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Natural products in drug discovery – Creating a new vision

Geoffrey A. Cordell
College of Pharmacy, University of Illinois at Chicago, 833 S. Wood St., Chicago, IL 60612, U.S.A. (Tel: 312-413-5381; Fax: 312-996-7107; E-mail: cordell@uic.edu)

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Abstract

"If only they had chosen to develop natural product drugs in a sustainable manner at the turn of the century". In 2050, when the Earth has a population of at least 9 billion, will this be our legacy as the world contemplates the costs and availability of synthetic and gene-based products for primary health care? For most people in the world, plants, in their various forms, remain a primary source of health care. However, in the developed countries, natural products derived from plants assume a very minor role as prescription and over-the-counter products, even with the widespread use of phytotherapeutical preparations. With the continuing decline of natural products in large scale, ultrahigh-throughput screening programs in pharmaceutical industry, and acknowledging the recent history of the relationship between humankind and the Earth, it is essential that we consider what are the health care issues that we are leaving for our descendants? Where do our responsibilities as global citizens and scientists coalesce? What is the vision for natural product research that we must create now in order to maintain the choices of drug discovery and pharmaceutical development for future generations? In order to assist us in creating this vision, we will examine some facets of how natural products must be involved globally in a sustainable manner for improving health care. We will discuss access to the biome, the acquisition, analysis and dissemination of plant knowledge, the safety and efficacy of traditional plant remedies, analytical and biotechnology development, and natural product structure diversification and drug discovery potential. Finally, we will address the question of who will fund this vision?

Abbreviations: ASP – American Society of Pharmacognosy; CBD – Convention on Biological Diversity; CYTED – Ciencia y Technologia para el Desarrollo; DAAD – Deutscher Akademischer Austausch Dienst; EU – European Union; GA – Gesellschaft für Arzneipflanzenforschung; IFS – International Foundation for Science; IUPAC – International Union for Pure and Applied Chemistry; JSPS – Japan Society for the Promotion of Science; NATO – North Atlantic Treaty Organization; NIE – National Institute for the Environment; NIH – National Institutes of Health; NSF – National Science Foundation; PSE – Phytochemical Society of Europe; RSC – Royal Society of Chemistry; SRC – Science Research Council; TWAS – Third World Academy of Science; UNIDO – United Nations International Development Organization; UNDP – United Nations Development Program; WHO – World Health Organization; WRI – World Resources Institute; WWF – World Wildlife Fund.

The current situation

Human inquisitiveness has extended to many corners of the Earth, to our solar system, and to the distant great clouds of nebulae which appear to be forming and reforming billions of suns and their solar systems. Inherent in the very existence of humankind has been the incessant desire to expand the boundaries of our knowledge and creativity, and thus a new vision of how life might continuously be improved on a global basis. For many humans, access to travel, to television, and to electronic communication has allowed, indeed encouraged us, to engage with the breadth and depth of human and biological experiences across national boundaries and up and down the global ecochasms.

The treasures now available from delving into these rich stores of biological and mineral wealth are amazing. Everything of a material nature that constitutes what we respectively regard as civilization has originated through our creative adaptation of the products from the continuous, transformational recycling of Earth's resources that has endured for over 4.5 billion years. As the application of our ingenuity to ameliorate disease and to prolong life substantially has increased, particularly in the last century, so have the issues which we must boldly face. This article is about one such issue and the creativity needed to address it.

In 1850, the world's population was 1 billion (The World Almanac and Book of Facts, 2001), and by 1930 had doubled (80 years). Within 45 years, it had doubled again to 4 billion, and by October 1999 had reached 6 billion. According to the Bureau of the Census, U.S. Dept of Commerce, global population will exceed 9 billion by 2050. Is it rational to think that the Earth has the physical and intellectual resources to sustain such a population for even one generation? In truth, we know little of the assets or the capacity of the Earth to sustain such an exploding population, but what we do know is not very encouraging. Approximately 1 billion barrels of oil are known in reserves, or approximately 70 years supply at present usage rates. Non-reusable fossil fuels approximate 82% of the present energy usage in the U.S. (The World Almanac and Book of Facts, 2001).

Three major industries, textiles, energy, and plastics have initiated substantial research programs aimed at examining the potential to develop their respective core resources in a sustainable manner (Reisch, 2001). Stunningly, drug discovery at all of the major pharmaceutical companies remains focused on the utilization of *non-renewable* resources for most of their drug discovery, development, and production. Although some efforts are currently aimed at the "greening" of numerous chemical industrial processes (Rouhi, 2002), there is no long term effort underway to examine how drugs will be made available globally in a sustainable manner from natural sources for future generations.

In a series of articles over the past fifteen years, I have tried to illustrate some of the issues which I am convinced the field is facing, and how they might be addressed (Cordell, 1987a, 1987b, 1990a, 1990b, 1991, 1992, 1993, 1994, 1995a, 1995b, 1999, 2000a, 2000b, 2001a, 2001b, 2002a, 2002b). I have tried to portray some of the successes, some of the missing elements in existing programs, and some of the potential opportunities. In this article, because we are rapidly running out of time and resources to make the needed changes, I am adopting a different approach, and will make some quite specific proposals for how to begin a dialogue for the global benefit of human health based on natural products.

As natural product scientists, we must recognize that we have important societal responsibilities, some of which will be presented towards the end of this presentation. One approach to this awareness is to ask ourselves the personal question "Whom are our studies in the natural sciences serving?" To begin to formulate a response, a considered discussion of the purposes, the aims, and the future of the natural product sciences is needed. Recognizing that pharmacognosy is "the study of biologically active natural products" (Cordell, 1990a), in the broader sense we can ask, "What is pharmacognosy for?"

Typically, international science conferences focus on past achievements, on results already generated, and, in many instances, already published. The presumption of a competitive environment frequently inhibits the generation of new ideas to be pursued, of new experiments to be proposed, for the fear of them being "stolen". While from a life-long learning perspective such a presentation may be useful, from a future thinking perspective these meetings don't challenge the integrity or the societal impact of the efforts that are being made. In addition, they do not utilize the collective talents available to create new initiatives, or even think in an open manner about the role of our sciences in a future world. As we shall see, there is a desperate need to create such opportunities for examining the options ahead. And how can the development of such plans become a collective vision? An international forum (or series of meetings) is needed to develop innovative programs for the future of the natural product sciences for the benefit of humankind.

The statistics regarding the use of natural products as drugs are now well-known and have been presented and discussed elsewhere (Farnsworth and Morris, 1976; Cragg et al., 1997; Newman et al., 2000; Rates, 2001). Global sales of phytochemical products will be valued at about $31 billion in 2002 (Anon, 1998), and about 50% of the prescription products in various countries in Europe and the US are either natural products or are natural product derivatives (O'Neill and Lewis, 1993). However, many people in the pharmaceutical industry, in the medical, dental, and nursing professions, and in the public at large, are unaware of this critical role that nature plays in providing

vital drugs for health care on a daily basis. In part, this has probably occurred as we have lost the connections between ourselves and nature and between food and disease treatment and prevention.

This background of achievement in discovering and developing drugs from natural sources (higher and lower plants, marine organisms and bacteria) for human health over the past 200 years does not impress the management of the major pharmaceutical companies in the world to continue to engage in natural product drug discovery; quite the reverse. Several major companies in the past few years (Abbott, Bristol Myers Squibb, Eli Lilly, GlaxoSmithKline, Merck, and Novartis) have essentially abandoned their natural product drug discovery programs. It should be noted that this list includes several companies for whom natural product drug sales exceed $1 billion per year. For example, sales of paclitaxel (taxol) for BristolMyersSquibb in 2000 were over $1.5 billion. At the global level of the major international agencies there are apparently no major natural product drug discovery programs underway, and quite limited programs at WHO aimed at enhancing the safety of traditional medicines (*vide infra*). For a number of reasons, including the dire need for new drugs for a host of tropical diseases, for many diseases which are developing drug resistance, and for the purpose of serving as templates for drug design and development candidates, this situation is both appalling and alarming. It will not suffice to serve for the future, and is not a situation that we can choose to ignore in the present.

Let us begin then with a brief appreciation of the natural products derived from plants which are consumed every day of our lives on a global basis. There is paper, there are the foodstuffs, the flavors and the spices, the perfumes and cosmetics, and the health grooming products, and there are the prescription and over-the counter products. In addition, there are numerous extracts and plant materials that are used on a daily basis all over the world for a variety of purposes, including as medicinal agents. It was estimated many years ago that over 80% of the worlds' population uses plant materials as their source of primary health care (Farnsworth et al., 1985). Presumably, this number is even higher today as populations in the developing world have continued to expand steadily.

During the past ten years there has been a dramatic increase in the use of phytotherapeutical products in many developed countries. In the United States, for example, approximately $4.2 billion of such dietary supplements were sold in 1998, although sales have declined since then (Anon, 2001b). In many countries in Europe, there are regulations which govern the labeling and use of phytotherapeutical entities. However, elsewhere in the world, there arises a very interesting and dramatic connection between the medicinal uses of plant materials in the developed and the developing worlds: NEITHER GROUP OF PRODUCTS IS REGULATED. Two aspects of this situation are particularly troubling. The first is that it is very much the era of "Buyer Beware" in both instances. Whether you are going to your local health food store or your local shaman or curandero, the fact is that you are "buying blind". Continuation of this situation, on a global basis, substantially undermines the credibility of natural product research and the role that it should be playing in health care. We need to re-vision this role for the stature of our science. This dangerous and unacceptable situation has arisen in developed countries because of the common belief in two myths. The first myth is that natural products are safe, particularly if they have been used for hundreds of years in a system of traditional medicine. The second myth is that the contents of a box or a bottle of a dietary supplement which contains plant or fungal or marine products are somehow regulated. This arises, in part, because of the placement of rows of dietary supplements across the store aisle from OTC products, which are regulated. Do we as natural product scientists wish to perpetuate this situation? Or do we have a different vision?

What do consumers all over the world have the right to expect for a plant-derived product in their marketplace? Probably the first aspect is plant authentication. Namely, that the correct plant part, of the correct genus and species is contained in the package. Consumers also need to know that their product is not contaminated with insects, pesticides, herbicides, heavy metals, microbial and fecal matter, and radiation. Consumers should be assured that the product they are purchasing is not adulterated by materials (natural or synthetic) which are either not approved, or not approved for the stated use. In addition to botanical standardization, consumers have the right to expect a product that is consistent, on a batch-to-batch basis, chemically and biologically. When a consumer buys a dietary supplement they should know how long the product will remain active. That a bag of candy has more information on it, and has more regulation involved with its presentation than a phytotherapeutical product, is absurd. Finally, when one buys a phytotherapeutical product, as when one buys a cup of coffee, you expect that it will work. That the desired

effect will be achieved. For how many of the myriad of products on the market has efficacy been scientifically established? In addition, many consumers are taking phytotherapeuticals and prescription or OTC drugs at the same time. Yet the interactions between these categories of products are not well studied and documented (Kroll, 2001). Do we have a different vision?

The uses of many (approximately 74%) of the plant-derived drugs that are presently marketed are similar or identical to their ethnomedical use (Farnsworth, 1988; Cordell et al., 2001). Yet, the knowledge of the medicinal use of plants has not been fully catalogued and accumulated, and there are now substantive issues involved in collecting that information following the Convention on Biological Diversity (CBD)(Anon, 2001c). Shamans are not training new apprentices (Balick and Cox, 1996; Cox, 2000), and thus the knowledge of the use of plants is being lost. We recognize that on a global basis, as a result of population growth and issues related to deforestation for timber and farmland, biodiversity, in all its forms, is decreasing (Wilson, 1988).

In spite of the exorbitant amortized costs (currently estimated at $500 million) to bring a single new drug to market, and the pressures of a potentially changing patent situation, there is a continuing need for the discovery of new medicinal agents. Resistance to known chemotherapeutic agents, including anticancer, antiviral, antifungal, and antibacterial agents is steadily increasing (Rothenberg and Ling, 1989). New diseases are appearing requiring new drugs, and old diseases, once thought to have been eradicated, are reappearing. Yet, as mentioned above, even though the role of natural products as pharmaceutical agents is well-established, pharmaceutical companies are eliminating such discovery programs. Why? Before answering that question, with a somewhat controversial answer, it is important to understand a little about the early stages of how new medicinal agents are currently discovered. For those agents will be the new drugs in the marketplace for the next 15–20 years.

The discovery of drugs is focused on evaluating a "library" of diverse chemical entities, usually in quite pure form and set-up in 384 or 1536-well plates, against a primary bioassay. Samples which provide a positive response to established criteria are then moved to the next stage of evaluation (frequently a secondary bioassay or a set of chemical inclusion criteria). The primary bioassay is often enzyme or receptor-based, and each of the steps, from construction of the library to the processing of the data from the tests, is fully automated. In this way, it is quite routine for a company to evaluate 1.5 to 2 million samples in a particular bioassay in a one to two month period (Thayer, 1998). Depending on their resources and their therapeutic interests, companies will run 15-50 bioassays a year. The "library" and its construction (i.e. which samples are included for bioassay) therefore becomes a very critical aspect of the discovery process, and much consideration is given by companies as to the nature of the samples to be screened from a much larger corporate library of samples. Some aspects of the types of samples which might be included have been discussed previously. However, as new corporate mergers have taken place in the past few years (e.g. GlaxoWellcome and SmithKline and Pfizer and Pharmacia), a new phenomenon is occurring as these corporate libraries are being merged. The question now arises of what samples (i.e. how many of a 3 million sample collection?) are to be screened because of cost and time considerations. Where do natural products "fit" in these libraries?

For those established natural products which are included in the libraries as individual compounds this is not a problem, because they are classed in the same way as a synthetic or semi-synthetic compound. It is worth noting at this point that for the class of compounds known as alkaloids 74% of the known compounds have never been evaluated against a single bioassay (Cordell et al., 2001). For an extract derived from a plant, a marine organism, a fungus or a bacteria, the situation is quite different. And it is at this point where the potential impact of natural products in the discovery process is being lost. It is important to state, very clearly, that *the major pharmaceutical companies are no longer interested in the evaluation of natural product extracts.* Consequently, they are eliminating all of those activities related to natural products from their basic discovery programs. The reasons are quite simple. Firstly, when an extract shows activity in a bioassay (i.e., is a "hit"), the active principle must be isolated and characterized. This is expensive and may take 1–4 months, depending on the availability of an appropriate amount of extract or plant material, the turnaround time for bioassay data, and the ease of unambiguously determining the structure (Corley and Durley, 1994). By this time, the other (synthetic) "hits" have been moved to the next stage of decision-making and the natural product is left behind. And that is assuming that recollection of the plant is not necessary, and that the extract of the recollected

plant retains the original biological activity. Two other factors also come into consideration before involving natural products in a drug discovery program; intellectual property issues and relative cost to obtain a "lead". The distinction between a "hit" and a "lead" has been explained elsewhere (Cordell, 2000a), and focuses on the level of preliminary chemical and biological studies, and the availability of the compound to enter the next stages of development. Having an adequate and sustained supply of a biologically active natural product available for more extensive animal pharmacology is a frequent deterrent to the further development of that compound.

For most scientists working in the area of natural product drug discovery, the intellectual property issues are now daunting. In the years since the Convention on Biological Diversity was signed by all of the major countries of the world (except the USA and Thailand), numerous countries in both the temperate and tropical areas of the world have put in place various forms of rules, regulations, legislation, and executive orders which control the acquisition of all biological materials and indigenous knowledge within their borders (Anon, 2001a). For research groups, both academic and industrial, in countries all over the world, these changes have fundamentally changed their *modus operandi*. It is no longer possible to collect a plant or a soil sample or a marine organism, even from your own country, without prior approval. Multilateral agreements between institutions and agencies in countries to access biological materials often take years to negotiate and finalize. Sometimes, even after substantial investment of time, money and personal effort, developing an agreement becomes impossible as governments, and their views, change. Pharmaceutical industry, which is operating in a very highly competitive environment to develop a new therapeutic entity based on rapidly changing science, has no patience for such a scenario. As a consequence, the hope that the CBD would lead to a higher level of international collaboration (including the involvement of the major drug companies) to investigate the biome for the potential to enhance human health has not materialized; indeed the effect has been the opposite. The corporate focus is set on combinatorial chemistry based on the identification of "hits" from individual synthetic or natural products present in their vast libraries (Adang and Hermkens, 2001), coupled with computational drug design (Clark and Pickett, 2000).

There are significant social and ethical issues in this overall approach by pharmaceutical companies. The first matter of concern is that the drugs that are being developed as a result of this approach are not sustainable. Their creation and production continuously depletes the non-renewable resources (oil and coal) of the Earth. For example, only 11% of the 252 drugs on the list of those regarded as basic and essential for global human health by WHO are derived from plants (Rates, 2001). Secondly, the drugs that are being developed are not for a global population, but for a privileged few in the developed and developing world who either have the health insurance coverage (private or national), or the personal financing to pay for a prescription product (and the research behind it). A major rethinking of our global priorities for drug discovery for health is needed to redress this health care imbalance.

Developing a drug beyond a certain stage is based on a marketing plan. At a strategic point in the development process, a pharmaceutical company must decide whether to invest millions of dollars in advanced pharmacological studies and eventually clinical trials. Numerous considerations come into play in making such a decision. One of those is whether the drug can reach a sales level of about $500 million within two to three years of introduction. Many potential new drugs are lost to further development at that decision gate. If the projected sales are not large enough, the compound will simply not be developed as a potential clinical entity. Consequently, unless these compounds are "rescued" as orphan drugs for development, and very few are, they will remain inaccessible (since they are patented and therefore must be licensed to be developed further) to the majority in the global health care system for whom they may be both useful and affordable.

With this very brief background, it is possible to imagine that as natural product scientists we are now deeply lost in the maze of drug discovery. That, with the continuous advances in chemical and robotic processing technology and the biotechnology of assay system development that we already may be too late to have an impact on the discovery process. The dedication (and success!) of the National Cancer Institute to bring natural products to clinical trials stands as a beacon, which the pharmaceutical industry has chosen to ignore for other disease states. With all of these issues, including the evolving situation with respect to access to the biome, it is tempting to think along the lines of completely divorcing the plant sciences from natural product drug discovery and development. As

we shall see there are other, more important reasons why we must be persistent now.

Visions for the future

First, it is time for our reality check. On one side, the population of the Earth is rising rapidly, the technology of drug discovery (bioassay systems, robotics, information systems) is continuously advancing, new diseases are appearing, and drug resistance is increasing. On the other side, oil supplies are diminishing and are expected to last only for another 70 or so years, and the biodiversity of the Earth's forests and oceans, and the indigenous knowledge associated with them, are disappearing at an alarming rate (Myers, 1988). As a result, we have some critical strategic choices to make for the future health of the Earth. Since we humans are an integral, not a separate, part of the Earth, our overall health as a human population has a direct correlation with the health of the Earth. I believe that it is essential that we find approaches to both drug discovery and traditional medicine that are sustainable. That will take vision. Much of the remainder of this article focuses on creating this new vision for the future of the natural product sciences and their impact on global health care.

When we speak of drug discovery involving plants we must think in terms of the options available for what constitutes a drug in various parts of the world. While some parts of the world are focused on the regulation of single drug entities, other governments regulate multicompound mixtures, single plant extracts and plant materials, and multiple plant extracts and plant materials. Thus our vision for the natural product sciences must embrace all aspects of these various approaches to the use of plants and other natural products as medicinal agents.

What is it that visionaries do? Some of the activities of visionaries include: communicating creativity and openness to change, doing what is right (as opposed to doing what is most expedient), being as truthful and honest as possible, trusting one's intuition that the pathway is correct, and developing a strategic plan. Over the years there have been many natural product scientists with deep visionary aptitudes. Dioscorides who compiled and recorded information on the medicinal use of plants so that it could be used more widely. Pelletier and Caventou who were the first to isolate important compounds from the then widely used medicinal plants. Kekule envisioned an oscillating ring structure for benzene, and Emil Fischer introduced the concept that organic molecules are not flat. Woodward had the vision that if you put your creative mind to it, you could synthesize any natural product (even vitamin B_{12}!), and Boyer and Cohen had the inspirational thought that DNA segments could be moved around. The American naturalist philosopher Ralph Waldo Emerson (1803–1882) was very clear about the negative impact of resistance or the inability to change or view a situation differently when he said "A foolish consistency is the hobgoblin of little minds". In drug discovery, I believe that we are at that point in terms of our long-term vision.

What are the basic visionary values that must be adopted for the natural products sciences? First of all, natural products must make a core contribution to the maintenance and enhancement of health care and to the efficacy of foods as nutraceuticals on a global basis. Secondly, there is a need to create value in people, in places, in plants, and in compounds. Finally, a strong vision is needed for the biology, the chemistry, the information systems, the technology and the biotechnology associated with the scientific developments related to natural products in the next twenty years. Some aspects of these areas have been discussed previously (Cordell, 2000a).

Fundamental to any meaningful work at the international level in the natural product sciences is the need to create alliances, both locally and globally. This topic was discussed previously in various formats (Cordell, 1990, 1993a, 1995a, 2000a). The need to set aside personal goals and aspirations for the greater good of the collaborative relationship and the research goals of the program have been highlighted as prime requirements for success. With instant internet verbal and video communications and the rapid transmission of results electronically, the ease of working between laboratories half a world apart is stunning. Alliances are of many different types (Cordell, 2000b), and all require frequent personal contacts and an openness as to what is required to make the program effective. Many of these alliances are operating formally or informally at the present time between academic institutions, although some Federally funded collaborative research programs do specifically require an industrial partner. In my estimation, there is a great need for other government research funding sources in Asia, Europe, and South America, as well as international funding agencies, to develop programs along these lines which can bring together academic and indus-

trial researchers to address national issues in a focused manner.

In Europe and the United States, the pharmaceutical industry has undergone convulsive change in the past 12 years (Thayer, 1998; Salvage, 2002), and this process continues with the recent Pfizer-Pharmacia merger to create the world's largest pharmaceutical company. As discussed elsewhere (Cordell, 2000a, 2002), this has and will continue to result in an even greater focus on certain diseases states and will increase the competitiveness for product development and approval. For a variety of reasons, in spite of their size, companies will not wish to embrace the plethora of scientific and technological areas in drug discovery and development within their corporate structures. As a result, there are numerous opportunities for small companies to interface with large corporations in various collaborative partnerships, sponsorships, and other outsourcing arrangements. Among these areas for collaboration is the development of selected libraries of natural product extracts and natural and synthetic (including combinatorial) compounds (Short, 2002), and the screening of corporate libraries against otherwise inaccessible bioassays (Borman, 1997, 2001; Thayer, 1998). There are numerous examples of these collaborative outsourcing relationships, and a corresponding number of financial arrangements, often depending on future development considerations. Some of these examples have been discussed elsewhere (Cordell, 2000a). One of the most recent corporate examples is that of Merlion Pharmaceuticals in Singapore, which has a unique and very large collection of natural product samples available for evaluation against corporate bioassays which are brought in-house under contract.

The most crucial aspect of such collaborative partnerships, be they short-term or long term, is that of access to technology, and consequently how to maintain leadership. This, in an environment in which the strategies for discovery, and the biological and analytical sciences which support them, are rapidly changing and evolving, and becoming increasingly expensive. Because much of this early discovery effort is highly speculative, and has only a very long term potential gain, the small number of very large pharmaceutical companies will increasingly see the breadth of the required effort as too high risk an investment to be doing in-house and will continue to outsource significant portions of the discovery program. In other words, there will be substantial opportunities appearing for companies which can provide a niche technology in the overall discovery effort, be that the biological aspects of the assays being used, in particular libraries of compounds, either synthetic, combinatorial or natural, or in the degree of automation, activity determination technology, or the processing of analytical results. Companies are also facing another very significant issue. While research and development expenditures have continued to grow to $30.3 billion in 2001, only 24 new drugs were approved by the U.S. Food and Drug Administration in 2001, a significant decline since 1996 when 53 drugs were approved (Salvage, 2002).

As discussed briefly above, the decline in the involvement of pharmaceutical industry in natural products, either as compounds or as extracts, is a very serious issue for a number of reasons, one of which is that many developing countries feel that they have at their disposal a vast storehouse of chemical and biological diversity which companies are highly desirous to investigate. While the first aspect is correct, the second is not. Unfortunately, those days are past, and as indicated above and elsewhere (Cordell, 2000a, 2002), pharmaceutical companies no longer see access to natural products from marine or terrestrial sources, whether collected on the basis of ethnomedical use or randomly, as having significance for their discovery efforts. To anticipate that this situation will change in the near future is not reasonable. Thus, while it is certainly within the rights of a country under the CBD to develop regulations monitoring who and how groups and individuals are accessing their biodiversity, the fact is that the demand for such access has declined substantially. Consequently, the economic arguments for maintaining biodiversity (Ehrenfeld, 1988; Randall, 1988), compared with a quick financial return for oil, gas, timber, range land, or mineral development, are becoming less valid. There are two approaches to this issue which would allow developing countries to potentiate the breadth of utility of their biodiversity. Both of these require the creation of value.

I have frequently quoted Emerson on this topic. In an essay on nature he said "What is a weed, a plant whose virtues have yet to be discovered?" He understood then what we are re-discovering today, that establishing the virtues of a plant, or of a marine organism, or a particularly rich ecological environment, adds value and is, inherently, an argument for protection and preservation. Consequently, demonstrating value in plants and in marine organisms, for medicinal and health purposes is a critical aspect of conserving the remaining biodiversity for future generations. It is

our responsibility to initiate the conduct of such global investigations, and these activities must begin locally, not in a far-flung laboratory in a developed country. Such an exploration will require two fundamental areas of excellence: places and people. For success to be achieved, these two facets must be brought together at the same time.

Creating value in places means linking the issues of conservation, research, and agro-industrial development in a way that enhances the real and the perceived value of an existing diverse environment. Various suggestions of how to achieve this have been offered (Wilson, 1988), including creating value in previously cleared land to grow building materials, so that the need to threaten biodiversity is reduced.

In the introduction, we saw how we have accumulated substantial knowledge regarding the biota of planet Earth. Yet in many ways we know very little about the potential of that biota to be an integral aspect of maintaining human health. Very few of the estimated diversity of fungi of the world have been catalogued; similarly, for many forms of marine animal and organism (Wilson, 1988). Therefore, one of the "gifts" that we can make to future generations is that of cataloguing and collecting type specimens, and of establishing gene and extract banks for future biological evaluation.

Very few countries in the world have a vertically integrated pharmaceutical industry; that is the ability to do drug discovery and then take a compound or concentrate through to a finished and approved product at the international level. Unfortunately, that situation is likely to remain for the foreseeable future as far as single compound drugs are concerned. However, as we have observed, most of the world uses plant materials (largely in an uncontrolled manner) as a primary source of health care, as well as for other personal hygiene products. There is a need for countries to be asking whether there is benefit to maintaining the *status quo* of importation for these natural products (including essential oils, perfumery and flavoring components), or whether there is the possibility to grow and extract any of these materials for local consumption, with an export market as the long term goal. What are the local issues which prevent such developments? How can countries develop programs for the production of their medicinal plants of commerce and develop a rational base for their standardization?

For this vision to become a reality, there will need to be local research centers of excellence where the infrastructure to pursue selected areas of the natural product sciences can be established. Such centers may take several years to develop, because they include both the buildings and the laboratories and offices, as well as the equipment and the information systems. There is the requirement for people who will set the priorities, design the experiments, do the work, interpret the data, and take the results to the next appropriate step nationally or internationally. Firstly though, there is the dire need for more persons trained to the Ph.D. level in the natural product sciences, and people with more advanced training to the postdoctoral level to lead the research programs. Specialized technology training programs in collaborating academic and industrial laboratories in developed countries, as well as on-site demonstration workshops are also needed.

What research will be conducted in these new centers of excellence? When we indicate work on plants here, it should be understood that, in principle, many of the same comments apply to studies of the marine environment. The first aspect is to recognize that there are numerous plant materials around the world which might be brought to commerce for the benefit of humankind, both locally, and internationally. This requires that the knowledge relating to these plants is available for consideration, i.e. collecting the information that is already in the public domain. If the knowledge is not published, it may be subject to local regulations enacted since the CBD regarding the use and development of indigenous knowledge. Safety and efficacy of traditional medicines are the highest priority to be investigated and established, particularly for those plant materials that are being marketed at the present time.

A full discussion of the impact of the Convention on Biological Diversity (CBD) on the natural product sciences is beyond the scope of this article, but it is apparent from the earlier discussion that the original intentions of the CBD are not being fulfilled. In fact there are many negative effects on the natural product sciences which have occurred as a result of the implementation of this Convention in various parts of the world. One of these, the withdrawal of investment by pharmaceutical companies in the global acquisition of plants was mentioned previously. The same is also true of academic institutions in developed countries which have either terminated relationships completely to focus on local plants, or have cut back substantially on the number of institutions with whom they collaborate for financial reasons. In our case, we have the time and the money to negotiate to collect plant materials and develop relationships with only two or three countries,

rather than the 28 countries with whom we used to collaborate.

With the sovereignty of the biota resting within the territorial limits of each country under the CBD, most states have now developed their own set of rules and regulations regarding issues that relate to access, to acquisition, to contemporary local development, to collaboration, and to future compensation rights. The application procedures to be granted permission to collect, and to reach a negotiated settlement for each of these countries are very different, the standards of performance are different, the value systems are often different, and the costs are different. Thus, development of the prior negotiated agreements required by the CBD can frequently be time-consuming, onerous for the many lawyers involved, and very costly. Personally, I do not believe that this was the intent of the Convention. Rather, the intended outcome was to *foster* interaction and *potentiate* relationships between developed and developing countries so that indigenous resources could be investigated for mutual benefit.

What is a reasonable vision for intellectual property issues for the future development of natural products? Firstly, there needs to be a harmonization within major regions of the world, of the processes and applicable regulations regarding access to the biome. Only in this way will there be some encouragement for academic and industrial groups in developed countries to collaborate. There must be a willingness on both sides, those who have the resources and those who wish to explore and potentially develop those resources, to initiate and maintain innovative agreements for the training of local personnel, for the establishment of local herbaria and research laboratories and for the distribution of royalty and licensing income (Soejarto et al., 2002). In addition, as Cox has recently pointed out (Cox, 2000, 2001), there is also ample opportunity to go beyond the minimum requirements and address broader social and economic issues, if the community so desires.

One aspect of the intellectual property issue also relates to information systems and the acquisition and correlation of ethnomedical uses of plants, since indigenous knowledge was explicitly included in the CBD. As a part of an international effort to rationalize the uses of medicinal plants, to optimize the scientific effort that is needed to bring safety and efficacy standards to certain widely-used plants, and to facilitate international commerce for those products, there is a need to collect and accumulate, in a non-profit environment, information on the uses of plants, on their biological activities, and on their constituents and their activities. Such information is exceptionally widely scattered, and is only partially available. Nevertheless, it is extremely important that such data is both accumulated to the extent possible, and made universally available. While the herbal pharmacopeias provide significant information on many plants in commerce in various countries, the need remains to see greater global harmonization of botanical, chemical, and biological standards of safety and efficacy.

We have seen that one of the most important aspects of drug discovery is the presentation of a diverse selection of compounds to a biological matrix in order to look for a response. Thus, one of the visions that we must hold for natural products is that their structures can be diversified. What are some of the available options for creating new natural products? The first is combinatorial chemistry. Relatively little work has been carried out on the combinatorial chemistry of natural products, in spite of the availability of a number of very good candidate molecules (Nicolaou et al. 2000). Combinatorial biosynthesis, the ability to move biosynthetic sequences either around in a single biosynthetic pathway, or between biosynthetic pathways, offers a myriad of potential new compounds for biological screening which have the advantage of being available for additional study should any of them prove to be of biological interest (Khosla and Zawada, 1996). A methanolic plant extract may contain 300–500 compounds, therefore another approach is to do chemistry on the plant extracts, such as reductions, oxidations, and hydrolytic reactions under different conditions to afford a whole new range of metabolites from an extract for biological evaluation (Cordell, 2000a). There are also two alternative sources of new natural products which are being actively explored. The first is the endophytic fungi and bacteria present inside the tissues of a plant (Tan and Zou, 2001). While the second source is the microbes present in soil which are difficult to culture, but which, through making eDNA cosmid libraries in *E. coli* and screening for viable clones, may produce biologically active secondary metabolites (Brady and Clardy, 2000).

What is our vision for natural products and drug discovery for the future? It is important to realize that drug discovery is a very inefficient process, and that of the 5,000 compounds which enter advanced pharmacological development only one will become a drug, and this from the prior screening of may be millions of compounds. This is very wasteful of both human and fiscal resources. For natural product extracts, there are

two important issues, one is that many plant materials, when recollected, do not confirm the original observed activity. The other is that many of the active principles isolated give rise to known active compounds. Although these compounds may be operating by novel mechanisms, synthetic modification is necessary to achieve patent protection, because the principal desire is for molecular novelty. One vision is therefore to be able to determine the active principle(s) in an extract without fractionation. Our approach to this issue has been to use a dereplication protocol (Cordell et al., 1997; Cordell and Shin, 1999). This has involved a HPLC/electrospray mass spectral/bioassay/database system using the NAPRALERT database to assess active extracts for known compounds. Only those extracts which indicate the presence of new active compounds are typically fractionated. Other procedures coming into application are HPLC/ESMS/NMR systems (Wolfender et al., 1998).

One can envisage that there will be increased automation, as well as an increased use of nanotechnologies and microarray systems, for the biological evaluation of chemicals (Smith, 2001) and their characterization (Henry, 2002). Microarray assay systems based on the enhanced knowledge of the human genome will be brought to the level of routine screening. This will have two effects on the screening process. The first is that the rate at which bioassays are introduced and discarded for new assay targets will continue to increase. Secondly, the range of disease states studied in the discovery stages at the major pharmaceutical companies will become even more focused, perhaps to the point where the discovery of new biologically active entities, whether large or small molecules, is almost completely outsourced. Natural products screening will have almost no place in this scenario, unless it can provide (probably from external sources) discrete molecular entities of high potency and/or unique structure. However, as we have alluded to previously, there remain numerous ways in which the natural product sciences can contribute very substantially to the global health care enterprise.

We discussed earlier the almost complete absence of consumer assurances with respect to plant materials used in primary health care and prevention on a global basis. For the traditional medicinal plants which are being brought to market at a steady pace, the quality control of those medicinal plants is typically very poor or non-existent. Consumers need to be assured of the authenticity, safety, efficacy, and shelf-life of any dietary supplement. Our vision must exceed these minimum standards. There is a need for programs which will provide complete literature evaluation, and determination and characterization of active principles in order to explore mechanism(s) of action. On a batch-to-batch basis there must be botanical, chemical, and biological standardization of products, and collateral studies which would establish both the safety of the product and a demonstration of its efficacy. HPLC/ESMS/NMR system developments will have a significant impact in the area of standardization. There is a significant need to collate the incidence and rationalize the potential for drug-herb interactions. Finally, the plant material(s) in a product must be made available on a sustainable basis, and not wild-crafted.

If we begin with botanical field work, I have indicated on several occasions (Cordell, 1990, 1995a, 2000a, 2002), that there is a tremendous waste of manpower and resources in bringing dried plant materials back to the laboratory for biological evaluation, unless the desire is to establish a library of plant extracts. Substantially more efficient is a process, similar in strategy to that used by many marine drug discovery groups, for the in-field biological evaluation of materials. There is a need to develop simple (in reporting capability), genomics-based tests for plant extracts so that when activity is observed, collection can take place of the same plant population. Consequently, it will be only those plants which show activity which will be collected, dried, and brought to a laboratory for further chemical and biological evaluation. Such studies would also require in-field access to large database systems, such as NAPRALERT, in real time to assess prior knowledge.

In order to investigate the chemical response of plants to infestation, substantial work has been directed at the use of random elicitors (such as jasmonic acid) to induce biosynthetic pathways (Ebel and Cosio, 1994). However, in spite of the numerous advances in understanding of the biosynthesis of natural products of plant and fungal origin, relatively little is known about two major aspects of these pathways, the genetics of the development of the pathways, in particular the enzyme systems which are responsible for the individual steps in a pathway, and the nature of the molecular "switches" which turn on and off the gene systems responsible for product formation. One illustration of this phenomenon is the propensity for plants in tissue culture to produce a group of metabolites not observed in the field-grown plant (Verpoorte, 1998). There is no single plant for which the full bio-

Table 1. Some Challenges for the Future of the Natural Product Sciences

• Catalog and preserve the bio- and chemo-diversity of the rainforests and the oceans
• Catalog the eco- and ethno-information on plants and their products
• Maintain equitable access to the biome and assure intellectual property rights
• Develop medicinal plant germbanks
• Develop integrated global information systems on medicinal plants
• Develop medicinal plants in a sustainable manner
• Enhance drug discovery technology in the areas of automation, genomics, and bioassay targets
• Develop genomics-based, in-field bioassays
• Optimize the chemical diversity of natural products
• Produce vaccines and drugs in fast growing secondary sites
• Assure the safety and efficacy of traditional medicines
• Develop integrated global alliances for plant product development
• Develop the facilities, the infrastructure and and the personnel to conduct the above programs

synthetic capacity to produce a diversity of chemical structures is known. If plants are to be "factories" for drug production in a reproducible manner, these molecular switches must be profoundly understood (Boonstra et al., 2001).

Beginning in the early 1990s, there developed a very substantial interest in the production of drugs, proteinaceous materials, and vaccines in secondary metabolic sites, such as fast growing plants or animals (Tacket et al., 1998; Burke, 2002). Under the appropriate conditions, and with carefully selected host and product target materials, this may well be a very significant way to meet the needs for drugs for large segments of the world population in the future, although there are significant concerns about cross-contamination with existing crops (Hileman, 2002). Such systems could have a significant impact on local situations regarding disease states or for vaccination purposes, if the technologies for their distribution can be transferred to the developing world through the establishment of centers of excellence. There are a number of advantages to using plants to manufacture recombinant drugs, including relatively low cultivation and operating costs, high biomass production, a relatively short time to go from gene to protein, quite good protein yields, and a low risk of pathogenic contamination. As a result, a wide variety of crops have been grown containing human proteins, including rice, soybean, corn, potato, tomato, tobacco, turnip, mustard, alfalfa, and bananas using stable and nuclear plastid transformations, and viruses for transient expression (Giddings et al., 2000; Daniell, 2001). Two enzymes, trypsin and aprotinin, both from bioengineered corn, are presently being scaled up in production (Hileman, 2002)

Mention has already been made of some aspects of combinatorial biosynthesis and how this might be a way to substantially enhance the number of compounds from a plant available for screening. Moreover, this strategy has the advantage (like that of fungal cultures) of being controllable in-house. In addition, there is the current use, which surely will be expanded, of genetically engineered hairy root cultures which are capable of conducting highly specialized transformations to produce important chemical intermediates and drugs (Boonstra et al., 2001). As a corollary to such an approach, there will be more diverse, and more rapidly growing systems used to produce the enzyme systems which might be used in the production of drugs. One example is the use of insect cell cultures to produce the primary enzyme in monoterpene indole alkaloid biosynthesis, strictosidine synthase (Kutchan et al., 1994). Such enzyme systems, which often can carry out reactions which have no counterpart in synthetic organic chemistry, will also be critical in conducting complex synthetic sequences comprised of multistep reactions over renewable enzyme systems integrated with wet chemical steps in a single reactor format.

We have already discussed many of the critical challenges which lie ahead for the future of the natural product sciences, and these are summarized in Table 1. However, there is a missing component: how will these goals be achieved? One of the visions which forms the core for future natural product science development is that countries will have an infrastructure that will allow them to develop their own sustainable medicinal agents from natural sources. The goal will be to

develop programs to assist countries to potentiate their resources, their facilities, and their scientists in order to evaluate and standardize natural product-based medicinal agents on a sustainable basis for their health care systems. My personal vision is that there will evolve in the years ahead a Global Alliance for Natural Product Development. Such an alliance will be composed of international agencies (WHO, UNIDO, UNDP, NATO, EU, etc), government agencies (NIH, NSF, NIE, SRC, DAAD, etc), pharmaceutical companies, academic institutions, non-government organizations (WWF, WRI, CYTED, TRAMIL, IFS, TWAS, etc), scientific societies (IUPAC, RSC, ASP, PSE, GA, JSPS, etc), and major foundations (Ford, Gates, MacArthur, Rockefeller, etc.). It will be an important component in the development of natural product based drugs for health care.

Conclusions

It was Ralph Waldo Emerson who also offered an important reminder about stewardship of the Earth "We did not inherit the Earth from our forefathers, we are borrowing it from our descendants". It is imperative that each of us consider what is the legacy for Earth that we are leaving our descendants. We must envision our sciences in the future when the pressures on available resources will be quite different. It is up to us to create these visions for the future, and maintain them for creative growth of individuals and societies. We must reconnect with the deep obligation that we have to the health care of those future generations. We must create innovative strategies for the natural product sciences in order to develop in a sustainable manner the foods and the health care products, including drugs, for an expanding global population. Finally, we must foster the development of multidisciplinary, international, collaborative research programs which are essential for the future health of the Earth.

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