The Realized Benefits from Bioprospecting in the Wake of the Convention on Biological Diversity

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In the mid-1980s, the convergence of several technological advances led to a serious resurgence of interest in surveying plant species for drug development. The emergence of methods to miniaturize *in-vitro* bioassays (a test used to quantify the biological effect of a chemical compound or extract against a specific disease target) run the bioassays with robotic equipment, and isolate and identify active compounds with a speed and precision never before possible. This allowed rapid evaluation of large numbers of plant samples with an efficiency many times what had ever been possible. For example, in the 1960s, the early phase of the Developmental Therapeutic Program at the National Cancer Institute (NCI) used transplantable tumor cell lines and looked for extracts that prolonged life in a statistically significant population of rodents. It often took months to evaluate a single extract in an expansive population of mice or rats. By the mid-1980s, the same NCI program was running sixty-two different cultured cell lines in 96-well microtiter plates and was able to evaluate hundreds of extracts per week.[1] The incorporation of these new technologies led to a resurgence in interest in natural products, and biological samples were evaluated at a rate never before imaginable.

In 1986, the NCI launched three contracts for the procurement of large numbers of plant samples, one each for tropical America, Africa

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1. KERRY TEN KATE & SARAH LAIRD, THE COMMERCIAL USE OF BIODIVERSITY: ACCESS TO GENETIC RESOURCES AND BENEFIT SHARING (1999).

and Madagascar, and tropical Asia.[2] Each program collected and supplied 1,500 samples per year, and the NCI screened and evaluated more than 50,000 samples of plants, representing more than 20,000 plant species, in the next twenty years.[3] In 1993, the Fogarty International Center of the National Institutes of Health (NIH) launched the International Cooperative Biodiversity Groups (ICBG), funding consortia of biologists collecting samples, others preparing and evaluating extracts, chemists determining structures and modes of action, and industrial partners providing additional bioassays and developmental capabilities.[4] These programs continue today and they have collectively evaluated huge numbers of plants, marine invertebrates, insects, and microbial cultures.[5] Pharmaceutical companies also joined the effort to evaluate plants, and large-scale screening of natural products took place at Bristol-Myers, Merck, Monsanto, Novartis, and Pfizer, among others.[6] This peak period of interest in screening large number of biological samples, primarily plants, in the 1980s and 1990s will be referred to here as the "bioprospecting surge."

At about the same time that interest peaked in natural products, discussions were beginning about the legal and ethical frameworks that should govern such efforts. In 1992, between June 3rd and June 14th, the United Nations Conference on Environment and Development, often called the Earth Summit, was held in Río de Janeiro, Brazil. During the conference, the Convention on Biological Diversity (CBD or the "Convention") opened for signature and was entered into force on December 29, 1993.[7] The Convention fundamentally changed the legal status of ownership of biological

2. Gordon Cragg et al., *Role of Plants in the National Cancer Institute Drug Discovery and Development Program*, *in* 534 AM. CHEM. SOC'Y SYMPOSIUM SERIES, HUMAN MEDICINAL AGENTS FROM PLANTS 80, 88–89 (A. D. Kinghorn & M. F. Baladrin eds., 1993); Gordon Cragg & D. Newman, *Natural Products Drug Discovery and Development at the United States National Cancer Institute*, *in* DRUG DISCOVERY AND TRADITIONAL CHINESE MEDICINE: SCIENCE, REGULATION, AND GLOBALIZATION**,** 19–32 (Y. Lin ed., 2001).

3. Cragg et al., *supra* note 2, at 88.

4. Joshua Rosenthal et al., *Combining High Risk Science with Ambitious Social and Economic Goals*, 37 PHARMACEUTICAL BIOLOGY Supp. 6, 6–21 (1999).

5. Rosenthal et al., *supra* note 4.

6. KATE & LAIRD, *supra* note 1.

7. LYLE GLOWKA ET AL., A GUIDE TO THE CONVENTION ON BIOLOGICAL DIVERSITY ix (1994).

resources, which had previously been viewed as a common heritage open to all countries free of any restrictions, to a new situation where biological organisms were now treated as sovereign possessions of the countries in which they occurred. In a post-Convention world, it was now legally mandated that benefits derived from natural sources be shared in an equitable manner with the country where the species was first collected. As many pharmaceuticals had historically been derived from natural sources at the time the Convention entered into force, it was anticipated that significant royalty payments would accrue to countries from which species that yielded bioactive compounds were derived. This anticipated flow of funds to developing countries that were home to the world's richest biodiversity did not happen because of several difficulties that followed in the wake of the Convention. Immediately, there were problems determining what equity meant, what was the fair-market value of access to biodiversity, and what was the full range of benefits (which were later interpreted as much more than financial dividends that happened only following market entry for new products, with the expanded view of benefits including training, capacity building, and fully collaborative research opportunities).[8]

The primary reason, however, that no major royalty payments flowed back to biodiversity-rich nations was that very few marketable discoveries were made. Though the FDA licensed new products in the period that followed the Convention entering into force, they had been discovered much earlier, were already in development, and had secured approval during the surge to evaluate natural products. For example, Taxol, derived from the Pacific Yew, *Taxus brevifolia*, was licensed for the treatment of refractory ovarian cancer in 1993, but it had been discovered more than ten years before the modern screening efforts began. The lack of anticipated discoveries may have been a consequence of several factors, one being that the twenty years following the Convention was simply too short a period of time for discoveries to work their way through the entire process of discovery, development, clinical testing, and

8. James Miller, *Impact of the Convention on Biological Diversity: The Lessons of Ten Years of Experience with Models for Equitable Sharing of Benefits*, *in* BIODIVERSITY AND THE LAW 58, 60–61 (C. McManis ed., 2007) [hereinafter Miller, *Impact of the Convention*].

approval. It may be that given more time, some of the bioactive compounds discovered will eventually be developed and marketed. Or some of the advances in natural products chemistry from the discovered compounds may indirectly contribute to the future development of new drugs. It is widely perceived, however, in industry that the zenith of natural products screening was disappointing because not many therapeutically useful discoveries were made. It has been speculated that the lack of discoveries was not indicative of the promise of plants to yield new compounds, but rather a consequence of the limitations of methodology used to evaluate extracts.[9]

The majority of natural products discovery in the 1980s and 1990s was attempted by evaluating crude extracts in bioassays.[10] Crude extracts may contain in excess of 500 individual compounds. Many are present in very low concentrations, often too low to demonstrate any effect in a bioassay. Frequently, the compounds present in higher concentrations are tannins, lignans, and others known to interfere with or mask the activity of other compounds.[11] By the mid-1990s, there was a trend toward fractionating crude extracts, but generally only into a small number of fractions and with the main goal of separating and removing the fraction that included the tannins. Ten years later in the mid-2000s, methods were described for partitioning fractions by separating them with chromotagraphic methods that create libraries of individual chemicals from extracts.[12] Once individual compounds have been isolated, they can be evaluated at adequate concentrations and free from other compounds that may interfere, compete with, or mask their activity.[13] One company,

9. *See* James Miller, *Nature's Potential: How Many Drugs Could Come from Plants?*, *in* 118 REALIZING NATURE'S POTENTIAL: PROCEEDINGS OF THE WILLIAM L. BROWN SYMPOSIUM HONORING DR. GORDON CRAGG 125, 133 (B. E. Ponman & James Miller eds., 2011).

10. *See id.*

11. Gary Eldridge et al., *High-Throughput Method for the Production and Analysis of Large Natural Product Libraries for Drug Discovery*, 74 ANALYTICAL CHEMISTRY 3963, 3967 (2002).

12. Peader Cremen & Lu Zeng, *High-Throughput Analysis of Natural Products Compound Libraries by Parallel LC-MS Evaporative Light Scattering Detection*, 74 ANALYTICAL CHEMISTRY 5492, 5497–98 (2002); Gary Eldridge et al., *supra* note 11, at 3963, 3967.

13. Cremen & Zeng, *supra* note 12; Eldridge et al., *supra* note 11.

Zinsser North America, offers automated units for the preparation of chemical libraries from crude natural products extracts. The intense natural products screening of the 1980s and 1990s should not be described as unproductive, but rather as having missed many potentially useful compounds that were never detected when screening complicated mixtures of chemicals in crude extracts.

The criticism that the period of greatest interest in natural products was unproductive is unfounded, despite the fact that few drug candidates were identified. In the wake of the Convention, discovery efforts were conducted via international partnerships unlike anything that had existed before and these relationships led to great advances in basic field biology, pharmacology, and related fields. But perhaps the greatest impact of these relationships was to redefine international collaboration to be a much more equitable enterprise with more meaningful participation by all participants. Discovery programs were also conducted in a manner that addressed important concerns, such as insufficient research capacity in developing countries; major efforts supported by discovery programs helped train scientists, improve their research facilities, and provide support for economic development in communities living in close proximity to project areas. And finally, discovery programs provided another vehicle for promoting the importance of biodiversity and supporting its protection, an explicit goal of the ICBG programs.[14]

During the 1980s and 1990s, the Missouri Botanical Garden (the "Garden") was an active partner in numerous efforts to discover and developed new pharmaceutical, agricultural, nutritional, and various other kinds of products. All of the efforts were partnerships with outside discovery groups, and most of the programs included an international partner to facilitate work in other parts of the world. The Garden's first effort began in 1986 and was a contract to provide plant samples from Africa and Madagascar to the NCI.[15] This program led to what was probably the first international agreement for discovery programs, in this case guaranteeing benefits to

14. Rosenthal et al., *supra* note 4.

15. James Miller et al., *Sampling a Diverse Flora for Novel Biochemicals: An Analysis of NCI Collections from Madagascar*, 59 ECON. BOTANY 221, 222 (2005).

Madagascar through the NCI relationship.[16] A drug discovery partnership with Monsanto began in 1990 and, shortly thereafter in 1993, the Garden was a partner in one of the new NIH ICBGs.[17] Additional relationships expanded discovery efforts to look for new pesticides, genes for crop improvement, nutritional products, fragrances, and other commodities. Seven years after the Garden's involvement in natural products discovery began, the Convention entered into force and international collecting agreements became a requirement.[18] The Garden's earlier agreements with African countries as part of the NCI collaboration were found to be fully compliant when signed, beginning in 1990.

THE BENEFITS OF BIOPROSPECTING

The most frequently discussed benefits from discovery of a new drug are financial benefits, generally milestone payments or royalties.[19] One consequence of the lack of successful drug development from the bioprospecting surge is that the period is often regarded as having produced no tangible benefits. While the royalty payments originally envisioned did not materialize, the nonmonetary benefits that resulted from discovery efforts were numerous and of definite value to both developing countries and society in general.[20] These benefits include significant contributions to general knowledge; building research, development, and conservation capacity; improved quality of life for rural communities; and changes in the ethics of international collaboration.

All natural products discovery programs require some form of collecting organisms in the wild and processing them for transport to the laboratories for evaluation. This collection requires basic biological skills, access to libraries and reference collection of specimens, and staff capable of accurately identifying the materials

16. James Miller et al., Appendix: History of a Landmark Collecting Agreement: the Origin of the National Cancer Institute's Letter of Intent, a Precursor to Modern Bioprospecting Agreements, in BIODIVERSITY AND THE LAW 58, 68–69 (C. McManis ed., 2007).

17. Rosenthal, *supra* note 4.

18. GLOWKA ET AL., *supra* note 7.

19. Miller, *Impact of the Convention*, *supra* note 8, at 60–61.

20. *Id.*

collected. Biological specialists with a strong understanding of the group of organisms that they are collecting are especially important. This kind of expertise helps provide accurate identifications for the species being studied, helps prevent repeatedly sampling common species, and is essential for finding additional materials should a particular sample prove to be of enough interest to merit the collection of more material. All of the discovery programs during the bioprospecting surge trained scientists in the countries where they operated at least in the practice of gathering samples for evaluation and specimens that document those samples.[21] Training was both formal and informal in the field and, in many cases, went beyond simple field methods to include identification, taxonomic study, and publication of new species. Additionally, discovery programs could only operate efficiently with access to sufficiently well-curated collections. The museums and herbaria of developing countries were often in rather poor condition, and programs helped rectify that situation by providing equipment and supplies. For example, the Garden's NCI program financed the installation of air conditioning equipment in the national herbarium of Ghana as an essential step toward controlling insects in the collection. Most programs also provided extensive curatorial training in methods for management of research collections to the staff of the institutions where their in-country work was based, and this education led to significant improvements in dozens of research institutions. All in all, discovery programs generally left collaborators that were better-educated and working in improved facilities.

While the bioprospecting surge did not yield new drugs, hundreds of novel bioactive compounds were discovered, even though none made it through the whole development pipeline. The Suriname/Madagascar ICBG alone discovered many dozens of new compounds with bioactivity against one or another of the many bioassays testing multiple disease targets.[22] While they may not have become new drugs, each new compound discovered added to our

21. Rosenthal et al., *supra* note 4; Miller, *Impact of the Convention*, *supra* note 8.

22. D. G. I. Kingston et al., *The Suriname International Cooperative Giodiversity Group Program: Lessons from the First Five Years*, 37 PHARMACEUTICAL BIOLOGY 6–21 (1999).

general pharmacological knowledge in ways that may indirectly contribute to developing new therapies in the future. If parts of any of these plant-derived bioactive molecules were used to produce synthetic new drugs, it may not even be apparent that natural products contributed to the success.

It has often been pointed out that while the world's largely tropical, developing countries are home to the vast majority of the world's biodiversity, they are notably short of adequately trained scientists and adequately funded research facilities.[23] Addressing this lack of research capacity was one of the primary goals of the NIH ICBG projects. Every program included both formal and informal training as well as support for the improvement of in-country research facilities.[24] During the first ten years of the Madagascar ICBG, the labs at the Centre National d'Application et des Recherches Pharmaceutiques were renovated, new equipment and supplies were obtained, and staff developed the capacity to evaluate plant extracts in a modern anti-malarial assay.[25] Many field biologists initially trained as part of discovery efforts eventually found funding from other sources to continue their education. Improving research capacity in developing countries may be one of the greatest contributions from natural product discovery programs.[26]

The collection of samples for evaluation was often based in small rural communities in close proximity to diverse tropical forests, and most of these communities were extremely poor. Discovery programs frequently provided at least temporary employment in communities where there we no jobs available. These programs also helped address some of the collateral consequences of poverty. In coastal villages in eastern Madagascar where malaria was rampant, the NCI program subsidized a mosquito net program that made repellant impregnated nets available at costs affordable to the local community, and malaria incidence in the community's children fell dramatically. The Madagascar ICBG program supported an effort to

23. KATE & LAIRD, *supra* note 1.
24. Rosenthal et al., *supra* note 4.
25. S. Cao & D. G. I. Kingston, *Biodiversity Conservation and Drug Discovery; Can They Be Combined? The Suriname and Madagascar Experiences*, 47 PHARM. BIOL. 809–23 (2009).
26. Rosenthal et al., *supra* note 4, at 1999; Cao & Kingston, *supra* note 25.

subsidize school supplies in the rural villages surrounding Zahamena National Park, making paper, notebooks, pens and pencils, and textbooks available to children who otherwise would not have had access to these essential items.

Perhaps the greatest contribution that the bioprospecting surge was the Convention's indirect influence on the ethics of international collaboration. The primary aim of the Convention was to establish systems that would capture benefits from the use of biological diversity, and one of those benefits was advancing science in biodiversity-rich developing countries.[27] Post-Convention improved ethics for international partnerships were rapidly adopted across constituencies. It was no longer tolerable to go to another country and expect their scientists to support research efforts with little acknowledgement or benefit to themselves or their institutions. It rapidly became an accepted practice to require deposition of at least one complete set of collected specimens in some local museum or herbarium. The contributions of developing-world scientists were to be acknowledged via authorship as credit for real participation in the project. Today, field research is jointly planned and executed; publications acknowledge multiple coauthors; and institutional benefits, including funding, are shared more equitably. These changes in international collaboration constitute a tremendous contribution and, while not entirely attributable to discovery programs, they were an important consequence of the Convention.[28]

The bioprospecting surge also contributed significantly to international conservation efforts. All partners in the discovery efforts of the time acknowledged that their success was dependent on access to biodiversity and that such access was essential to preserve the species on which this whole endeavor depended. The NCI program officers who spoke regularly at national and international professional meetings stressed the importance of conserving the full complement of species that had yet to be evaluated as possible drug sources. When the ICBG program was founded, conservation was an explicit goal of the original call for proposals, and the partnership that included the Garden also included Conservation International to

27. GLOWKA ET AL., *supra* note 7.
28. Miller, *Impact of the Convention*, *supra* note 8.

support direct conservation efforts. During the five years the program operated in Suriname, ICBG support contributed at least indirectly to efforts to secure protection for the Central Suriname Nature Reserve, which is now protected as a UNESCO World Heritage Site. Later in Madagascar, the same program helped secure protected status for Orangea, a forest in northeastern Madagascar that is rich in endemics but was rapidly being degraded and deforested. Together these conservation actions add another layer of justification for the preservation of biological diversity.

CONCLUSION

While the bioprospecting surge may not have yielded the much-anticipated wealth of new drugs, the discovery projects that were conducted did result in numerous positive benefits. These included advancements in biological and pharmacological knowledge, capacity building in developing countries, economic benefits to poor rural communities, promotion of conservation of biological diversity, and influence on the ethics of international collaboration. These benefits accrued to individual scientists, the fields of biology and pharmacology in general, communities in developing countries, and humankind in the broadest sense. All of these advances contribute collectively, and will continue to do so in the future, to international scientific collaboration that is more equitable, helps address pressing economic issues in developing countries, and helps to promote the conservation of biological diversity.