinement of the above-mentioned scientific capacity is, of course, far more costly both in terms of equipment and the level of training required to perform these tasks, but even so it is not beyond the capacity of many developing countries and could be done on a regional basis in either federal or multinational R & D consortia. Countries could seek the specialized training in the development and use of screens which is given to selected foreign nationals by the U.S. National Cancer Institute's Natural Products Branch and affiliated universities. Post-graduate training in related disciplines could be given priority by State funding agencies, and universities could develop interdisciplinary programmes to prepare scientists to work at various levels in the areas of molecular biology and chemistry, and to hone skills in genetic engineering. The ultimate aim would be to develop screens relevant to local disease problems which the transnational pharmaceutical companies will very likely ignore, and to utilize existing screens, which can be acquired from the NCI, to screen extracts from local biodiversity as possible sources of drugs to combat cancer and AIDS.

Aiming for the creation of a local pharmaceutical industry may not be cost-effective, but may make sense for non-economic reasons. If a domestic pharmaceutical industry is already in existence or if domestic fine chemistry and molecular biology capacity has been established, then every effort could be made to develop or acquire screens to assay local biodiversity for potentially active compounds. The difficulty, however, is in arriving at a useful compound that is more effective than existing remedies, easily deliverable, passes toxicity requirements, is neither complicated nor costly to produce, and is not patented already by someone else (although this is not a problem in most Third World countries). In conjunction with attempts to find active compounds for allopathic medicines, a country could also focus on local health problems and the domestic primary health care services market, with a view to developing drugs from biodiversity that are based on traditional medicine practices yet have been scientifically substantiated. These medicines should be very carefully evaluated, their dosages standardized, their quality carefully controlled, and their distribution monitored (*The Lancet*, 1994, pp. 1513-1515).

Countries without sufficient scientific infrastructure to do bioassay-guided fractionation, structural elucidation, and develop screens, could research agricultural production techniques to achieve maximum yield of specific economically important plants. Those with some agricultural biotechnology expertise could study maximization of the production of the active compound by the plant. This is not inconsequential, because "natural product drugs are often very complex molecules with many chiral centers and, as such, pose formidable challenges to their synthetic production. Thus, such important plant-derived anticancer drugs as vinblastine and vincristine are still isolated from the source plant, *Catharanthus roseus*, despite over 20 years of efforts to produce them synthetically. Likewise, microbially-derived anticancer drugs, such as the bleomycins and daunorubicin, are still produced by fermentation rather than total synthesis" (Cragg, 1993b).

In sum, initial findings indicate that biodiversity prospecting for new pharmaceuticals is not a panacea for development, but lucrative rewards might be gained in the long run if countries have or establish the relevant scientific infrastructures, intellectual property laws, conservation areas, and good negotiating skills, and if they have the political will to collaborate both with each other and with developed country industries. The market for essential oils (particularly for use in cosmetics) and for phytopharmaceuticals and herbal preparations, however, is much greater and easier to get into than that for new compounds to be tested for possible pharmaceutical use. The long testing period for pharmaceuticals makes immediate returns unlikely, though there is long-term potential. Moreover, there are important spillover effects for other economic sectors, particularly in agriculture and industry, from developing the scientific capacity to add value to the various stages of the biodiversity prospecting/drug development process, and these might make the necessary investment seem more rational in spite of the limited immediate financial returns.

(Original: English)

[40] Commentary by James McChesney during the discussion following the presentation by Cragg and others at the Ciba Foundation Symposium No. 185 (Cragg and others, 1994a, p. 194).

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