Journal of Natural Products
Vol. 58, No. 9, pp. 1325-1357, September 1995

NATURAL PRODUCT DRUG DISCOVERY AND DEVELOPMENT: NEW PERSPECTIVES ON INTERNATIONAL COLLABORATION[1]

JOSEPH T. BAKER,

Australian Institute of Marine Science, PMB.3.M.C., Townsville, Queensland, Australia 4810

ROBERT P. BORRIS,

Merck Research Laboratories, P.O. Box 2000, Rahway, New Jersey 07065

BRAD CARTÉ,

SmithKline Beecham Pharmaceuticals, 709 Swedeland Road, King of Prussia, Pennsylvania 19406

GEOFFREY A. CORDELL, DJAJA D. SOEJARTO,
Program for Collaborative Research in the Pharmaceutical Sciences,
Department of Medicinal Chemistry and Pharmacognosy,
College of Pharmacy, University of Illinois at Chicago,
833 South Wood Street, Chicago, Illinois 60612

GORDON M. CRAGG,*

Natural Products Branch, Developmental Therapeutics Program, Division of Cancer Treatment,
National Cancer Institute, Frederick Cancer Research and Development Center,
P.O. Box B, Frederick, Maryland 21702

MAHABIR P. GUPTA,

Center for Pharmacognostic Research on Panamanian Flora (CIFLORPAN), College of Pharmacy,
University of Panama, Estafeta Universitaria, Panama, Republic of Panama

MAURICE M. IWU,

Walter Reed Army Institute of Research, Walter Reed Army Medical Center, Washington, D.C. 20307

DOMINGO R. MADULID,

National Museum, Botany Division, P.O. Box 2659, Manila, Philippines

and VARRO E. TYLER

Department of Medicinal Chemistry and Pharmacognosy, School of Pharmacy and Pharmacal Sciences,
Purdue University, West Lafayette, Indiana 47907

ABSTRACT.—Until recently, the prevailing attitude in developed nations regarded the world's genetic resources, which are mainly concentrated in the developing world, as a common resource of humankind, to be exploited freely irrespective of national origin. With the devastation being wreaked in the tropical rainforests and the resurgence in interest in recent years in the discovery of novel drugs from natural sources, particularly plants and marine organisms, the international scientific community has realized that the conservation of these global genetic resources and the indigenous knowledge associated with their use are of primary importance if their potential is to be fully explored. With this realization has come a recognition that these goals must be achieved through collaboration with, and fair and equitable compensation of, the scientists and communities of the genetically rich source countries. The signing of the United Nations Convention on Biological Diversity by nearly all of the world's nations has emphasized the need for the implementation of such policies. In this review, the articles of the Convention

[1]The authors of this article are members of the Ad Hoc Committee on Indigenous Materials appointed by the President of the American Society of Pharmacognosy to develop a set of guiding principles for members of the Society pursuing research involving the use of indigenous knowledge and resources. Apart from the policy statements which have been approved by the relevant organizations, this paper is the product of this Committee and does not necessarily reflect the opinions of any of the organizations which employ the Committee members or of the American Society of Pharmacognosy.

of relevance to the activities and practices of the natural products scientific community are briefly discussed. This discussion is followed by a summary of policies for international collaboration and compensation being implemented by several developed country organizations, and the perspectives on the current developments given by representatives of some of the source countries located in the regions of greatest biodiversity.

Throughout the ages, Nature has provided humans with sources of the essentials of life, including food, medicines, and raw materials for the manufacture of clothing and shelters. In particular, higher plants have been the source of medicinal agents since earliest times, and today they continue to play a dominant role in the primary health care of about 80% of the world's population (1). Natural products, and medicinal agents derived therefrom, are also an essential feature in the health care systems of the remaining 20% of the population residing mainly in developed countries, with more than 50% of all drugs in clinical use having a natural product origin (2). Of the world's 25 best-selling pharmaceutical agents, 12 are natural product-derived (3), and natural products continue to play an important role in drug discovery programs of the pharmaceutical industry and other research organizations (4–6). Research into the chemical and biological properties of natural products over the past two centuries has not only yielded drugs for the treatment of many human ailments, but has provided the stimulus for the development of modern synthetic organic chemistry, and the emergence of medicinal chemistry as a major route for the discovery of novel and more effective therapeutic agents.

Members of the American Society of Pharmacognosy (ASP) have been leaders in the natural product drug discovery and development process, and their contributions in the area of cancer chemotherapy have been outstanding. The pioneering studies of the active constituents of *Podophyllum peltatum* L. by the late Dr. Jonathan Hartwell (7), and the co-discovery and development of the antileukemic agents, vinblastine and vincristine, from *Catharanthus roseus* (L.) G. Don by the late Dr. Gordon Svoboda (8), provided convincing evidence that plants could be sources of novel, potential cancer chemotherapeutic agents. Prompted by such discoveries, the National Cancer Institute (NCI), in collaboration with the United States Department of Agriculture (USDA), established a systematic effort in 1960 to collect and screen plants for antitumor activity (9). Through support provided by contracts and grants awarded by the NCI, Drs. Monroe Wall and Mansukh Wani discovered taxol, now approved for the treatment of ovarian and breast cancer (10), and camptothecin, which has been converted through semi-synthesis to several analogues that are currently showing promise in advanced clinical trials (11). Significant contributions to the discovery of a broad range of bioactive chemotypes were made by a number of other natural product research groups, most notably that of the late Dr. Morris Kupchan (12). The role played by plants in the provision of novel agents having potential in the treatment and prevention of many diseases such as cancer, acquired immunodeficiency syndrome (AIDS) and related infections, and malaria has been reviewed in an American Chemical Society Symposium Series volume (4). In the area of marine natural products, both plants and animals are investigated routinely (5); several marine products, such as didemnin B (13) and bryostatin 1 (14) have advanced to clinical trials as potential anticancer agents, and many others have shown significant bioactivity.

GENETIC RESOURCES AND TRADITIONAL KNOWLEDGE

As mentioned earlier, plants have formed the basis for the treatment of diseases throughout the ages, and continue to be a major source of primary health care for about 80% of the world's population. Sophisticated plant-based traditional medicine systems have been in existence for thousands of years in countries such as China (15) and India

(16), and medicinal plants are used extensively in African traditional health systems (17,18). Numerous phytomedicines are registered and extensively used in Europe, and more than 600 botanical items have been officially recognized in various editions of the *United States Pharmacopoeia* (19), though current regulations prohibit most from being marketed as drugs. In Australia, the traditional therapeutic use of native plants by indigenous people was not recorded in written form, and the extent of that use and knowledge is only now becoming evident.

Of 119 plant-derived drugs commonly in use in one or more countries, 74% were discovered as a result of chemical studies directed at the isolation of the active constituents of plants used in traditional medicine (1). Well-known examples include the cardiac glycosides from *Digitalis purpurea* L., the antihypertensive agent and tranquilizer, reserpine, from the East Indian snakeroot, *Rauvolfia serpentina* (L.) Bentham ex Kurz; the antimalarial agent, quinine, from *Cinchona* spp.; and the analgesics, codeine and morphine, from *Papaver somniferum* L. (2). Secondary metabolites isolated from medicinal plants have also served as precursors or models for the preparation of effective agents through semi-syntheses or lead-based total syntheses. Examples include the anticancer agent, etoposide, a semi-synthetic derivative of epipodophyllotoxin isolated from *Podophyllum* spp. (9), and anticholinergic drugs modeled on the belladonna alkaloids (e.g., atropine) isolated from *Atropa belladonna* L. and other medicinal plant species (1).

Of the estimated 250,000 currently known higher plant species, very little is known about their secondary metabolites; this is particularly true for tropical flora, which constitute over 60% of this estimated number (2,20). Even less is known about the far more abundant (though taxonomically relatively unexplored) insect and microbial worlds (20), as well as the biologically rich and enormously diverse marine environment (21). Given the rapid destruction of tropical habitats, especially the rainforests, and the degradation of some marine ecosystems, this lack of knowledge is alarming. Considering that the 119 drugs mentioned above were isolated from only about 90 plant species (1), the potential for drug discovery from plants and other natural sources is enormous, but little time remains to explore this rapidly diminishing resource.

Although the long-established traditional medicine systems, such as those existing in China and India, have recorded much of their knowledge, including the use of many medicinal plants, in written texts, ethnobotanists and anthropologists have expressed alarm at the rapid loss of the knowledge of traditional healers, particularly amongst indigenous groups in the Neotropics (20). Before the late 1980s, the developed world displayed little interest in such indigenous knowledge, and minimal effort was expended to assist indigenous communities in preserving their unique knowledge and traditions. With the resurgence of interest in the screening of plants and other natural resources for potential medicinal properties, western research organizations are beginning to place greater value on such knowledge (22). Where such knowledge is accessible, the search for bioactive substances might be expected to be more effective and efficient than in cases where all samples are collected with no basis for selection; this latter form of collecting is often referred to as biodiversity prospecting or bioprospecting. Several publications addressing the issues of biodiversity prospecting and the recognition of the intellectual property rights of indigenous peoples have appeared in recent years (23–25).

The search for novel drugs can also be enhanced by observation of interactions between different organisms, and a study of the natural history of organisms in their response to environmental pressures, such as predation or infestation. Such pressures often result in the production of bioactive secondary metabolites as a means of chemical defense, and developing an improved understanding of such chemical ecology might

allow researchers to predict where to find potentially valuable molecules (26).

The conservation of genetic resources and of indigenous traditional medical knowledge, now concentrated mainly in the developing world, is, therefore, of prime importance if the natural products scientific community involved in drug discovery and development is to have even a remote opportunity of exploring fully the potential of remaining genetic resources. As noted later in this article in the presentation of the Australian Perspective, Australia, through its unique position as the only megabiodiverse country currently classed as being "developed," may well be the best placed of the developed nations to bring together the interests of other megabiodiverse countries of the world.

DECLARATIONS PROMOTING THE CONSERVATION OF BIODIVERSITY AND TRADITIONAL KNOWLEDGE

Until recently, the prevailing attitude in developed nations regarded the world's genetic resources as existing for the common good of humankind, to be used freely, irrespective of the national origin of the particular resource. The implication was that research organizations and companies could have relatively open access to the world's genetic resources without consideration of the issues of compensation of the source countries or their indigenous peoples. There has been increasing awareness in developing countries that the use of medicinal products is often associated with substantial financial returns to the pharmaceutical companies that have developed the commercial products. In those cases where the commercial product is derived from a natural product, no significant reward was forthcoming to the country of origin.

The emerging situation is that the country of origin seeks adequate recognition and compensation for the natural product that is the source of the commercial product. Over the past seven years a number of international organizations have issued declarations or resolutions urging greater international collaboration and coordination in efforts to promote the conservation of biological and cultural diversity worldwide (27–32). A central theme has been the fact that the developing countries and their indigenous peoples are the custodians of the vast majority of the world's genetic resources, and that conservation of these resources requires fair and equitable collaboration and compensation in the development of their resources, as well as just recognition of the inventive and intellectual contributions of the indigenous peoples to the knowledge of the use of these resources. Emphasis has also been given to training, the exchange of ideas, results and technology, the promotion of traditional health care systems, and the completion of species and traditional knowledge inventories, with the dissemination of this information to all interested parties in native tongues.

The Manila Declaration Concerning the Ethical Utilization of Asian Biological Resources (Appendix 1) developed at the Seventh Asian Symposium on Medicinal Plants and Spices and other Natural Products (ASOMPS VII) held in Manila in February 1992, deserves special mention because it incorporates a suggested code of ethics for foreign plant collectors and a proposed set of contract guidelines for use by source countries in negotiating with collecting organizations The Declaration explicitly requires supply agreements with an appropriate source country organization as opposed to individuals of the country, and the contract guidelines suggest minimum standards related to sample size, sale of extracts, royalty shares, and exclusivity limits. Other more detailed guidelines for the negotiation of contracts related to biodiversity prospecting have been published (23,25).

Most of the proposals cover both terrestrial and marine source material. The specific concern for the biodiverse coral reefs was exemplified when, in December 1994, a number

of nations announced the formation of the International Coral Reef Initiative (ICRI) to address the problem of coral reef degradation. The aim of ICRI is to increase the capacity of countries and regional groups to "effectively use existing resources and sustainably manage coral reefs and the ecosystems over the long term" (33).

It is clear that, without suitable economic, intellectual, and technological incentives for sustainable development, the genetically rich source countries and their communities will be unable to preserve these valuable resources for research into their beneficial uses for humankind. Although the focus has been on the depletion of plant resources, similar arguments apply equally well to the conservation of other organisms.

THE UNITED NATIONS CONVENTION ON BIOLOGICAL DIVERSITY

The above-cited Declarations were issued as recommendations for interactions between source countries and research and development organizations; however, the U.N. Convention on Biological Diversity (Appendix 2), signed by more than 150 countries (although not by the United States of America) at the "Earth Summit" in Rio de Janeiro in June 1992, represents a treaty, which, if ratified by the signatories, will dictate certain codes of behavior in the study and sustainable use of biological diversity. The U.S.A. subsequently signed the Convention in June 1993; however, it remains to be ratified. The Convention, while binding on the Contracting Parties (i.e., national governments and their agencies), will not have any binding effect on private citizens unless it is ratified and incorporated into domestic legislation.

The Convention contains 42 articles, and Articles 20–42 deal with financial resources and mechanisms and issues related to arbitration and administrative matters that do not directly influence natural product scientists. Although the convention does not specifically mention biodiversity prospecting, most of the first 19 articles are of relevance to the activities and practices of the natural products scientific community, and a brief discussion of these is presented below. A more detailed analysis of the Convention has been presented by Gollin (34).

Article 1 clearly defines the objectives of the Convention in terms of conservation of biodiversity, the sustainable use and development of genetic resources, and the fair and equitable sharing of any resulting benefits. The principle of appropriate transfer of relevant technologies in return for appropriate access to genetic resources is a key feature.

Article 3 establishes the sovereign right of source countries to exploit their domestic resources according to their own environmental policies, subject to the responsibility that such activities do not damage the environments of other countries. This principle of sovereign rights is expanded in *Article 15*, with commitments to facilitation of access to genetic resources for environmentally sound uses (15 ¶2), such access being subject to mutually agreed terms between the Contracting Parties (15 ¶4) and the prior informed consent of the Party providing the resources (15 ¶5). Article 15 ¶6 implies full collaboration of the Contracting Parties in research performed on the genetic resources, with such research being performed in the source country, where possible. Article 15 ¶7 requires the commitment to the fair and equitable sharing of results and benefits arising from the commercial use of the genetic resource with the source country.

Articles 6–10 address issues of conservation of biological diversity. Of particular note for research organizations involved in the development of potential commercial products from biological resources, are the obligations to identify activities that might have adverse impacts on the conservation and sustainable use of biological diversity, to monitor their effects (Article 7c), and to adopt measures to avoid or minimize any adverse effects (Articles 8l and 10b). National laws implementing the Convention are likely to place an obligation on such organizations to inform source countries of the potential for

adverse impacts of activities, such as large-scale recollections, and to collaborate with those countries in implementing measures to avoid such effects (Article 10e); these requirements are further emphasized in *Article 14*. The need for collectors to deposit voucher specimens in source country holdings is implied in Article 9a, while the protection of, and respect for, indigenous and local knowledge relevant to the conservation and sustainable use of biodiversity is advocated in Article 8j. This article also encourages "the equitable sharing of the benefits arising from the utilization of such knowledge, innovations, and practices."

Article 16 elaborates on the access to and transfer of technologies, including biotechnology, relevant to the conservation and sustainable use of genetic resources (16 ¶1), which presumably could be a two-way process involving biotechnology transfer from developed nations, and transfer of genetic and biological material with taxonomic and traditional knowledge transfer from source (mainly developing) nations. Article 16 ¶2 provides for technology transfer to developing (source) countries under "fair and most favorable terms, including on concessional and preferential terms where mutually agreed." Articles 16 ¶3 and 16 ¶4 call for "legislative, administrative or policy measures, as appropriate" to facilitate transfer of technology to developing (source) countries, including transfer from the private sector (16 ¶4). Gollin (34) notes that the terminology in these sections caused some concern for critics of the Convention from developed countries, inasmuch as it appears to "suggest that a developed country government would be required to take a compulsory license from a domestic biotechnology company and provide the technology to a developing nation;" Gollin, however, maintains that the inclusion of phrases such as "on mutally agreed terms" (16 ¶3) and use of language recognizing the need for "the adequate and effective protection of intellectual property rights" (16 ¶2) should dispel such concerns. Indeed, the biotechnology industry in the United States of America and Europe accepted the language of the convention as not unduly restrictive. Article 16 ¶5 further recognizes the need for cooperation in the handling of patents and other intellectual property rights subject to national legislation and international law.

Article 17 promotes the exchange of information, "from all publicly available sources, relevant to the conservation and sustainable use of biological diversity, taking into account the special needs of developing countries" (17 ¶1), including "results of technical, scientific, and socio-economic research" (17 ¶2). *Article 18* requires the promotion of "international technical and scientific cooperation in the field of sustainable use of biological diversity" (18 ¶1) through "human resources development and institution building" (i.e., training; 18 ¶2 and 18 ¶4; see also *Article 12*), establishment of clearinghouse mechanisms (18 ¶3), and "joint research programmes" (18 ¶5).

Article 19 reinforces Article 16 in promoting the "effective participation in biotechnological research activities by the Contracting Parties, especially developing countries, which provide the genetic resources for such research" (19 ¶1), and "advance priority access on a fair and equitable basis by Contracting Parties, especially developing countries, to the results and benefits arising from biotechnologies based upon genetic resources provided by those Contracting Parties" (19 ¶2). Once more, Gollin feels that the inclusion of the sentence "Such access shall be on mutually agreed terms" (19 ¶2) "may be interpreted as allowing only consensual agreement for two-way technology transfer in a non-compulsory manner" (34).

It is clear that the overall thrust of the Convention is: (a) The promotion of the conservation of biodiversity, (b) The development of socially beneficial and commercial products (pharmaceutical, agricultural, and industrial) through the sustainable use of biodiversity, (c) The promotion of collaboration and cooperation in the study and

sustainable use of the genetic resources of source countries, (d) The promotion of research and training and the facilitation of technology transfer to source countries, (e) The fair and equitable sharing of the results and benefits arising from the commercial and other utilization of source country genetic resources.

POLICIES FOR INTERNATIONAL COLLABORATION AND COMPENSATION

Many organizations in developed countries, in particular large, multinational pharmaceutical companies, have been strongly criticized by the media and spokespeople representing source country communities and interests for their attitudes toward the investigation of natural resources. In many ways, these criticisms are a reflection of the actions of a bygone colonial era when the rights of source countries and communities were largely subjugated to the interests of colonial powers. Although we recognize that inequities did (and in some instances, still do) exist, it is not our purpose to make apologies for such past actions, but rather to focus on the changes in both philosophy and action that have occurred in recent years.

Fortunately, the times and attitudes are changing, and many organizations and companies, as well as governments, have become more enlightened and responsible citizens of the world community. Few members of corporate management, at least in the pharmaceutical industry, would disagree with the fundamental concept of a nation's sovereignty over its own natural resources. The acquisition of biological samples for investigation is frequently viewed in the same way as the acquisition of any other commodity; some form of significant compensation is required. In this respect, it must be noted that the probability of discovering a compound that is potentially marketable from any particular sample of the biota is extremely small, and the monetary value that is attached to these materials is, therefore, also quite modest.

The scientific and industrial communities of the developed nations generally are not at all averse to the concept of compensation for the use of the intellectual property of indigenous peoples. This is a direct extension of the practice of licensing patented processes or products from other corporations. There are, however, a few caveats involved. First, the intellectual property in question must be of some value to the study being performed. The existence of an ethnobotanical use of a particular plant, for example, is of little or no importance to a taxonomically driven survey of a local flora unless the plant is included in the survey on the basis of that use. Second, a large body of ethnobotanical information already exists in the public domain in the form of books or journal articles. This information is readily and equally available to all members of the scientific community, and it is unrealistic to expect compensation for the use of information that has been previously published by a third party without restriction. It should be noted, however, that Australia is still analyzing the rights of its indigenous people in respect to medicinal plants occurring on their land; even though literature may exist that suggests an ethnobotanical use of a plant, consideration could be given to the possibility that the information may have been published without the permission or knowledge of the indigenous people.

Compensation for samples provided for investigation may take a number of different forms, including, among others, up-front payments and royalties. Royalties, the real compensation for use of relevant intellectual property, are potentially the most lucrative form of compensation and will accrue once a commercial product has been developed, either directly by a company, or through licensing of a product to a company from a non-profit research organization. The size of a royalty payment to the source country individual or community will reflect their intellectual contribution to the discovery and development of the final commercial product. There is frequent criticism of the

apparently small size of such payments stipulated in acquisition contracts and agreements, typically 1–3% at present, but it should be noted that a 1% royalty over the life of a patent on sales of a billion-dollar drug will rapidly dwarf an apparently generous up-front payment. Unfortunately, as indicated above, the probability of developing such a product is extremely small, and there is an unavoidable delay between the time a research sample is collected and the time that sales begin to generate revenues, normally of the order of ten to fifteen years.

Another potential form of compensation resulting from the development of a commercial product is the mass production and processing of the source raw material. Although while it is often assumed that the commercial product will be produced by synthesis, experience has shown that development of an economically feasible total synthesis is often fraught with substantial problems. The natural resource often proves to be the best economic source, and some current agreements specify that, when possible, production via sustainable raw material collection or cultivation will be performed in the original source country, subject to mutual agreement of all parties on the terms of production.

Up-front payments can be used for infrastructure development in the source country. Such development can take the form of the improvement of local laboratory facilities for the processing of samples, provision for the improved health care of collaborating communities, and support for local conservation efforts. While companies can choose to support such infrastructure development through up-front payments, nonprofit research organizations usually are not in the position to provide such support; however, because most of these organizations are state-funded, support for these activities is generally provided through other government programs. In the case of the United States, substantial support is channelled through the U.S. Agency for International Development (USAID) (33).

Potentially the most valuable form of compensation is that of scientific exchange and training, and technology transfer. Through such means a country may be empowered to enhance its own capacity for in-country drug discovery and development, as well as develop its own pharmaceutical industry. The greater the in-country capability in these spheres, the greater will be the benefits accruing to the country in terms of maximum utilization of its genetic resources. In order to promote in-country bioprospecting or chemical prospecting, the establishment of a "Biotic Exploration Fund" to support the formation of biodiversity institutes worldwide has been proposed (35). Through partnerships with organizations and industries interested in screening their repositories of materials, these institutes should eventually become self-sustaining and thereby generate revenues for conservation of their natural resources. A prime example of such an institute is the Instituto Nacional de Biodiversidad (INBio), which has developed partnerships with research organizations and companies, such as Merck, in the investigation of the genetic resources of Costa Rica. Such ventures should provide benefits, not only to the source countries, but to a broad range of industries, including the pharmaceutical, agrochemical, flavoring, perfume, and food industries. Although it is necessary for a country to have a core of professionals with advanced scientific training, the existence of this core may be insufficient to allow it to develop an industry that can compete effectively in a global or a national free market. Much can be gained by exposing these core scientists to the inner workings of the state of the art research and development departments of a successful multinational corporation to learn why, in addition to how, such an organization functions. When such exposure is coupled with some level of technology transfer that provides the tools for performance of competitive research, the end-product is a team of scientists with the expertise, perspective, and tools to effectively start an industrial research program.

Many natural product scientists have long-established interactions and collaborations with scientists in genetically rich source countries, though such collaborations may not always be formalized in terms of signed collaborative agreements. Even before the signing of the Convention on Biological Diversity, a number of developed country organizations and companies had formulated official policies promoting collaboration with organizations and peoples in countries providing genetic resources for biological and pharmacological research. These policies include terms for the promotion of training and collaboration in research activities, addressing health care needs of local populations, as well as the provision for compensation in the event of development of a commercial product from such resources. Some examples of organizations that have adopted such policies are discussed below.

United States of America Government Organizations

The United States National Cancer Institute.—In September 1986, NCI initiated plant and marine invertebrate collections through contracts with four qualified organizations. The current collections are being carried out in more than 25 countries situated mainly in tropical and subtropical regions. In performing these collections, the NCI contractors work closely with qualified organizations and scientists in each of the source countries.

Recognition of the value of the natural resources being investigated, and the significant contributions being made by the source country scientists and, in some instances local traditional healers, prompted NCI, with support from several of its contractors, to begin formulating policies aimed at promoting collaboration with, and compensation of, countries participating in the drug discovery program. The first policy statement, referred to as the Letter of Intent, was issued in 1988, but the terms have been adapted to address legitimate concerns of source country representatives, and the document is now referred to as the Letter of Collection (LOC). The LOC has formed the basis for formal agreements with organizations or agencies in sixteen countries, and negotiations are proceeding with several other countries.

In the short term, NCI provides summaries of test results to relevant source countries, subject to data on active leads being held confidential until NCI scientists have had sufficient time to assess the potential for development of new drugs; each source country receives only data related to organisms collected within its borders. Senior scientists from source countries are invited for short visits to NCI to discuss the goals of the program, and explore the scope for expanded collaboration; more than forty scientists from twenty-eight countries have participated thus far. Qualified scientists are also invited to spend up to one year working in NCI or equivalent facilities of approved organizations carrying out joint research projects on topics of mutual interest. Many of these visits involve training in separation and screening methodology and are accompanied by significant knowledge and technology transfer. Eighteen scientists from thirteen source countries have thus far participated in this program, which has led to the establishment of several productive collaborations. NCI also accepts novel, pure compounds from suppliers worldwide for testing in the human cancer cell line and anti-HIV screens, and will consider collaboration in the development of any agents exhibiting significant activity.

In the long term, NCI requires any licensee of an NCI-patented drug to negotiate acceptable terms of compensation (e.g., percentage of the royalties accruing from the sale of the drug) directly with the appropriate organization or government agency in the source country of the organism yielding the drug. In addition, NCI collaborates with the source country in developing adequate supplies of the source raw material, either through sustainable harvest or cultivation, and will require the licensee to seek as its first source of supply, the raw material produced in the source country. In this respect, NCI,

through a contractor, is currently collaborating with Cameroon scientists in studying the cultivation of *Ancistrocladus korupensis,* source plant of the potential anti-HIV agent, michellamine B.

NCI has developed policies for the distribution of extracts from the Natural Products Repository to carefully selected organizations. One of the major factors in selecting organizations is the agreement by such organizations to abide by the terms of the NCI Letter of Collection related to compensation and use of source country resources. The selected organizations are committed to these terms through the signing of a legally binding Material Transfer Agreement.

International Cooperative Biodiversity Group (ICBG) Program.—In March 1991, the National Institutes of Health (NIH), the National Science Foundation (NSF), and USAID sponsored a conference on Drug Development, Biological Diversity, and Economic Growth attended by representatives of six developing, source countries, the environmental and intellectual property rights communities, the pharmaceutical industry, and other experts in these areas (32). This meeting led to the establishment of the ICBG program supported by the three agencies. After a peer review of competing applications for funding, the award of five Cooperative Agreements was announced in late 1993. Each ICBG has at least one developing country component, one U.S. Research organization, and one pharmaceutical company as members.

The goals of the program are conservation of biological diversity, natural product drug discovery, and promotion of sustainable economic activity in the participating developing countries. Each ICBG project has developed its own mechanism for ensuring close collaboration between developing and developed country partners, as well as contractual agreements for equitable distribution of benefits and compensation to all those who contribute to product development; such agreements cover contributors whether or not they are project partners, and include research institutions and indigenous people in all countries who provide useful traditional knowledge.

In order to be awarded ICBG funds, the research and development program and the contractual arrangements among partners were required to address a set of principles outlined in the original request for applications, but the mechanisms by which the groups addressed these originated with the members themselves. Agreements covering intellectual property rights (IPR) vary depending on source country partners, and may involve different types of IPR protection (e.g., patents, trade secrets, petty patents). The agreements consider indigenous concepts of intellectual property, and require full disclosure and informed consent in the use of traditional knowledge and/or indigenous resources. They also require procedures for compliance with local environmental laws relating to permits, biological impact studies, sustainable development, and plans for the early resolution of possible disputes arising from different attitudes to the ethic of public access to information and the need for confidentiality of information having potential commercial value.

Resources returning to developing country partners include screening for therapeutic potential, training opportunities, equipment donations, fees for samples and up-front payments, profit-sharing (e.g., percentage royalty payments) from sales of products developed through the ICBG program, and inclusion of indigenous or local people as co-inventors on patents, where appropriate.

The collaboration of the three U.S. Government agencies in sponsoring the ICBG program is significant in that it permits different issues to be addressed which could not be supported financially or technically by any one of the agencies alone. Thus, in addition to joint funding, NIH offers technical support for the drug discovery aspects, while NSF supports conservation and training activities, and USAID advises on sustainable

economic activity and infrastructure development. Another novel aspect of this program is the requirement for the direct involvement of source country organizations. The composition and activities of the ICBG awardees are listed below:

- Cornell University is collaborating with INBio of Costa Rica, the University of Costa Rica, and Bristol-Myers Squibb Pharmaceutical Research Institute in the investigation of insects and related species from the dry tropical forests of the Guanacaste Conservation Area in Costa Rica.
- The University of Arizona, together with Louisiana State University and Purdue University, is collaborating with the Institute of Biological Resources of Buenos Aires and the National University of Patagonia in Argentina, the Catholic University of Chile, the National University of Mexico, and the Medical and Agricultural Divisions of Wyeth-Ayerst Laboratories in the study of arid land plants in Argentina, Chile, and Mexico.
- Virginia Polytechnic Institute and State University and Missouri Botanical Garden are collaborating with Conservation International-Suriname, the Forest People of Suriname, the National Herbarium of Suriname, Bedrijf Geneesmiddelen Voorziening Suriname, and Bristol-Myers Squibb Pharmaceutical Research Institute in studying rainforest plants of Suriname.
- Walter Reed Army Institute of Research, together with the Smithsonian Institution and the Biodiversity Support Program (a consortium of the World Wildlife Fund, the Nature Conservancy and the World Resources Institute), is collaborating with the Bioresources Development and Conservation Programme (a consortium of the University of Yaoundé in Cameroon, the University of Nigeria, Nsukka, and the Ministry of Science and Higher Education, Cameroon), Shaman Pharmaceuticals and Southern Research Institute, in investigating rainforest plants of Cameroon and Nigeria as sources of potential agents for the treatment of parasitic diseases.
- Washington University in St. Louis is collaborating with the Natural History Museum of Peru, the Cayetano Peruvian University, the Central Organization of Aguaruna Communities of the Alto Maranon, and Searle Pharmaceuticals in the examination of medicinal plants from the Andean rainforests of Peru.

Academic Institutions and Research Organizations

The University of Illinois at Chicago (UIC).—In the procurement of samples, UIC will deal only with the owners of those samples (usually the source country) or the owner's bona fide representatives, termed consultants. UIC requires documented evidence that the consultants and those affiliated with the consultants have permission from the owners to collect and export samples, and are abiding by the source country's applicable laws and regulations governing such activities.

The samples are provided to UIC for purposes of evaluation and investigation as potential sources of active, commercial products. In pursuing these investigations, UIC claims ownership to resultant products, including extracts, separated fractions, or purified compounds (or derivatives thereof), as well as data produced during the investigations. UIC may file patent applications on inventions made during these investigations, and will generally negotiate license agreements with a third party, usually a pharmaceutical company, for development of the inventions. UIC may also transfer samples to other organizations for evaluation and investigation, and allow such organizations to file patents on inventions. In either case, revenue derived by UIC from a patented product will be shared through the consultant with the owner of the original source material. The owner's share of this revenue will be determined by the level of the

intellectual contribution made by the consultant or source country collaborators and/or informants (e.g., indigenous peoples); where the intellectual input is considered substantial, co-inventorship on the patent application will be considered. In determining the ownership of samples and intellectual input by indigenous people in a particular invention, UIC relies on the judgement and management of the source country organizations or agents, acting through the consultants. It is the general practice of UIC to afford the primary collectors of samples co-authorship on any publications resulting directly from their samples in recognition of their intellectual contribution to the project.

UIC will provide the consultant, annually and under strict confidentiality, all test data resulting from plants collected through the collaboration, and will likewise provide results generated through collaboration with a partner developing a drug. It will also help organize and implement sponsored research and training programs in source countries or at UIC, contingent upon receiving the required funds for these activities from an external source.

Regarding the large-scale production of an active agent by a licensee or manufacturer, UIC will ask the licensee to exercise its "best efforts" to purchase any necessary raw materials from the country of origin. Likewise, UIC will ask the licensee to exercise its "best efforts" to provide the country of origin with the final product under preferential terms. In neither case is UIC in a position to obligate the licensee to perform these actions.

The University of Mississippi Research Institute of Pharmaceutical Sciences (UMS).—UMS has established a program to identify natural products with specific activity in one of a variety of assays, including anticancer, antifungal, antimicrobial, antiprotozoal, and antiviral. The long-term goal of the program is to carry promising natural products into pharmaceutical development, and ultimately commercial use.

In achieving these goals, UMS seeks to enter into collaborative agreements with research laboratories and organizations worldwide, whereby natural product extracts, partially purified fractions, and structurally defined compounds may be submitted for evaluation in one or more of the available assays. Where active extracts are identified, isolation, purification, and characterization of the active component(s) are coordinated between representatives of the collaborating organization and UMS, and the further development of any products showing significant activity is planned jointly by the collaborating parties.

In establishing agreements for the submission of samples for screening, the submitter and UMS agree that, once positive leads have been identified, decision points for the negotiation of preclinical development agreements, patent questions, licensing issues, and publication of results will be formulated. The terms of the agreements recognize the relative responsibilities of the collaborating partners and seek to reward fairly the efforts of all parties in the collaboration. Results are published jointly and at a mutually agreed time, which ensures that the publication or public disclosure does not jeopardize any potential patent interests. Patentable inventions made by the collaborating organization are owned by that organization, while UMS owns patentable inventions made solely by its scientists. Joint inventions are jointly owned, with each collaborating partner having an equal and undivided interest. In the event of commercialization of any products developed from the collaborative partnership, the royalties accruing to the partnership will generally be shared equally between the collaborating partners. UMS is dedicated to the preservation of Earth's biodiversity and the sustainable development of these resources. In the event of the commercialization of a product isolated from a natural resource collected in a particular country, UMS will negotiate an agreement with

a collaborating center in that country for reinvestment of a portion of the royalties into the country.

Through the enlistment of collaborating institutions in developing countries, UMS intends to promote the effective transfer of the UMS philosophy and technology of drug discovery and development to those organizations. Such transfer is achieved through inviting representatives from collaborating organizations and source countries to participate in intensive workshops on the process of natural product based drug discovery and development at UMS, and the provision of full or partial support for the graduate education of over twenty international students and visiting scholars, as well as hosting students and visiting scholars supported by agencies of their home governments.

Pharmaceutical Companies

The Bristol-Myers Squibb Company (B-MS).—B-MS has had a longstanding interest in the discovery and development of pharmaceuticals from natural sources. Although that interest may be exemplified most recently by the company's successful development of the anti-cancer compound Taxol®, B-MS has long maintained a biomolecular screening program for natural products within its Pharmaceutical Research Institute. Indeed, scientists within the Institute have been working actively with researchers from U.S. and foreign institutions to discover new drugs from natural sources. Currently, certain of those efforts are being pursued under the auspices of two federal programs that were created, at least in part, as a result of the successful development of Taxol®.

Specifically, the first type of program in which B-MS has participated involves National Cooperative Natural Products Drug Discovery Groups (NCNPDDG) funded by the NIH. These programs involve collaborative relationships with U.S. research institutions, which, either directly or through local parties, collect biological samples from different countries and provide them to B-MS for analysis and possible development. To date, B-MS has established agreements with United States universities and research institutes for the collection and analysis of extracts of marine organisms and plant species.

The second type of program in which B-MS has participated involves collection of biological material in a particular country by a resident research organization in collaboration with scientists from U.S. institutions. These programs have been developed as part of the ICBG program sponsored by NIH and other federal agencies. Under the program, B-MS has entered into an agreement to evaluate tropical rainforest plants from Suriname with the Virginia Polytechnic Institute and State University, Conservation International, Missouri Botanical Garden, and Bedrijf Geneesmiddelen Voorziening Suriname. The company also has an arrangement with Cornell University and INBio to identify potentially important compounds from tropical insects in Costa Rica.

The agreements governing these relationships vary necessarily to some extent depending on the particular circumstances involved. However, for all agreements, B-MS subscribes to certain basic principles governing prospecting of biological diversity. These include the requirement that the company's research partners (and, in turn, their agents) only acquire biological samples in an environmentally responsible manner. Such collectors must, at all times, comply with applicable laws and regulations and obtain prior consent from the host government. Moreover, where such collecting is to be based on ethnobotanical knowledge, B-MS has agreed to collaborate in such efforts only where those providing such information have given their written consent (after being informed as to how such information will be used and what their rights could be to potential benefits).

Beyond adhering to these principles, B-MS recognizes the importance of compensating countries and their indigenous peoples for the use of biodiversity resources. To that end, B-MS seeks to provide, when appropriate, advance benefits to the country whose biological resources are being investigated. These benefits may include assistance in screening natural products for diseases particularly troubling in that country, and financial support for patent protection. At the same time, B-MS provides royalties to the resident research organization on any products that are developed commercially. It is expected that such royalties are to be used, in part, for conservation and protection of biological diversity in the country. Where B-MS does not, itself, enter into such agreements, the company anticipates that its collaborators will do so and return a share of their royalties to the country and its indigenous peoples.

The actual royalty that B-MS provides is based on a number of different factors, including the relationship between the drug ultimately marketed and the compound originally discovered from biological sampling. No matter what the royalty payment, however, B-MS also commits itself to consider utilizing the country as a source of supply and/or cultivation of necessary raw natural product materials for any commercially developed product (where collection/cultivation and extraction is a commercially and regulatorily viable option). In addition to royalty payments, such arrangements may instill a value in the protection of the country's biological diversity and ultimately further the purposes of the U.N. Convention on Biological Diversity.

The Glaxo Group of Companies.—Glaxo Research and Development Ltd. (GRD) is the arm of the Glaxo Group that undertakes the discovery and development of new drugs, and its policy relating to acquisition of natural product source materials and mode of conduct has been officially published in a document amended as of 6 January 1994. In this document, GRD declares that it is aware of, and sensitive to, issues relating to biodiversity and conservation, and recognizes the importance of matters considered by the U.N. Convention on Biological Diversity. Furthermore, GRD affirms its understanding of the impact that unauthorized and/or unrestrained removal of natural materials from their indigenous habitats can have on the environment and the economy of a country.

In seeking access to natural materials, GRD's policy is to collaborate with organizations that possess the expertise and the authority to obtain such materials from whatever source, and agreements are concluded only with suppliers that provide documentary evidence that they have permission from the appropriate government authorities to collect such materials. The supply of the materials must be reproducible and sustainable, and GRD will neither seek, nor knowingly support, the collection of endangered species. Agreements have been concluded with organizations such as the Royal Botanic Gardens at Kew, the University of Illinois at Chicago, and the Institute of Medicinal Plant Development in Beijing. Bona fide suppliers are reimbursed for the costs of collection and their expertise in areas such as the determination of taxonomic classification of samples. All shipment costs are borne by GRD.

Intermediate forms of compensation may involve options to provide funds for training, provision of equipment, and/or financial support for patent protection of an identified active agent if the supplier wishes to own the intellectual property to this material. Funds for training and laboratory facilities have been provided to young scientists at some of the foreign institutes collaborating with GRD.

The precise nature of the financial terms in a GRD supply agreement are negotiated on a case-by-case basis, but royalty obligations are a constant feature of all agreements. In the event of development of a commercial product, the magnitude of the financial return will recognize the relative contribution of the discovery of the bioactive principle

to the subsequent development of the commercial product. GRD's arrangements with suppliers further require that they contribute at least 40% of the royalty payments to the source country to support scientific training and education at the community level. The selection of the appropriate beneficiary in the source country, whether it be an indigenous people with relevant ethnomedical knowledge, a community which cultivates the source material, a local academic institution, or some other organization, is left to the supplier, on the assumption that the supplier is best placed to make such choices.

Philanthropic support for conservation efforts is handled separately from the above issues, and is a matter for consideration by the Appeals Committee of Glaxo Holdings.

Merck & Co., Inc.—In establishing collaborations related to the sourcing of plant-derived natural product samples, Merck tailors its agreements to meet the specific needs of the collaborating organizations. Implicit in such agreements is the recognition of the scientific contributions of collaborators in the source countries and developed country organizations, and the need to compensate the source countries with royalties based on the profits accruing from the sale of drugs resulting from the research. All plant collections undertaken on Merck's behalf conform to the strictest interpretation of all applicable local, national, and international laws, and explicitly exclude the collection of endangered or threatened species. Merck currently maintains two major collaborations for the acquisition of plant samples for screening, with INBio of Costa Rica and with the New York Botanical Garden.

Under this agreement, a relatively small number of plant, insect, and environmental samples are provided by INBio. In return, Merck has provided a number of different forms of compensation, with a unique feature of the agreement being the allocation of 10% of the total collaborative budget to the promotion of conservation through support of the Costa Rican system of National Parks and Protected Areas. In addition to making up-front payments to cover research expenses, Merck has also established and equipped a laboratory at INBio in which relevant research work is being performed. Costa Rican scientists have been trained in extraction methods and in advanced phytochemical techniques, both in the laboratory at INBio and in the Department of Natural Products Chemistry at Merck in New Jersey. Publications that may result from this research will be co-authored by scientists from both institutions, and resultant patents will include inventors from both institutions as appropriate under prevailing patent law. If a marketable product results from a discovery made under this collaborative agreement, Merck will pay royalties to INBio, a portion of which will be used to support the Costa Rican system of National Parks and Protected Areas.

While less publicized than the INBio agreement, the agreement with the Institute of Economic Botany of the New York Botanical Garden (NYBG) is very similar in content. In return for plant samples collected by NYBG botanists from habitats around the globe, Merck has established and equipped a laboratory at NYBG, trained NYBG scientists in various aspects of plant processing and extraction, and provides up-front payment to support the research. Any publications that result from the work are co-authored by scientists from Merck and the NYBG, as well as collaborators in the source countries, where appropriate. Patents resulting from the work will include inventors from both organizations as appropriate under patent law. Merck has also agreed to pay royalties should a marketable product result from this research, with the proceeds being split between NYBG and its collaborators in the relevant source countries.

Shaman Pharmaceuticals, Inc.—In comparison with other organizations, Shaman Pharmaceuticals has a unique approach to the development of new therapeutic agents in that it is totally committed to working with indigenous and forest-dwelling peoples of tropical countries in the discovery process. This commitment is reflected in the

company's policies on compensation, which are defined and driven as much as possible by the specific needs and desires of the local people and groups that have contributed their traditional knowledge on the use of medicinal plants, as well as collaborating source country institutions.

In the short term, prior to initiating a collaborative research expedition, the company ethnobotanist, accompanied by a developed country-trained physician, will ask local indigenous leaders what specific and immediate reciprocal benefits can be provided as part of the research expedition. Requests are generally directed at health-care needs, ranging from the need to expand an airplane landing strip to enable the emergency medical evacuation of a family chaperon in addition to the patient, to the piping in of fresh spring water to a village, or the provision of mefloquine to treat chloroquine-resistant malaria. In providing medical attention, great care is taken to work with the local shaman and to emphasize the efficacy of their traditional botanical medicine in the treatment of many of the local diseases.

Medium-term compensation takes the form of provision of support for developing source country laboratories working on traditional medicines, and the provision of scholarships to research scientists working in such laboratories. In addition, scientists from source countries may be invited to company laboratories to facilitate and enhance the capabilities for drug discovery and development in those countries. In one instance, a stipend has been provided to the son of a shaman to enable him to continue full-time apprenticeship with his father rather than seek periodic employment to help support the family. The company also respects the intellectual contributions of the indigenous groups through including proper acknowledgement in publications and credit for the discovery and use of the relevant source plant in the promotional information about a new drug.

Company policy for long-term compensation requires that all participants from collaborating source countries and communities receive a portion of the profits derived from any and all commercial products developed; such compensation is channelled through a non-profit foundation, The Healing Forest Conservancy, founded by the company. A further long-term component is the promotion of economic development through the creation of new sustainable natural product supply industries in collaborating countries.

SmithKline Beecham.—SmithKline Beecham (SB) recognizes that all nations have sovereignty over biological resources and indigenous knowledge present within their recognized territorial boundaries. They do not collect biological resources or utilize indigenous knowledge from within the territorial boundaries of any country without first informing government authorities of the nature and extent of a collecting program and obtaining the necessary collecting permits and informed consent from indigenous populations. Plant natural products are obtained through collaborations with arboreta and research organizations dedicated to the collection of plant resources for biomedical research. Agreements are negotiated on a case-by-case basis to most effectively meet the needs and goals of the individual collaborations. Agreements have included short-term benefits of immediate payments for sustainable supplies of taxonomically authenticated plants and long-term benefits of royalty payments or equivalent revenues from the development of any commercial products arising from the collaboration. Agreements have stipulated that these benefits are to be shared equally between the collection organization and the plant source countries. In collaboration with the University of the South Pacific and the Rainforest Alliance, SB has recently been awarded a Biodiversity Conservation Network (BCN) planning grant from the USAID. The purpose of this planning grant is to develop a multi-year research proposal that will address the complex

interrelated issues of natural product drug discovery, conservation of biodiversity, and sustained economic development in developing countries.

Marine natural products are normally obtained through a variety of collaborations with academic research groups in both the U.S. and developing countries. A major goal of SB's marine collecting efforts is to work closely with local scientific research organizations and endeavor to provide training and education of native persons in technologies and skills used by SB in the collecting program or in related technologies and skills. SB has recently initiated a marine natural product collaboration with Rhodes University in South Africa. As part of this collaboration they are currently funding an affirmative action scholarship in the natural products field at Rhodes University, are transferring equipment and mixed-gas technical diving technology to the Department of Ichthyology and Fisheries at Rhodes University to enable them to extend their taxonomic surveys and fisheries research to deeper waters, and are exploring opportunities for the transfer of natural product screening technology to the Department of Pharmacy at Rhodes University.

SOURCE COUNTRY PERSPECTIVES

An African Perspective: Dr. Maurice Iwu, Bioresources Development and Conservation Programme, Nigeria, and Walter Reed Army Institute of Research, Washington, D.C.—In the past, genetic resources were considered the common heritage of humankind and therefore not regulated by any trade treaty. Although the raw materials were treated as common property belonging to humanity, the active agents isolated from these materials, mainly by developed country organizations, were treated as the exclusive property of those organizations, with the intellectual property rights associated with these agents being protected by patent rights or other legal instruments. These rights fail to recognize the rights of millions of people in cultures and traditional societies that consider nature as sacred and natural resources as belonging to the community; furthermore, medicinal products derived from these resources are often regarded as being beyond individual ownership. In this respect, many Africans still regard claims of propriety on products derived from their natural resources as being equivalent to theft.

As discussed earlier in this paper, two of the key articles of the Convention on Biological Diversity involve the granting of improved access to biological resources (Article 15), and, in return, access to and transfer of relevant technologies to those countries granting such access (Article 16). Although Article 15 is explicit in its prescription for access, Downes (36) points out that it does not create a patent-like property-rights situation over genetic resources. The Convention, therefore, is more relevant to the concerns of biotechnology firms than is generally recognized. On the other hand, to reduce the clauses in Article 16 to mere payment of royalties betrays a lack of understanding of the spirit of the Convention. Any agreement involving genetic materials must treat these two issues of "access" as inseparable.

The Convention accords recognition to the contribution of indigenous peoples and their knowledge to the preservation of fragile ecological systems and the sustainable utilization of genetic materials (Article 8j). The declaration of 1993 by the United Nations as the International Year of Indigenous Peoples, and the decade of 1995–2004 as the International Decade for the World's Indigenous Peoples adds a further dimension to the issue of equity in trade on genetic materials and recognition of the vital role the knowledge of indigenous peoples plays in the use of plants for medicinal purposes. While there is an apparent relationship between these two factors, there is a contradiction that is not immediately obvious. Recognition of indigenous rights poses a serious dilemma for those who wish to respect the sovereign rights of nations to regulate access

to their genetic materials and, at the same time, accept the rights of indigenous communities.

These considerations have made the question of just compensation of indigenous communities one of the most intractable issues arising from the Convention. The Convention vests the ownership of genetic resources in national governments, yet the knowledge of the use of these resources belongs mainly to individuals and communities. The interests of indigenous communities are not necessarily in harmony with those of the ruling parties that control national governments. A rigid enforcement of the Convention to mean that all genetic resources should be considered a patrimony belonging to the nation state may, in fact, be construed as denying indigenous communities and individuals the ownership of rights to their land, and completely remove from them the fundamental right of self-determination. This clearly is not the intention of the Convention.

A welcome change taking place within the international scientific community is the realization that the methods used in developed countries to protect and perfect intellectual property rights (patents, copyrights, trademarks, trade secrets, and appellation of origin) are not adequate to protect the biological resources or ethnomedical heritage of indigenous communities. It is misguided and wrong to rely solely on these legal instruments to protect indigenous rights when it is obvious that ownership patterns in developed countries differ enormously from those of traditional communities. Just as it is unacceptable to industrialized countries when some developing nations refuse to recognize the proprietary rights and patent restrictions on products developed through the exercise of intellect, so it was wrong for developed countries not to accept the doctrine of perpetual and communal ownership of biological resources. All compensation and reciprocity arrangements should acknowledge and respect this difference.

In designing cooperative agreements, the ownership of genetic materials has to be separated from ownership of knowledge regarding that material. The domestic, intranational issues have to be separated from international concerns. It is not yet resolved whether indigenous communities can enter into international agreements without the endorsement or concurrence of their national governments. Despite a plethora of conferences and workshops, no blueprint or viable mechanism for achieving the inseparable goals of access to genetic resources and to technology, while fully addressing the rights of indigenous peoples, has been devised.

Cooperative agreements with indigenous peoples should not be conceived as mere business deals, because what is being traded is not just a commodity but a priceless resource which embodies the cultural views, life-style, and even religious icons of a community. The aim should be to establish a relationship, a friendship, which should be nurtured over time. Perhaps what is needed is not just a legal agreement or contract but a covenant, or a commitment, to begin a new type of relationship between nations and cultures which will entail a reordering of priorities and values (37). In negotiating agreements between indigenous communities and foreign research organizations, it is imperative that knowledgeable, local institutions be involved as facilitators. Even in negotiations involving local institutions, it is helpful if the negotiating parties are relatively matched in size and capabilities.

While it is not easy to reconcile the cultural role that genetic resources, and in particular plants, play in African life with the demands and processes of "free market economy," any policy initiative must deal with the conceptual issue of whether to respect and address the concerns of traditional societies or to satisfy profit-motive interests. Although the much-reported agreement between INBio and Merck may be most appropriate for Costa Rica, a country without a large indigenous population, it will be

unsuitable for multi-ethnic societies or in countries that lack governments with responsive leadership, including many of those in Africa. In order to achieve a proper linkage between "access" and "equity," various legal frameworks can be used as long as the issue of fair compensation is agreed to by all parties. The points to be negotiated include method of sample collection, payment for the samples and other forms of compensation, assurance for future supply of materials, reciprocity and equity considerations, and intellectual property issues. The discussion of IPR and compensation must not be reduced to determination of share of royalties. A commitment to involve developing countries in the research and development activities, with a small percentage of the R & D budget channelled to the source countries, is far more valuable to these countries than the promise of large royalty payments that may never materialize. Screening strategies should include parasitic infections and diseases (e.g., malaria) to aid in the search for new treatments for diseases of primary concern to source country inhabitants, and project objectives should not be limited to the generation of pure chemical isolates as pharmaceutical leads, but should include the standardization of phytomedicines for the benefit of traditional healers and their patients. The inclusion of such measures will contribute to an improvement of the quality of life of source country inhabitants.

There is an impression gaining ground among developing countries that all their economic problems would be solved overnight by the royalties generated from genetic materials supplied to pharmaceuticals companies. The potential of developing a commercial new drug from genetic materials is considerably less than is often perceived. Unrealistic expectations of a windfall from sales of a multi-million dollar drug, if not realized, may lead to a backlash against conservation and may also jeopardize future collaborations. The real benefit of establishing a biodiversity prospecting partnership is that it may provide the necessary stimulus or seed money to establish or improve in-country capacity to conduct research on genetic resources and support indigenous biotechnology and pharmaceutical industries. Indigenous communities recognize the value and need for purely academic research, and they will willingly participate in global initiatives, such as the anticancer and anti-AIDS program at NCI, as partners, not just sources of plant material.

An Asian Perspective: Dr. Domingo A. Madulid, National Museum, Manila, The Philippines.—The Philippines has a rich history of involvement in natural products research dating back to the late 1800s, when efforts of Spanish explorers and missionaries to gather and record the use of medicinal plants by various ethnic groups marked the beginning of ethnobotanical research in the country. The early 1900s saw the beginning of active phytochemical and pharmacognostic studies of Philippine flora, with the development of intense activity after World War II as evidenced by the publication of numerous scientific articles in local journals. During the past decade there has been a dramatic rise in the popularity of research in the area of natural products drug discovery and development. This research has been led by scientists from local universities and government institutions, sometimes working in collaboration with scientists from universities, research organizations, and pharmaceutical companies based in other Asian countries, Europe, or the United States. Much of this collaborative research was restricted to basic ethnobotany and chemical isolation, with few projects advancing to preclinical or clinical development. One notable exception, however, was the development of several affordable phytomedicines from ten indigenous medicinal plants for the treatment of common ailments such as coughs, diarrhea, worms, and asthma. This project was performed by the Department of Science and Technology and the Philippine Council for Health Research and Development through a government-sponsored program.

Development of conventional drugs to treat diseases such as cancer, AIDS, and

diabetes, however, has been hindered by a lack of adequate funds, suitably equipped laboratories, and scientists trained in the specialized research fields necessary for preclinical and clinical drug development. Recognition of these factors has led the Philippines natural product research community to consider greater collaboration with foreign research organizations and companies with the provision that certain guarantees are met, including an assurance of equitable return of benefits, payment of royalties, and protection of intellectual property rights and indigenous knowledge.

In September 1990, a Memorandum of Understanding prescribing detailed Guidelines for the Collection of Biological Specimens by foreign and local collectors was signed by several government departments, including Agriculture, Environment and Natural Resources, and Science and Technology. This agreement specifies procedures for the application for collecting permits, as well as conditions such as respect for indigenous communities, submission of a complete set of voucher specimens to the National Museum, co-authorship of publications arising from collection projects, and the protection of rare and endangered species. The Guidelines also contain a Code of Ethics for Collectors of biological specimens and a Contract binding the Collector and the collaborating Philippines research partner to adherence to the terms of the agreement subject to penalties for deliberate disregard of such terms. These guidelines emphasize the conservation of biological resources, but they fail to address adequately the issues of Intellectual Property Rights of indigenous people, training and development of personnel, technology transfer, and equitable return of benefits to the Philippines in the event of development of a drug from a local biological sample.

The need for a national policy and guidelines for bioprospecting felt by a number of concerned scientists was heightened by the adoption of the resolution by ASOMPS VII, held in Manila in February 1992 (the Manila Declaration; Appendix 1) and the ratification of the U.N. Convention on Biological Diversity by the Philippines Government in March 1993. In August 1994, concerned citizens made a start on the drafting of a document governing bioprospecting in the Philippines. It is intended to present this document, entitled "Prescribing Guidelines and Establishing a Regulatory Framework for the Prospecting of Biological and Genetic Resources, their By-Products and Derivatives, for Scientific and Commercial Purposes, and for Other Purposes," to the President of the Philippines for signing as an Executive Order. Some of the salient requirements stipulated in the document are: (a) Limits on the quantities that can be collected and exported; (b) deposition of a complete set of voucher specimens with the National Museum; (c) recognition and respect of local and indigenous community rights; (d) payment of royalties on commercial products derived from biological and genetic resources collected; (e) participation by Filipino scientists in sample collections; (f) promotion of participation by Filipino scientists in the technological development of products derived from biological and genetic resources collected in the Philippines; (g) payment of a fixed fee to the Philippines Government. When signed, the Executive Order will serve as national policy on bioprospecting, and it will be implemented with immediate effect.

An Australian Perspective: Dr. Joseph T. Baker, Australian Institute of Marine Science, Townsville, Queensland.—Australia is a country with rich genetic resources in its vast terrestrial and marine areas. The United Nations Convention on the Law of the Sea, which came into effect in November 1994, effectively makes Australia's area of responsibility for its genetic resources two-and-one-half times the area of its terrestrial shape. Of the twelve most megabiodiverse countries, Australia is the only country currently classed as "developed" and is therefore giving very careful consideration to the complex issues of access to its biodiversity.

There have been several attempts to establish a pharmaceutical industry in Australia. In the past this has been an initiative of foreign country industries, notably those from the United States, Switzerland, and Germany. Aitken, Andrews, and Baker (38) analyzed the history of development of the pharmaceutical industry in Australia based predominantly on natural products. The Australian Government has initiated programs to stimulate the development of an Australian-owned pharmaceutical industry, and several companies are emerging as having a strong foundation for success. Notable among these are AMRAD based in Melbourne and Fauldings based in Adelaide. AMRAD has built very strong links to research groups in Australian universities and in government laboratories.

Australia has given significant attention to the question of access to its biodiversity, noting the complexity of introducing new arrangements, including regulations, to be consistent with several international treaties or agreements (e.g., the International Undertaking on Plant Genetic Resources; the United Nations Law of the Sea Convention; the United Nations Working Group on Indigenous Populations; the Convention on Biological Diversity; and the Convention on International Trade in Endangered Species of Wild Fauna and Flora). The publication, "Access to Australia's Biological Resources" (39), was a first attempt to draw together the issues confronting a country that exchanged biological material for farming and forestry for many decades. Currently a Commonwealth State (Officials) Working Group is analyzing the detail necessary to develop an Australian Policy and, if necessary, legislation, to regulate the access to Australian biodiversity.

Much of the initial emphasis on the development of an Australian position came through the Australian Institute of Marine Science during the 1980s when it held contracts with the NCI, U.S.A. and later when it sought to formulate agreements for work based on Australian marine organisms by the Marine Biotechnology Institute of Japan. A series of papers in the early 1990s has further demonstrated Australian scientific interest in responsibly managing access to Australia's biodiversity and Australian scientists' access to the biodiversity of neighboring countries (40–45). It is expected that the current national debate and deliberation will result in a definitive policy document by the end of 1995, and that special consideration will be given to the rights of Australia's indigenous people.

Given its unique position of being the only megabiodiverse country currently classed as being "developed," Australia may well be best placed of the developed nations to bring together the interests of other megabiodiverse countries of the world.

A Central and South American Perspective: Dr. Mahabir P. Gupta, CIFLORPAN, Universidad de Panama.—Most developing countries have a rich biological and cultural diversity and have sovereign rights over their genetic resources. However, sovereign rights are sometimes difficult to assign to a country, inasmuch as a given species is likely to be available in more than one country.

International cooperation is needed to explore the potential of the native flora. This cooperation should recognize the rights of source countries, their indigenous peoples, and their scientists and institutions. Keeping in mind the low probability of discovering a potentially marketable candidate from a given sample, cooperation between developed and developing countries should be fair to both parties and constructed in good faith. The element of good faith is a key point that needs to be stressed. Without good faith, it is not possible to have an effective collaboration.

International cooperation is needed for developing countries to determine their biodiversity and to explore its pharmaceutical potential. Because of the recent resurgence of interest in natural products as a source of new drugs, the developing countries should

be prepared to take advantage of this new initiative for improving their infrastructure and skills. If unfair demands are made, the developing countries will find it difficult to study their biodiversity since the resources and technology will be lacking.

Two forms of collaboration should be recognized: between scientists of developed and developing countries, and between industry and the developing country's scientists. In any collaborative agreements the heterogeneity of the source countries in so far as their infrastructure, stage of scientific development and technical expertise should be taken into account. The agreements should be on a case-by-case basis in order to address the differing needs and capabilities of the source countries.

For developing countries to benefit from such a collaboration, they should receive up-front compensation in the form of equipment, literature, herbarium upgrading, training both *in situ* and *ex situ*, and costs to cover plant collection, processing and shipment of samples.

Attempts should be made to perform as much of the processing as possible in the source country in order to maximize the value of the country's resources. The source countries at least should prepare their own extracts instead of sending plant samples. The higher the value added, the better it is for the source countries and for the fairness and equity of the collaboration.

Appropriate recognition of the contributions of source country scientists should be made in publications and patents, and the results of research should always be made available to the developing country counterparts. When results are to be shared with a pharmaceutical company or a licensee, provision should be made for royalty payments, even though negotiations in good faith could be made at a later stage.

The material transfer and contractual agreements that are currently being used have been designed by developed country scientists and institutions, and some aspects of these agreements seem unfair to the source countries. For example, scientific visits or "training" of indigenous people for two weeks in developed country institutions is deemed inadequate. In addition, some developing country scientists feel that the practice of some industrialized country institutions and scientists of dealing only with the indigenous people is a strategy to avoid dealing with them and the source country governments.

In the case of Panama, we immensely appreciate and need international cooperation. This has allowed us to strengthen our research centers and to perform collaborative studies of our flora which we would not have been able to perform ourselves. Science has no frontiers, and we as scientists should always work in close collaboration and should always agree to negotiate any differences.

Because only a fraction (about 10%) of the estimated 250,000 species of higher plants have been studied so far, we believe that it is only through international collaboration that it will be possible to determine the extent and potential of our genetic resources. Developing countries alone will not be in a position to subject all these species to even a small number of the available bioassays, and thus the true potential of their respective floras will never be known. If developing countries enact laws which discourage or prohibit material transfer for collaborative research, both they and humanity will suffer. On the other hand, unfair and egotistic practices by organizations of developed countries may also lead to that end. Irrespective of the source of a plant or other organism yielding a potential lifesaving drug, the whole world ultimately benefits.

SUMMARY

The signing of the United Nations Convention on Biological Diversity by most of the world's nations has served to emphasize the international concern for diminishing

diversity of naturally occurring ecosystems and for the contribution that these ecosystems afford, directly and indirectly, to the quality of life of the earth's inhabitants, human and non-human.The challenge we now face is multifaceted as we attempt to achieve the objectives of the Convention, respect the cultural, social, and developmental priorities of the different indigenous populations, and continue to advance human health by the discovery and development of bioactive substances which are socially beneficial and commercially viable.

Developing countries and their indigenous populations are the custodians of the vast majority of the world's genetic resources. Representatives of several genetically rich source countries have placed great emphasis on the value of collaboration between the scientific communities of the developing and developed countries as a means of promoting in-country capabilities through training and technology transfer, this emphasis being of similar significance to their requirement of fair and equitable compensation in the commercial development of their resources, as well as just recognition of the contributions of the indigenous peoples to the knowledge of their use and application.

Contributions from a cross-section of developed country organizations have indicated that there is a growing awareness of the need for such collaboration and compensation, and that some progress has been made in addressing the achievement of these goals. There remains however, an urgent need for the whole natural products scientific community to adopt similar policies in working with source countries if the remaining valuable genetic resources are to be conserved for research into their future beneficial use for humankind. This paper analyzes several of the issues relevant to that urgent need.

ACKNOWLEDGMENTS

The authors gratefully acknowledge contributions by the following persons and approval for publication by their respective organizations: Dr. Steven King, Shaman Pharmaceuticals, Inc.; Dr. James McChesney, University of Mississippi; Dr. David Turner, Glaxo Research and Development Limited. We also appreciate, for approval for publication of a summary of their policies: Bristol-Myers Squibb Company; Fogarty International Center, NIH; Merck and Co., Inc.; National Cancer Institute; SmithKline Beecham Pharmaceuticals; University of Illinois at Chicago. Finally, we also acknowledge the comments and helpful suggestions of Dr. Michael Gollin, Keck, Mahin & Tate, Washington, D.C.; Dr. Bruce Mannheim, Fox, Bennett & Turner, Washington, D.C.; Ms. Kate Mazan, NCI Office of Technology Development; Dr. Joshua Rosenthal, Fogarty International Center, NIH.

LITERATURE CITED

1. N.R. Farnsworth, O. Akerele, A.S. Bingel, D.D. Soejarto, and Z. Guo, *Bull. W.H.O.*, **63**, 965 (1985).
2. M.F. Balandrin, A.D. Kinghorn, and N.R. Farnsworth, in: "Human Medicinal Agents from Plants." Ed. by A.D. Kinghorn and M.F. Balandrin, ACS Symposium Series 534, Washington, DC, 1993, p. 2.
3. M. O'Neill and J.A. Lewis, in: "Human Medicinal Agents from Plants." Ed. by A.D. Kinghorn and M.F. Balandrin, ACS Symposium Series 534, Washington, DC, 1993, p. 48.
4. A.D. Kinghorn and M.F. Balandrin (Eds.), "Human Medicinal Agents from Plants." ACS Symposium Series 534, Washington, DC, 1993.
5. "Marine Natural Products Chemistry." *Chem. Rev.*, **93**, 1993, pp. 1671–1944 (15 articles by 24 authors).
6. J.H. Berdy, in: "Progress in Industrial Microbiology." Ed. by M.E. Bushell and U. Grafe, Elsevier, Amsterdam, 1989, Vol. 27, p. 3.
7. I. Jardine, in: "Anticancer Agents Based on Natural Product Models." Ed. by J.M. Cassady and J.D. Douros, Academic Press, New York, 1980, p. 319.
8. S.K. Carter and R.B. Livingston, *Cancer Treat. Rep.*, **60**, 1141 (1976).
9. G.M. Cragg, M.R. Boyd, J.H. Cardellina II, M.R. Grever, S.A. Schepartz, K.M. Snader and M. Suffness, in: "Human Medicinal Agents from Plants." Ed. by A.D. Kinghorn and M.F. Balandrin, ACS Symposium Series 534, Washington, DC, 1993, p. 80.

10. D.G.I. Kingston, in: "Human Medicinal Agents from Plants." Ed. by A.D. Kinghorn and M.F. Balandrin, ACS Symposium Series 534, Washington, DC, 1993, p. 138.
11. M.E. Wall and M.C. Wani, in: "Human Medicinal Agents from Plants." Ed. by A.D. Kinghorn and M.F. Balandrin, ACS Symposium Series 534, Washington, DC, 1993, p. 149.
12. S.M. Kupchan, *Cancer Treat. Rep.*, **60**, 1115 (1976).
13. K.L. Rinehart, T.G. Holt, N.L. Fregeau, P.A. Keifer, G.R. Wilson, T.J. Perun, Jr., R. Sakai, A.G. Thompson, J.G. Stroh, L.S. Shield, D.S. Siegler, L.H. Li, D.G. Martin, C.J.P. Grimmelikhuijzen, and G. Gade, *J. Nat. Prod.*, **53**, 771 (1990).
14. P.A. Philip, D. Rea, P. Thavasu, J. Carmichael, N.S.A. Stuart, H. Rockett, D.C. Talbot, T. Ganesan, G.R. Pettit, F. Balkwill, and A.L. Harris, *J. Natl. Cancer Inst.*, **85**, 1812 (1993).
15. H.-M. Chang and P.P.-H. But, "Pharmacology and Applications of Chinese Materia Medica," World Scientific Publishing Company, Singapore, 1986.
16. L.D. Kapoor, "CRC Handbook of Ayurvedic Medicinal Plants," CRC Press, Boca Raton, FL, 1990.
17. M. Iwu, "Handbook of African Medicinal Plants," CRC Press, Boca Raton, FL, 1993.
18. J.M. Watt and M.G. Breyer-Brandwijk, "Medicinal and Poisonous Plants of Southern and Eastern Africa," E. and S. Livingstone Ltd., Edinburgh, 1962.
19. V.E. Tyler, in: "Human Medicinal Agents from Plants." Ed. by A.D. Kinghorn and M.F. Balandrin, ACS Symposium Series 534, Washington, DC, 1993, p. 25.
20. A. Gentry, in: "Human Medicinal Agents from Plants." Ed. by A.D. Kinghorn and M.F. Balandrin, ACS Symposium Series 534, Washington, DC, 1993, p. 13.
21. E.A. Norse (Ed.), "Global Marine Biological Diversity. A Strategy for Building Conservation into Decision Making, Island Press, Washington, DC, 1994.
22. D.J. Chadwick and J. Marsh (Eds.), "Ethnobotany and the Search for New Drugs." CIBA Foundation Symposium 185, John Wiley and Sons, Chichester, UK, 1994.
23. W.V. Reid, S.A. Laird, C.A. Meyer, R. Gamez, A. Sittenfeld, D.H. Janzen, M.A. Gollin, and C. Juma, "Biodiversity Prospecting." World Resources Institute, Baltimore, 1993.
24. J.R. Axt, M.L. Corn, M. Lee, and D.M. Ackerman, "Biotechnology, Indigenous Peoples, and Intellectual Property Rights," CRS Report for Congress, Congressional Research Service, The Library of Congress, Washington, DC, 1993.
25. T. Greaves (Ed.), "Intellectual Property Rights for Indigenous Peoples. A Source Book." Society for Applied Anthropology, Oklahoma City, OK, 1994.
26. L.H. Caporale, *Proc. Natl. Acad. Sci., U.S.A.*, **92**, 75 (1995).
27. International Conference of Experts of Developing Countries on Traditional Medicinal Plants, Arusha, Tanzania. *Natural Products Research Network for Eastern and Central Africa (NAPRECA) Newsletter*, **7**, 9 (1990).
28. "The Chiang Mai Declaration," in: "Conservation of Medicinal Plants." Ed. by O. Akerele, V. Heywood and H. Synge, Cambridge University Press, Cambridge, UK, 1991, pp. XIX.
29. "The Declaration of Belem," in: "International Traditional Medicine Newsletter." Ed. by D.D. Soejarto and C. Gyllenhaal, **4**, 1 (1992).
30. "The Kunming Action Plan," in: "International Traditional Medicine Newsletter." Ed. by D.D. Soejarto and C. Gyllenhaal, **4**, 1 (1992).
31. T. Eisner and J. Meinwald, "The Goteborg Resolution," *Chem. Ecol.*, **1**, 38 (1990).
32. J. Schweitzer, F.G. Handley, J. Edwards, W.F. Harris, M.R. Grever, S.A. Schepartz, G. Cragg, K. Snader, and A. Bhat, *J. Natl. Cancer Inst.*, **83**, 1294 (1991).
33. T.E. Wirth, *U.S. Department of State Dispatch*, **5**, 857 (1994).
34. M.A. Gollin, in: "Biodiversity Prospecting." World Resources Institute, Baltimore, 1993, Annex 3, 289.
35. T. Eisner, *Proc. Amer. Philosoph. Soc.*, **138**, 385 (1994).
36. D. Downes, *Bioscience*, **44**, 381 (1994).
37. D. Posey, *Anthropology Today*, **6**, 13 (1990).
38. M. Aitken, P Andrews, and J. Baker, "Natural Products and the Australian Pharmaceutical Industry," Australian Department of Industry, Science and Technology Publication, 1993.
39. Commonwealth-State (Officials) Working Group, Office of the Chief Scientist, Department of Prime Minister and Cabinet, Canberra ACT 2600, Australia.
40. P. Murphy and J.T. Baker, "Rich Biological Resources: A Scientific and Commercial Asset for the Region—and a Political Problem," Proceedings of the Seventh Asian Symposium on Medicinal Plants, Spices, and Other Natural Products, Manila, Philippines, 200 (1992).
41. M.J. Garson, *Chemistry in Australia*, 62 (1995).
42. J.A. Armstrong and K. Hooper, *Nature Medicine, Landscape*, **9**, 11 (1994).
43. J.A. Armstrong and I. Abbott, *Pacific Conservation Biology*, in press.
44. J.A. Armstrong and I. Abbott, "Bioprospecting and Sustainable Conservation—A Practical Ap-

proach to Conserving Biological Diversity," Proceedings of Eighth Asian Symposium on Medicinal Plants, Spices, and Other Natural Products, Melaka, Malaysia, in press.
45. J.T. Baker, J.O. Bell, and P.T. Murphy, "*J. Ethnopharmacol.*, in press.

Received 20 March 1995

APPENDIX I

THE MANILA DECLARATION
concerning
THE ETHICAL UTILIZATION OF ASIAN BIOLOGICAL RESOURCES

Developed at the Seventh Asian Symposium on Medicinal Plants and Spices, and other Natural Products (ASOMPS VII) which was held in Manila, Philippines from February 2 to 7, 1992 and was attended by 280 scientists from 37 countries

Given that:

- the maintenance of biological and cultural diversity is of global concern,
- developing countries are major centers of biological and cultural diversity,
- there is increased interest in biological material with medicinal and other economic values,
- indigenous peoples frequently possess knowledge that provides a key to natural products of economic value.

Recognizing that:

- all national governments have sovereignty over their biological resources,
- current practices of exploitation of biological resources and indigenous knowledge are frequently inequitable, favouring technologically advanced organizations often based in developed countries, to the disadvantage of both conservation and development in the country or region of origin,
- there is a need for further investment in training and technology in developing countries and for equitable partnerships with developed countries in order to obtain new products from biological material,
- there has been insufficient acknowledgement of the essential roles that indigenous knowledge (i.e. intellectual property) plays in identifying important natural products.

Thus, it is recommended that:

- national governments, with advice from appropriate professional organizations within the region, develop adequate legislation to exercise control over the collection and export of biological material,
- as a high priority, governments, international agencies, multinational corporations and academic institutions, through training, laboratory construction and technology transfer, should support the development of human and material resources needed for all aspects of local biological evaluation of indigenous materials for conservation and for managed development,
- for all collecting, the authorising agreements(s) should include provision for any subsequent commercial development that may eventually arise,
- internationally recognized professional societies develop a code of ethics that facilitates the development of equitable partnerships in the development of new natural products from biological material,
- mandatory royalty or licence agreements be established to ensure fair and equitable distribution of benefits to the region of origin,
- supply agreements should only be made by the appropriate country organization and not with individuals within that country,
- in order to avoid over-exploitation of promising species, the country organization should adopt methods to protect the identity and provenance of its biological material,
- specific regulations be established to ensure that the collection and export of biological material is adequately monitored and controlled in the interest of the country supplying the material. These should include the requirements that:
    - collections are made together with local counterparts appointed by the country organization involved,
    - adequately annotated, preserved voucher specimens of biological material are lodged in appropriate national institutions,
    - sufficient funds are provided by the external organization to cover the support costs which may be incurred,
    - if there is a threat of destructive harvesting, provision must be made for sustainable harvesting or development of alternative supplies,
    - the traditional knowledge of local participants contributing to development of new natural products must be recognized as significant intellectual property.

A code of ethics for foreign plant collectors and guidelines for contracts are appended.

CODE OF ETHICS FOR FOREIGN COLLECTORS

Developed at the Botany 2000 Herbarium Curation Workshop held in Perth, Western Australia, October 15 to 19, 1990, and modified in April 1992, to cover other biological material.

1. Arrange to work with a local scientist(s) and institute(s).
2. Respect regulations of the country visited; for example, by entering on a research/collecting visitor visa, not a tourist visa, and by observing regulations for export of biological specimens, quarantine, CITES etc.
3. Obtain official permission for all collections in National Parks or protected areas.
4. Ascertain whether items used in scientific work and which are difficult to obtain can be contributed.
5. When applying for a travel/study grant, include equal travel expenses for local counterpart(s) and an amount to cover the cost of processing museum specimens or other costs of the visit to the host institute.
6. Leave a complete set of adequately labelled duplicates with the Institute before leaving the country.
7. Ensure that types of species described as a result of the research are deposited in the National Museum or Herbarium of the country of origin.
8. Inform the Institute in the country of origin where the duplicate specimens are to be deposited.
9. Not exploit the natural resources of the host country by removing high value biological products through collecting wild specimens, for example plants with potential horticultural, medicinal, cultural or other economic value without prior permission.
10. Obtain a list of rare and endangered plants of the country visited and not collect these species without permission.
11. Collect no more specimens than is strictly necessary; for live plant specimens collect cuttings or seeds rather than uprooting whole plants; for marine specimens, wherever possible, collect subsections rather than whole organisms.
12. Leave copies of photographs/slides for the host institute(s).
13. Inform the host institute/appropriate organization of new localities of rare/endangered species found.
14. Remember to send copies of research reports and publications to collaborators and host institute(s).
15. Acknowledge collaborator(s) and host institute(s) in research reports and publications.
16. Collect identified reference voucher specimens for all biological products to be exported.

CONTRACT GUIDELINES

ASOMPS VII recognizes that there is considerable variation in the levels of technical expertise for the development of new natural products in the region. There is also recognition that every effort should be made to reduce dependency by developing countries on technology held by developed countries. However, in the short-term, efficient development of new natural products may involve sharing of biological resources and technology between developed countries and countries of origin.

In order to avoid contracts which do not achieve equity in partnerships between developed and countries of origin, there are suggested minimum standards which should be used:

- The amount of material collected for initial screening should not normally exceed 100–500 grams (dry weight) unless specific permission is obtained.
- Payment should include all handling expenses and infrastructure costs.
- Where screening of extracts is carried out with the aid of a partner organization in the developed world, a minimum of 60% of any income arising from the supply of extracts to commercial organizations should be returned to the appropriate country organization.
- The country organization should receive a minimum of 51% of any royalties arising from external collaboration that result in marketable products. Since a fair royalty would be of the order of 3–5%, the appropriate country organization should receive a minimum royalty of 1.5–2.5%.
- The country organization should not sign agreements that give indefinite exclusive rights to any external party. Exclusivity should be limited to no more than a two-year period.
- Complete evaluation of results of any screening should be reported to the supplying country organization within a reasonable specified period.
- If there is a threat of destructive harvesting, costs of sustainable harvesting or development of alternative supplies must be borne by the external organization.
- The contribution of research participants should be recognized through co-authorship of publications.
- Initial preparation of extracts and screening should be done in the country of origin and assistance to develop this expertise should be provided wherever practicable.

APPENDIX 2

UNITED NATIONS CONVENTION ON BIOLOGICAL DIVERSITY
ARTICLES 1–19

Preamble

The Contracting Parties,

Conscious of the intrinsic value of biological diversity and of the ecological, genetic, social, ecological, genetic, social, economic, scientific, educational, cultural, recreational and aesthetic values of biological diversity and its components,

Conscious also of the importance of biological diversity for evolution and for maintaining life sustaining systems of the biosphere,

Affirming that the conservation of biological diversity is a common concern of humankind,

Reaffirming that States have sovereign rights over their own biological resources,

Reaffirming also that States are responsible for conserving their biological diversity and for using their biological resources in a sustainable manner,

Concerned that biologically diversity is being significantly reduced by certain human activities,

Aware of the general lack of information and knowledge regarding biological diversity and of the urgent need to develop scientific, technical and institutional capacities to provide the basic understanding upon which to plan and implement appropriate measures,

Noting that it is vital to anticipate, prevent and attack the causes of significant reduction or loss of biological diversity at source,

Noting also that where there is a threat of significant reduction or loss of biological diversity, lack of full scientific certainty should not be used as a reason for postponing measures to avoid or minimize such a threat,

Noting further that the fundamental requirement for the conservation of biological diversity is the *in-situ* conservation of ecosystems and natural habitats and the maintenance and recovery of viable populations of species in their natural surroundings,

Noting further that *ex-situ* measures, preferably in the country of origin, also have an important role to play,

Recognizing the close and traditional dependence of many indigenous and local communities embodying traditional lifestyles on biological resources, and the desirability of sharing equitably benefits arising from the use of traditional knowledge, innovations and practices relevant to the conservation of biological diversity and the sustainable use of its components,

Recognizing also the vital role that women play in the conservation and sustainable use of biological diversity and affirming the need for the full participation of women at all levels of policy-making and implementation for biological diversity conservation,

Stressing the importance of, and the need to promote, international, regional and global cooperation among States and intergovernmental organizations and the non-governmental sector for the conservation of biological diversity and the sustainable use of its components.

Acknowledging that the provision of new and additional financial resources and appropriate access to relevant technologies can be expected to make a substantial difference in the world's ability to address the loss of biological diversity,

Acknowledging further that special provision is required to meet the needs of developing countries, including the provision of new and additional financial resources and appropriate access to relevant technologies,

Noting in this regard the special conditions of the least developed countries and small island States,

Acknowledging that substantial investments are required to conserve biological diversity and that there is the expectation of a broad range of environmental, economic and social benefits from those investments,

Recognizing that economic and social development and poverty eradication are the first and overriding priorities of developing countries,

Aware that conservation and sustainable use of biological diversity is of critical importance for meeting the food, health and other needs of the growing world population, for which purpose access to and sharing of both genetic resources and technologies are essential,

Noting that, ultimately, the conservation and sustainable use of biological diversity will strengthen friendly relations among States and contribute to peace for humankind,

Desiring to enhance and complement existing international arrangements for the conservation of biological diversity and sustainable use of its components, and

Determined to conserve and sustainably use biological diversity for the benefit of present and future generations,

Have agreed as follows:

Article 1. Objectives

The objectives of this Convention, to be pursued in accordance with its relevant provisions, are the conservation of biological diversity, the sustainable use of its components and the fair and equitable sharing of the benefits arising out of the utilization of genetic resources, including by appropriate access to genetic resources and by appropriate transfer of relevant technologies, taking into account all rights over those resources and to technologies, and by appropriate funding.

Article 2. Use of Terms

For the purposes of this Convention: "Biological diversity" means the variability among living organisms from all sources including, *inter alia*, terrestrial, marine and other aquatic ecosystems and the ecological complexes of which they are part; this includes diversity within species, between species and of ecosystems.

"Biological resources" includes genetic resources, organisms or parts thereof, populations, or any other biotic component of ecosystems with actual or potential use or value for humanity.

"Biotechnology' means any technological application that uses biological systems, living organisms, or derivatives thereof, to make or modify products or processes for specific use.

"Country of origin of genetic resources" means the country which possesses those genetic resources in *in-situ* conditions.

"Country providing genetic resources" means the country supplying genetic resources collected from *in-situ* sources, including populations of both wild and domesticated species, or taken from *ex-situ* sources, which may or may not have originated in that country.

"Domesticated or cultivated species" means species in which the evolutionary process has been influenced by humans to meet their needs.

"Ecosystem" means a dynamic complex of plant, animal and micro-organism communities and their non-living environment interacting as a functional unit.

"*Ex-situ* conversation" means the conservation of components of biological diversity outside their natural habitats.

"Genetic material" means any material of plant, animal, microbial or other origin containing functional units of heredity.

"Genetic resources" means genetic material of actual or potential value.

"Habitat" means the place or type of site where an organism or population naturally occurs.

"*In-situ* conditions" means conditions where genetic resources exist within ecosystems and natural habitats, and, in the case of domesticated or cultivated species, in the surroundings where they have developed their distinctive properties.

"*In-situ* conservation" means the conservation of ecosystems and natural habitats and the maintenance and recovery of viable populations of species in their natural surroundings and, in the case of domesticated or cultivated species, in the surroundings where they have developed their distinctive properties.

"Protected area" means a geographically defined area which is designated or regulated and managed to achieve specific conservation objectives.

"Regional economic integration organization" means an organization constituted by sovereign States of a given region, to which its member States have transferred competence in respect of matters governed by this Convention and which has been duly authorized, in accordance with its internal procedures, to sign, ratify, accept, approve or accede to it.

"Sustainable use" means the use of components of biological diversity in a way and at a rate that does not lead to the long-term decline of biological diversity, thereby maintaining its potential to meet the needs and aspirations of present and future generations.

"Technology" includes biotechnology.

Article 3. Principle

States have, in accordance with the Charter of the United Nations and the principles of international law, the sovereign right to exploit their own resources pursuant to their own environmental policies, and the responsibility to ensure that activities within their jurisdiction or control do not cause damage to the environment of other States or of areas beyond the limits of national jurisdiction.

Article 4. Jurisdictional Scope

Subject to the rights of other States, and except as otherwise expressly provided in this Convention, the provisions of this Convention apply, in relation to each Contracting Party:

(a) In the case of components of biological diversity, in areas within the limits of its national jurisdiction; and

(b) In the case of processes and activities, regardless of where their effects occur, carried out under its jurisdiction or control, within the area of its national jurisdiction or beyond the limits of national jurisdiction.

Article 5. Cooperation

Each Contracting Party shall, as far as possible and as appropriate, cooperate with other Contracting Parties, directly or, where appropriate, through competent international organizations, in respect of areas beyond national jurisdiction and on other matters of mutual interest, for the conservation and sustainable use of biological diversity.

Article 6. General Measures for Conservation and Sustainable Use

Each contracting Party shall, in accordance with its particular conditions and capabilities:

(a) Develop national strategies, plans or programmes for the conservation and sustainable use of biological diversity or adapt for this purpose existing strategies, plans or programmes which shall reflect, *inter alia*, the measures set out in this Convention relevant to the Contracting Party concerned; and

(b) Integrate, as far as possible and as appropriate, the conservation and sustainable use of biological diversity into relevant sectoral or cross-sectoral plans, programmes and policies.

Article 7. Identification and Monitoring

Each Contracting Party shall, as far as possible and as appropriate, in particular for the purposes of Articles 8 to 10:

(a) Identify components of biological diversity important for its conservation and sustainable use having regard to the indicative list of categories set down in Annex I;

(b) Monitor, through sampling and other techniques, the components of biological diversity identified pursuant to subparagraph (a) above, paying particular attention to those requiring urgent conservation measures and those which offer the greatest potential for sustainable use;

(c) Identify processes and categories of activities which have or are likely to have significant adverse impacts on the conservation and sustainable use of biological diversity, and monitor their effects through sampling and other techniques; and

(d) Maintain and organize, by any mechanism, data derived from identification and monitoring activities pursuant to subparagraphs (a), (b) and (c) above.

Article 8. *In-Situ* Conservation

Each Contracting Party shall, as far as possible and as appropriate.

(a) Establish a system of protected areas or areas where special measures need to be taken to conserve biological diversity;

(b) Develop, where necessary, guidelines for the selection, establishment and management of protected areas or areas where special measures need to be taken to conserve biological diversity;

(c) Regulate or manage biological resources important for the conservation of biological diversity whether within or outside protected areas, with a view to ensuring their conservation and sustainable use;

(d) Promote the protection of ecosystems, natural habitats and the maintenance of viable populations of species in natural surroundings;

(e) Promote environmentally sound and sustainable development in areas adjacent to protected areas with a view to furthering protection of these areas;

(f) Rehabilitate and restore degraded ecosystems and promote the recovery of threatened species, *inter alia*, through the development and implementation of plans or other management strategies;

(g) Establish or maintain means to regulate, manage or control the risks associated with the use and release of living modified organisms resulting from biotechnology which are likely to have adverse environmental impacts that could affect the conservation and sustainable use of biological diversity, taking also into account the risks to human health;

(h) Prevent the introduction of, control or eradicate those alien species which threaten ecosystems, habitats or species;

(i) Endeavor to provide the conditions needed for compatibility between present uses and the conservation of biological diversity and the sustainable use of its components;

(j) Subject to its national legislation, respect, preserve and maintain knowledge, innovations and practices of indigenous and local communities embodying traditional lifestyles relevant for the conservation and sustainable use of biological diversity and promote their wider application with the approval and involvement of the holders of such knowledge, innovations and practices and encourage the equitable sharing of the benefits arising from the utilization of such knowledge, innovations and practices;

(k) Develop or maintain necessary legislation and/or other regulatory provisions for the protection of threatened species and populations;

(l) Where a significant adverse effect on biological diversity has been determined pursuant to Article 7, regulate or manage the relevant processes and categories of activities; and

(m) Cooperate in providing financial and other support for *in-situ* conservation outlined in subparagraphs (a) to (l) above, particularly to developing countries.

Article 9. *Ex-situ* Conservation

Each Contracting Party shall, as far as possible and as appropriate, and predominantly for the purpose of complementing *in-situ* measures:

(a) Adopt measures for the *ex-situ* conservation of components of biological diversity, preferably in the country of origin of such components;

(b) Establish and maintain facilities for *ex-situ* conservation of and research on plants, animals and micro-organisms, preferably in the country of origin of genetic resources:

(c) Adopt measures for the recovery and rehabilitation of threatened species and for their reintroduction into their natural habitats under appropriate conditions;

(d) Regulate and manage collection of biological resources from natural habitats for *ex-situ* conservation purposes so as not to threaten ecosystems and *in-situ* populations of species, except where special temporary *ex-situ* measures are required under subparagraph (c) above; and

(e) Cooperate in providing financial and other support for *ex-situ* conservation outlined in subparagraphs (a) to (d) above and in the establishment and maintenance of *ex-situ* conservation facilities in developing countries.

Article 10. Sustainable Use of Components of Biological Diversity

Each Contracting Party shall, as far as possible and as appropriate;

(a) Integrate consideration of the conservation and sustainable use of biological resources into national decision-making;

(b) Adopt measures relating to the use of biological resources to avoid or minimize adverse impacts on biological diversity;

(c) Protect and encourage customary use of biological resources in accordance with traditional cultural practices that are compatible with conservation or sustainable use requirements;

(d) Support local populations to develop and implement remedial action in degraded areas where biological diversity has been reduced; and

(e) Encourage cooperation between its governmental authorities and its private sector in developing methods for sustainable use of biological resources.

Article 11. Incentive Measures

Each Contracting Party shall, as far as possible and as appropriate, adopt economically and socially sound measures that act as incentives for the conservation and sustainable use of components of biological diversity.

Article 12. Research and Training

The Contracting Parties, taking into account the special needs of developing countries, shall;

(a) Establish and maintain programmes for scientific and technical education and training in measures for the identification, conservation and sustainable use of biological diversity and its components and provide support for such education and training for the specific needs of developing countries;

(b) Promote and encourage research which contributes to the conservation and sustainable use of biological diversity, particularly in developing countries, *inter alia*, in accordance with decisions of the Conference of the Parties taken in consequence of recommendations of the Subsidiary Body on Scientific, Technical and Technological Advice; and

(c) In keeping with the provisions of Articles 16, 18, and 20, promote and cooperate in the use of scientific advances in biological diversity research in developing methods for conservation and sustainable use of biological resources.

Article 13. Public Education and Awareness

The Contracting Parties shall:

(a) Promote and encourage understanding of the importance of, and the measures required for, the conservation of biological diversity, as well as its propagation through media, and the inclusion of these topics in educational programmes; and

(b) Cooperate, as appropriate, with other States and international organizations in developing educational and public awareness programmes, with respect to conservation and sustainable use of biological diversity.

Article 14. Impact Assessment and Minimizing Adverse Impacts

1. Each contracting Party, as far as possible and as appropriate, shall:

(a) Introduce appropriate procedures requiring environmental impact assessment of its proposed projects that are likely to have significant adverse effects on biological diversity with a view to avoiding or minimizing such effects and, where appropriate, allow for public participation in such procedures;

(b) Introduce appropriate arrangements to ensure that the environmental consequences of its programmes and policies that are likely to have significant adverse impacts on biological diversity are duly taken into account;

(c) Promote, on the basis of reciprocity, notification, exchange of information and consultation on activities under their jurisdiction or control which are likely to significantly affect adversely the biological diversity of other States or areas beyond the limit of national jurisdiction, by encouraging the conclusion of bilateral, regional or multilateral arrangements, as appropriate;

(d) In the case of imminent or grave danger or damage, originating under its jurisdiction or control, to biological diversity within the area under jurisdiction of other States or in areas beyond the limits of national jurisdiction notify immediately the potentially affected States of such danger or damage, as well as initiate action to prevent or minimize such danger or damage; and

(e) Promote national arrangements for emergency responses to activities or events, whether caused naturally or otherwise, which present a grave and imminent danger to biological diversity and encourage international cooperation to supplement such national efforts and, where appropriate and agreed by the States or regional economic integration organizations concerned, to establish joint contingency plans.

2. The Conference of the Parties shall examine, on the basis of studies to be carried out, the issue of liability and redress, including restoration and compensation, for damage to biological diversity, except where such liability is a purely internal matter.

Article 15. Access to Genetic Resources

1. Recognizing the sovereign rights of States over their natural resources, the authority to determine access to genetic resources rests with the national governments and is subject to national legislation.

2. Each Contracting Party shall endeavor to create conditions to facilitate access to genetic resources for environmentally sound uses by other Contracting Parties and not to impose restrictions that run counter to the objectives of this Convention.

3. For the purpose of this Convention, the genetic resources being provided by a Contracting Party, as referred to in this Article and Articles 16 and 19, are only those that are provided by Contracting Parties that are countries of origin of such resources or by the Parties that have acquired the genetic resources in accordance with this Convention.

4. Access, where granted, shall be on mutually agreed terms and subject to the provisions of this Article.

5. Access to genetic resources shall be subject to prior informed consent of the Contracting Party providing such resources, unless otherwise determined by that Party.

6. Each Contracting Party shall endeavor to develop and carry out scientific research based on genetic resources provided by other Contracting Parties with the full participation of, and where possible in, such Contracting Parties.

7. Each Contracting Party shall take legislative, administrative or policy measures, as appropriate, and in accordance with Articles 16 and 19 and, where necessary, through the financial mechanism established by Articles 20 and 21 with the aim of sharing in a fair and equitable way the results of research and development and the benefits arising from the commercial and other utilization of genetic resources with the Contracting Party providing such resources. Such sharing shall be upon mutually agreed terms.

Article 16. Access to and Transfer of Technology

1. Each Contracting Party, recognizing that technology includes biotechnology, and that both access to and transfer of technology among Contracting Parties are essential elements for the attainment of the objectives of this Convention, undertakes subject to the provisions of this Article to provide and/or facilitate access for and transfer to other Contracting Parties of technologies that are relevant to the conservation and sustainable use of biological diversity or make use of genetic resources and do not cause significant damage to the environment.

2. Access to and transfer of technology referred to in paragraph 1 above to developing countries shall be provided and/or facilitated under fair and most favorable terms, including on concessional and

preferential terms where mutually agreed, and, where necessary, in accordance with the financial mechanism established by Articles 20 and 21. In the case of technology subject to patents and other intellectual property rights, such access and transfer shall be provided on terms which recognize and are consistent with the adequate and effective protection of intellectual property rights. The application of this paragraph shall be consistent with paragraphs 3, 4 and 5 below.

3. Each Contracting Party shall take legislative, administrative or policy measures, as appropriate, with the aim that Contracting Parties, in particular those that are developing countries, which provide genetic resources are provided access to and transfer of technology which makes use of those resources, on mutually agreed terms, including technology protected by patents and other intellectual property rights, where necessary, through the provisions of Articles 20 and 21 and in accordance with international law and consistent with paragraphs 4 and 5 below.

4. Each Contracting Party shall take legislative, administrative or policy measures, as appropriate, with the aim that the private sector facilitates access to, joint development and transfer of technology referred to in paragraph 1 above for the benefit of both governmental institutions and the private sector of developing countries and in this regard shall abide by the obligations included in paragraphs 1, 2 and 3 above.

5. The Contracting Parties, recognizing that patents and other intellectual property rights may have an influence on the implementation of this Convention, shall cooperate in this regard subject to national legislation and international law in order to ensure that such rights are supportive of and do not run counter to its objectives.

Article 17. Exchange of Information

1. The Contracting Parties shall facilitate the exchange of information, from all publicly available sources, relevant to the conservation and sustainable use of biological diversity, taking into account the special needs of developing countries.

2. Such exchange of information shall include exchange of results of technical, scientific and socio-economic research, as well as information on training and surveying programmes, specialized knowledge, indigenous and traditional knowledge as such and in combination with the technologies referred to in Article 16, paragraph 1. It shall also, where feasible, include repatriation of information.

Article 18. Technical and Scientific Cooperation

1. The Contracting Parties shall promote international technical and scientific cooperation in the field of conservation and sustainable use of biological diversity, where necessary through the appropriate international and national institutions.

2. Each Contracting Party shall promote technical and scientific cooperation with other Contracting Parties, in particular developing countries, in implementing this Convention, *inter alia*, through the development and implementation of national policies. In promoting such cooperation, special attention should be given to the development and strengthening of national capabilities, by means of human resources development and institution building.

3. The Conference of the Parties, at its first meeting, shall determine how to establish a clearing-house mechanism to promote and facilitate technical and scientific cooperation.

4. Contracting Parties shall, in accordance with national legislation and policies, encourage and develop methods of cooperation for the development and use of technologies, including indigenous and traditional technologies, in pursuance of the objectives of this Convention. For this purpose, the Contracting Parties shall also promote cooperation in the training of personnel and exchange of experts.

5. The Contracting Parties shall, subject to mutual agreement, promote the establishment of joint research programmes and joint ventures for the development of technologies relevant to the objectives of this Convention.

Article 19. Handling of Biotechnology and Distribution of Its Benefits

1. Each Contracting Party shall take legislative, administrative or policy measures, as appropriate, to provide for the effective participation in biotechnological research activities by those Contracting Parties, especially developing countries, which provide the genetic resources for such research, and where feasible in such Contracting Parties.

2. Each Contracting Party shall take all practicable measures to promote and advance priority access on a fair and equitable basis by Contracting Parties, especially developing countries, to the results and benefits arising from biotechnologies based upon genetic resources provided by those Contracting Parties. Such access shall be on mutually agreed terms.

3. The Parties shall consider the need for and modalities of a protocol setting out appropriate procedures, including, in particular, advance informed agreement in the field of the safe transfer, handling

and use of any living modified organism resulting from biotechnology that may have adverse effect on the conservation and sustainable use of biological diversity.

4. Each Contracting Party shall, directly or by requiring any natural or legal person under its jurisdiction providing the organisms referred to in paragraph 3 above, provide any available information about the use and safety regulations required by that Contracting Party in handling such organisms, as well as any available information on the potential adverse impact of the specific organisms concerned to the Contracting Party into which those organisms are to be introduced.

For Articles 20–42 and Annexes I and II, see Reid *et al.* (23).