Securing Economic Benefits and Promoting Conservation through Bioprospecting

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Bioprospecting has frequently been cited as a sustainable use of biodiversity. Nevertheless, the level of bioprospecting in biodiversity-rich tropical regions falls below its potential, with the result that bioprospecting has produced only limited economic benefits. We present a bioprospecting program that, in addition to promoting drug discovery, provides economic benefits to and promotes conservation in Panama through the sustainable use of biodiversity. The program was initiated using insights from 20 years of nonapplied ecological research to enhance the likelihood of finding treatments for human disease. Samples are not sent abroad; rather, most of the research is carried out in Panamanian laboratories. Panama has received immediate benefits for the use of its biodiversity in the form of research funding derived from sources outside Panama, training for young Panamanian scientists, and enhanced laboratory infrastructure. Over the long term, discoveries derived from bioprospecting may help to establish research-based industries in Panama.

Keywords: biodiversity conservation, benefit sharing, Convention on Biological Diversity, ecological economics, ecosystem services

It is widely recognized that developing countries in the tropics that harbor a large fraction of the world's biodiversity could, in principle, obtain substantial benefits from their biodiversity. The challenge has been to harness the economic value of sustainable uses of biodiversity in order to justify the conservation of habitat in its natural state. Promising strategies for meeting this challenge include ecotourism, carbon credits obtained from intact forest, and ecosystem services, such as the provision of clean water. Here we focus on how bioprospecting, the investigation of biodiversity as a source of useful medicines or genes (ten Kate and Laird 1999), might, in practice, provide the expected benefits.

The Convention on Biological Diversity (1992–1993) and more recent agreements recognize that nations have ownership of, and can control access to, species ("genetic resources") within their boundaries; these agreements mandate equitable sharing of the benefits derived from biodiversity (Gollin 1993, 1999). A principal focus has been on the legal issues concerning bioprospecting, such as the definition of prior informed consent for the use of traditional knowledge and specification of benefit-sharing arrangements (Blaustein 2006, CBD 2006). This emphasis resulted from the many cases—some recent—of the use of biodiversity without recompense, as occurred with the insecticide from the Indian tree *Azadirachta indica* (neem), which has low toxicity to vertebrates, and with a heat-stable enzyme from the bacterium *Thermus aquaticus,* which is a key research tool. As a consequence, many governments have inhibited basic research on biodiversity (Grajal 1999, Gómez-Pompa 2004). It is very likely that biodiversity-based research carried out by pharmaceutical and agricultural companies also has been inhibited, although the extent of this inhibition is difficult to quantify. Even though bioprospecting research could promote substantial economic growth in areas with high biological diversity, such as the tropics, countries there have failed to capture the value of their biodiversity.

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Promoting research on the uses of biodiversity and correcting misconceptions

Progress depends neither on belaboring past problems nor on expecting that "raw," unstudied biodiversity must in itself be a source of wealth. These issues are already fully addressed in the Convention on Biological Diversity. The convention specifies that research on the uses of biodiversity should be facilitated, with all contracting parties providing for appropriate access to biodiversity (article 15) and for transfer of technology (article 16). This visionary document states that nations "shall endeavour to create conditions to facilitate access to genetic resources for environmentally sound uses" and to "develop and carry out scientific research based on genetic resources" (article 15). In this article we argue that, to derive benefits from the use of biodiversity, developing countries will benefit by striking a balance between these two aspects of the convention, the expectation of equitable benefits and the need for nations to capture the value of their natural resources.

The history of the perception that "raw" biotic resources have a high value to biologically diverse countries and the reason this is a misconception are important. In part, unrealistic expectations of high payments for biotic resources arose because of a $1.1 million agreement between Costa Rica's National Biodiversity Institute and Merck, a large pharmaceutical company seeking exclusive rights to develop and patent products from species found in Costa Rican rainforests (Aldhous 1991). It was this large access payment by Merck that fueled the expectations of biodiversity-rich nations for similarly substantial access payments. However, because the success rate for drug discovery is exceedingly low, other financial benefits, such as milestone payments or royalties, are highly unlikely (McChesney 1996). Furthermore, in the case of royalties, the time frame is long, perhaps 10 to 12 years from discovery to receiving benefits (DiMasi et al. 2003). Thus this model, with the source country offering biological materials and the developed country supplying the research, provides few or no benefits for the source country.

Because bioprospecting by exporting samples adds little value to biodiversity, the only practical mechanism by which bioprospecting can provide benefits is by conducting as much of the research as possible in laboratories in the source country. In this manner, uncharacterized samples, or "raw" biotic resources, having low value are converted to research-based resources with the potential to yield much higher value to the source country. The benefits from host-country research include jobs, training, investment in infrastructure, and the likelihood that scientific discoveries will lead to new investments in research and development (R&D). Even though the idea of providing benefits by basing research in the source country is not new (Laird and ten Kate 2002), this approach to bioprospecting is in its infancy. In fact, no substantial programs within the biodiversity-rich countries of the world attempt to link the study of the uses of biotic resources with conservation and with scientific and economic development. This fact undercuts the conservation argument that medicines and genes from nature will provide economic development. Instead, refocusing on the central goals of the Convention on Biological Diversity will bring economic benefits to the source countries, benefits derived from the discovery of new uses of those countries' biodiversity.

Bioprospecting research and development

Bioprospecting R&D has the potential to provide considerable economic opportunities in developing countries.

Nature as a source of medicines. Recent studies clearly show that nature is still a productive source of new medicines (Newman et al. 2003, Koehn and Carter 2005). A key function of bioprospecting is to provide some of the thousands of compounds discovered annually that have interesting structures or activities. A subset of these become new "lead compounds," that is, compounds that are promising enough to merit substantial investment in continued investigation. In a typical year, relatively few lead compounds become approved medicines. Hence the drug discovery process can be thought of as a pyramid whose broad base is composed of thousands of compounds with new activities, and many of these compounds are derived from bioprospecting (McChesney 1996). These essential beginning steps of the drug discovery process provide research opportunities to many academic investigators in industrialized countries, and we believe that developing countries can expect similar research benefits. These include improvements in scientific capacity, policymaking, resource management, tourism, conservation, and, in the long run, investment in start-up biotech companies (box 1).

Expenditures on research and development. The estimates of expenditures in these areas clearly indicate that substantial benefits can be obtained from participation in preclinical research, even if no product makes it to market. Many billions in research funds are granted annually to scientists in academia by the US government (National Institutes of Health) and by nonprofit institutions (Howard Hughes Foundation, Medicines for Malaria Venture, Institute for OneWorld Health). Although actual research spending by the largest pharmaceutical companies is uncertain, it probably exceeds $25 billion per year worldwide (Agnew 2000, Erickson 2006). Moreover, in an effort to reduce costs, research-driven industries also outsource their R&D to small firms with expertise in a particular field of research (Jankowski 2001). Based on funding for R&D in pharmaceuticals and biotechnology, about 17 percent of R&D worldwide (UNCTAD 2005) is carried out in small firms. For a small company, such investments can make up a substantial part of its budget. According to the *World Investment Report,* the typical external investment in a small R&D company exceeds $20 million per year (UNCTAD 2005). At the international level, a growing number of small, commercially funded R&D companies are based in the developing world. The *World Investment Report* notes, "The traditional view, of more complex production

activities being undertaken in the North and simpler ones in the South, is less and less a true reflection of the reality" (UNCTAD 2005, p. v). In fact, between 1996 and 2002, R&D investments from transnational corporations to affiliates based in the developing world increased from 2 percent to 18 percent of total investment (UNCTAD 2005). In addition to receiving considerable funds, laboratories in academia, government, and small biotech companies provide the research basis for perhaps a third or more of new drugs, including many of the most innovative medicines (Angell 2004).

Opportunities for research and development in developing countries. About one-third of the total research effort in large pharmaceutical companies encompasses research similar to the initial steps of bioprospecting (ten Kate and Laird 1999). Such research includes the discovery of active compounds through bioassay, purification, and structure elucidation; their modification to enhance activity; and their testing in vertebrate models. These can be carried out in most developing countries. Even though the pharmaceutical industry is one of the most internationalized (UNCTAD 2005), and in principle much early-stage R&D could be based in tropical, biodiversity-rich countries, there is no indication of such an investment trend.

The synergistic link between bioprospecting and conservation

The focus on economic factors also helps to clarify the unique technological and commercial basis for the link between conservation and bioprospecting. One of the more remarkable characteristics of bioprospecting is that issues of great importance that are often at odds—conservation, sustainable economic development, and human health—become interconnected and mutually beneficial. Bioprospecting is primarily a high-technology, laboratory-based activity, with most of the benefits accruing to urban areas. Urbanites are an increasingly important fraction of the population in developing countries. The urban population of Latin America and the Caribbean, for example, was about 42 percent in 1950; it is expected to increase to 85 percent by 2030 (United Nations 2003, Aide and Grau 2004). Therefore, in addition to demonstrating that intact ecosystems have value, it will be imperative to resolve the conflict that urban citizens, the private sector, and government presume to exist between conservation and the use of natural resources for development. Thus a likely route by which urban-based interests in developing countries can become engaged in conservation will be via economic considerations, particularly ecotourism and, perhaps, bioprospecting.

Research, development, and training in Panama

In this section we describe a project that was conceived not only to investigate potential medicines but also to provide economic benefits to Panama and promote conservation there through the sustainable use of the country's biodiversity.

Box 1. Benefits from in-country bioprospecting funded nationally or internationally.

Science and education

- Research experience and publications enhance the competitiveness of Panama's educational and scientific institutions.
- Research experience allows young scientists to compete successfully for international funding and training at the master's and doctoral levels.
- Panama's established researchers can obtain external funding.
- Knowledge of the uses of Panama's biodiversity can benefit researchers there and permit Panama to collaborate on an equal footing with academics and companies from outside the country.

Economic investment, policy, tourism, and conservation

- External funding: Investments in research and development from outside the country provide jobs without the use of government funds.
- Support for national policymakers: Improved knowledge of terrestrial and marine organisms at the molecular, whole-organism, and ecosystem levels will aid the management of natural resources.
- Ecotourism: Guides trained in the uses of Panama's biodiversity can provide information of exceptional interest to visitors, greatly enhancing the ecotourism experience.
- Scientists as citizens: Investigators from fields that do not have an environmental orientation, such as chemists and microbiologists, can contribute to conservation, economic development, and the rational use of resources.
- Urban citizens as advocates: Members of the urban and commercial sectors can perceive the value of biodiversity and can be motivated to support its conservation and sustainable use.

Overview of the International Cooperative Biodiversity Groups program. In an effort to create a bioprospecting program that would confer immediate and tangible benefits to the source country, in 1998 we began a collaborative project in Panama under the auspices of the International Cooperative Biodiversity Groups (ICBG), an imaginative and ambitious program created in 1992 and currently supported by the National Institutes of Health, the National Science Foundation, and the US Department of Agriculture (Fogarty International Center 2006). The goals of the ICBG are to combine drug discovery with biodiversity conservation, scientific capacity building, and economic development (Rosenthal et al. 1999, Rosenthal and Katz 2004). The ICBG program is based on "biodiscovery partnerships" in which systematists,

chemists, cell biologists, conservationists, and lawyers from academia, business, and government in the United States and in developing countries have succeeded in promoting biodiversity-based research by developing novel institutional and legal arrangements.

Legal agreements. In the Panama ICBG, agreements with the Panamanian government assure that Panama will receive milestone payments and royalties should a drug make it to market. However, these future and uncertain benefits are not the focus of the project. The emphasis of the Panama ICBG is to ensure that Panama receives immediate advantages from bioprospecting in terms of research training and research opportunity. Indeed, most of the drug discovery research for this project is carried out in Panama (Kursar et al. 1999).

Participants, infrastructure, and training. Because bioprospecting requires the free exchange of samples and information, close collaboration is essential. Hence the project is highly interactive; it has included representatives from five departments at the University of Panama, Panama City; Panama's national laboratories (Institute of Advanced Scientific Investigations and High Technology Services) and the Smithsonian Tropical Research Institute, also in Panama City; and several universities in the United States. The participants also work closely with Panama's biodiversity agency, Autoridad Nacional del Ambiente. The sophisticated infrastructure provided by the Smithsonian has allowed us to meet the project goals of technology transfer and training in Panamanian laboratories. Using ICBG funds, two laboratories were set up in Panama, and several existing laboratories were enhanced. The ICBG acquired the first nuclear magnetic resonance facility in Panama (Bruker Avance 300 MHz). Considerable emphasis has been placed on training, with over 70 undergraduates receiving research experience during seven years. This experience, along with the opportunity to establish a publications record, makes the students competitive for graduate study abroad, and 22 of them continued studies for graduate degrees in scientific fields.

Isolation of active chemicals. The project infrastructure and technical capacity have supported the isolation and structure elucidation by scientists in Panama of over 100 compounds, most with medicinally relevant activities (figure 1). These represent a large fraction of the published studies of the uses of Panama's biodiversity in which all or nearly all of the research had been accomplished in Panama-based laboratories. For example, in the laboratory of two of the authors (M. P. G. and P. N. S.), over 40 compounds were isolated, most of which were active against cancer and 13 of which were new to science (Hussein et al. 2003a, 2003b, 2004, 2005). In another of our laboratories (L. C.-R.), a similar number of isolated compounds were isolated, many of them new to science or active in bioassay against malaria, Chagas disease, or leishmaniasis (Montenegro et al. 2003, Torres-Mendoza et al. 2004, Cherigo et al. 2005, Correa et al. 2006).

Innovative bioassays. Our bioassay program focuses on the discovery of treatments for tropical diseases. At Panama's national laboratories, assays have been developed for leishmaniasis (Williams et al. 2003), trypanosomiasis, and malaria, with a dengue assay under study. A major success has been the development of bioassays that do not depend on radioactivity. For example, one of the authors (E. O.-B.) developed an antimalarial assay that takes advantage of the absence of a nucleus and DNA in the red blood cell within which the parasite lives, and detects *Plasmodium* growth using a DNA-sensitive fluorescent probe (Corbett et al. 2004). Scientists from Bolivia, Madagascar, and Peru have traveled to Panama to learn the methodology for the assay. Laboratories at the University of Panama, as well as those in Puerto Rico and Spain, have used this assay to evaluate the activity of new natural products (e.g., Wei et al. 2004, Gutiérrez et al. 2005a, 2005b).

Productivity in relation to funding. The economic benefits from the ICBG amount to about $500,000 expended each year in Panama. But the most substantial benefits provided by the ICBG to Panama have been nonfinancial, including unique opportunities for doctoral-level Panamanian lab leaders and their students to investigate the uses of their own biodiversity; training for many young scientists; and improved infrastructure. The technology transfer and training within the Panama ICBG has been recognized in Panama and internationally as a model program (Dalton 2004, The Economist 2005, Blaustein 2006).

Tropical and neglected diseases

The bioassay component emphasizes tropical diseases, with many of the most interesting compounds being active against the causative agents of leishmaniasis, Chagas disease, and malaria (figure 1). Many considerations point toward the need for bioprospecting-based research on these neglected diseases. Most treatments now available are not safe, effective, or affordable (Trouiller et al. 2001, Gelb and Hol 2002), and the loss of economic productivity caused by mortality and cost of treatment attributable to these diseases is substantial (Marsh 1998, Cohen 2006). In the case of malaria, for which nearly all therapeutic drugs derive from natural products, resistance to the highly effective drug artemisinin (derived from the plant *Artemisia annua*) has appeared (Jambou et al. 2005, Towie 2006), with no new medicines to replace it. In the case of Chagas disease, treatment with nifurtimox and benznidazole results in serious adverse side effects (Viotti et al. 1994). In our in vitro bioassay of nifurtimox, activity is quite low, with an inhibitory concentration (IC_{50}) of only 2 to 11 µg per ml. With sufficient investment, the discovery of natural products that have in vitro activity much superior to that of nifurtimox seems likely. The challenges presented by the need for treatments for tropical diseases also provide an

opportunity for biodiversity-rich countries to develop research capacity and establish small biotech companies.

Overcoming obstacles and realizing opportunities

In developed countries, alliances and collaborations between the large pharmaceutical companies, small R&D companies, and academia have considerable economic importance. In developing countries, few scientists participate in the more advanced stages of bioprospecting research, such as using biodiversity-based intellectual property to attract funding and establish biotechnology companies. Despite the investment trends mentioned previously, there has not been substantial investment in bioprospecting R&D in the developing world. In addition, the pharmaceutical industry is one of the most internationalized (UNCTAD 2005) and, in principle, much early-stage R&D could be based in tropical, biodiversity-rich countries. Serious barriers remain to be overcome in order to realize economic and scientific development through bioprospecting. Obstacles include underdeveloped institutional and scientific capacity and legal constraints.

Developing institutional and scientific capacity. The reason for low R&D investment in developing countries is the lack of capacity there to carry out the type of high-caliber, biodiversity-based research that would lead to patentable, licensable discoveries and the creation of R&D companies. Developing such capacity is key. To create the necessary capacity, substantial investments must be made in researchers and laboratories in developing countries. The bottleneck lies in the low level of sustained support from donors and governments of developed countries for carrying out science in developing countries. Unless this situation changes, the idea of linking bioprospecting with economic development and conservation cannot be realized. Therefore, this crucial step deserves to be a focus of development efforts (Kettler and Modi 2001, Annan 2003, Holmgren and Schnitzer 2004).

The advent of a nuclear magnetic resonance facility in Panama, joined by another at Panama's national laboratories, has been a key infrastructure development. These instruments have permitted both doctoral-level scientists and students to see their projects through to a logical end point, something that previously was impossible. They also represent resources for training and an attraction that will encourage scientists to relocate or return to Panama. Hence our experience indicates that providing state-of-the-art infrastructure will play an important role in enhancing research in the developing world.

Attracting established scientists or highly qualified postdoctoral associates from developed countries is an essential step. In addition to providing salary, laboratory space, and the funds to set up a laboratory, it is essential to maintain options for such scientists to return to an institution in the United States or Europe should they so choose.

Because indiscriminate funding can actually be an impediment to scientific development, funding to developing-country researchers needs to be awarded on a competitive basis, with researchers held accountable for the use of funds and productivity. The same approach can mitigate the institutional limitations that exist in some developing countries.

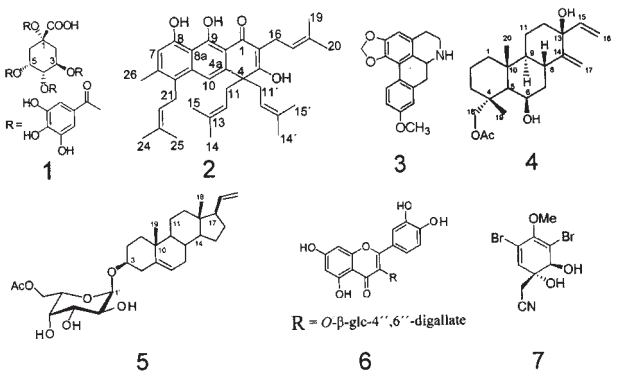

Figure 1. Novel or active compounds isolated in the Panama bioprospecting program. (1) A previously described galloyl derivative of quinic acid isolated from mature leaves of* Hirea reclinata *(Malpighiaceae) with activity against HIV (Hussein et al. 2003b). (2) Ferruginin C, not previously described, isolated from the young leaves of* Vismia macrophylla *(Clusiaceae) with moderate anticancer activity (Hussein et al. 2003a). (3) Xylopine, a previously described aporphine alkaloid isolated from young leaves of* Guatteria *spp. (Annonaceae) and having selective activity against the causative agent of leishmaniasis,* Leishmania mexicana *(Montenegro et al. 2003). (4) A cassane diterpene, not previously described, isolated from mature leaves of* Myrospermum frutescens *(Fabaceae) with activity against the causative agent of Chagas disease or American trypanosomiasis,* Trypanosoma cruzi *(Torres-Mendoza et al. 2003). (5) A novel galactosyl triterpene isolated from an octocoral in the genus* Muricea *(Gutiérrez et al. 2004). (6) A flavonol glycoside, not previously described, isolated from the young leaves of* Triplaris cumingiana *(Polygonaceae) with moderate anticancer activity (Hussein et al. 2005). (7) Aeroplysinin-1, a previously described dibromotyrosine derivative from a new species of sponge in the genus* Aplysina*, first collected in Coiba National Park, Panama, with activities against the causative agents of malaria,* Plasmodium falciparum*, and* T. cruzi *(Gutiérrez et al. 2005b).

The rapid and substantial successes of fields such as genetics and cell biology, as well as their ability to attract funding, can be assigned in large part to the premium placed on collaborating and sharing materials and techniques among competing laboratories, both nationally and internationally (Edwards 2004). Thus bioprospecting will be most competitive where an open, dynamic research environment is created. Nevertheless, one barrier to collaboration is the tendency by some to view bioprospecting as a confidential activity. The Panama

ICBG places a premium on collaboration and, to the extent possible, maintains open access, welcomes visits by other researchers, and shares materials and techniques. In support of this approach, the legal and regulatory requirements within developing countries could facilitate research collaborations.

Legal constraints. Collaborations are essential for research, but can be difficult because of the need for legal agreements with academic and industrial collaborators. In the case of the Panama ICBG, the initial agreement between the Smithsonian and Panama's biodiversity agency required about three years of negotiations. These long negotiations were due to inexperience on both sides.

Lack of experience and restrictive regulations, leading to slow and expensive legal processes, probably block many bioprospecting projects. At present, sufficient experience exists worldwide that, in principle, developing countries could be provided with legal advice that is consistent with the Convention on Biological Diversity and protects the interests of all parties, and also allows negotiations to be completed rapidly (Fogarty International Center 2006, PIIPA 2006). In some developing countries, strengthening of intellectual property protection may be required before R&D investments can be realized.

Recommendations for developing bioprospecting as a discipline

The scope of bioprospecting often is restricted to drug discovery, but the concept of its domain could be expanded to refer to all research on the uses of biodiversity. In fact, the term "biodiversity partnerships" better represents the full range of research opportunities and also communicates that these endeavors reach beyond for-profit motives and encompass many vital societal goals.

Link basic biodiversity studies with bioprospecting. The nonapplied areas of biodiversity research, ecology, conservation, systematics, evolution, and related studies can have valuable spin-offs, as has been the case in Panama. Finding compounds that lead to marketable drugs is a highly unlikely process, and our project benefited from nonapplied ecological research that was carried out in Panama between 1975 and 1995 (Kursar and Coley 2003). Although many programs make random collections, we found that using biological insight enhanced discovery (Coley et al. 2003). Such approaches are underexploited.

Perform in vivo testing and test for mechanism of action and medicinal chemistry. Very few of the thousands of active compounds discovered in academic laboratories and published each year are investigated for safety and efficacy in vertebrate models. In effect, the research process ends before the utility of these compounds has been determined. This provides an opportunity to extend bioprospecting research to the logical next step. Promising compounds can also be investigated for mechanism of action and medicinal chemistry (Ivinson 2005). By taking these additional steps, researchers also would establish more substantial intellectual property.

Develop safer pesticides for agriculture. With respect to agriculture, the urgent need for safer pesticides is underappreciated. Most modern, synthetic pesticides are highly toxic, and users may be unaware that they pose grave risks to human health (Dinham and Malik 2003, Alavanja et al. 2004). Pesticides may have disproportionate impacts on children (Weiss et al. 2004), and in some regions, poisonings due to pesticide misuse may cause more deaths than infectious diseases (Eddleston et al. 2002). There is a critical need for developing countries to find less toxic means of controlling crop pests. Research carried out in developing countries will be needed to solve these problems, and biodiversity is a likely source of such products. Chemicals made naturally by fungi and plants (e.g., strobilurin fungicides and spinosyn, an insecticide), organisms with exceedingly high diversity in many developing countries, could result in pesticides or fungicides with low toxicity to nontarget organisms.

Investigate medicinal, veterinary, and other applications. Because medicinal plants are commonly used in many developing countries, accurate information about their safety, efficacy, and risks represents an important unmet health-care need (Lila and Raskin 2005). Investigations of the uses of biodiversity have also contributed to discoveries in veterinary medicine, cosmetics, foods, industrial enzymes, bioremediation, biocontrol, nanotechnology, and biomimetic materials, and to the development of manufacturing processes that are less polluting (Beattie and Ehrlich 2001, Bar-Cohen 2006).

Conclusions

With appropriate infrastructure, technology transfer, and training, many developing countries could carry out exciting, high-quality research in laboratories in their own countries (Morel et al. 2005). By developing state-of-the-art technical knowledge of their own biodiversity, developing countries can collaborate and negotiate more effectively with colleagues in academia and industry. In our experience, a self-sustaining research capacity can be developed in a relatively short time, such that investigators can independently obtain their own funding. Such research provides immediate economic benefits and has the potential to grow into a substantial industry. Because research on the uses of biodiversity in developing countries has been limited by low investment and regulatory constraints, most biodiversity-based innovations are discovered in the less biodiverse, more developed regions of the world. Since many of the mechanisms by which biodiversity provides value can be realized only through research, we propose that we return to the vision outlined in the Convention on Biological Diversity. More resources must be directed toward facilitating and promoting high-technology research and local innovation in the uses of biodiversity, especially key infrastructure improvements such as the nuclear magnetic resonance facility described here. Such research, when properly

constituted, provides considerable benefits for developing countries and, at the same time, establishes that biodiversity can provide valuable services. Hence, in order to promote scientific development, sustainable development, and conservation in a manner that is transparent to the public and spreads benefits in a broad, equitable manner, we believe that biodiversity-based research, including bioprospecting, deserves strong encouragement at both the national and the international levels.

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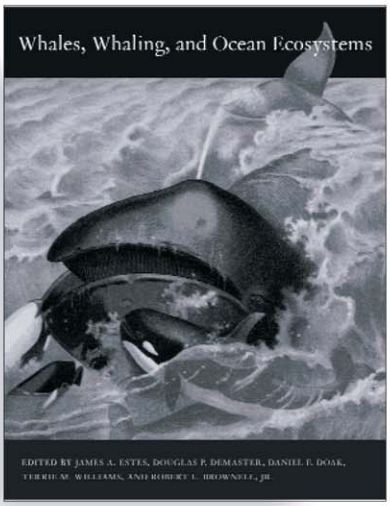

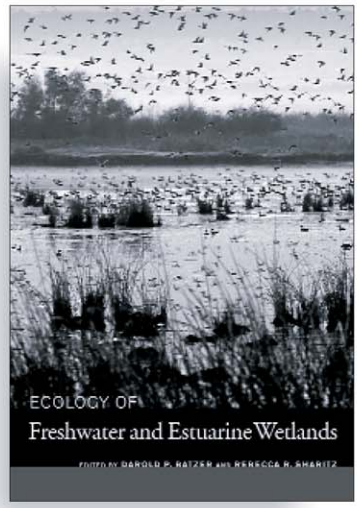

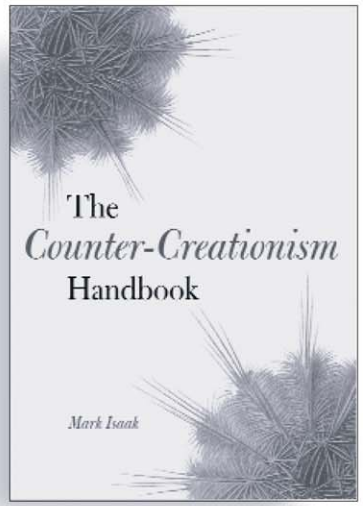

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