Accepting Our Gifts from Nature - Now and in the Future. Part III

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"What is a weed; a plant whose virtues have yet to be discovered".

Ralph Waldo Emerson, Nature, 1836

In the first article in this series[1] we examined the history of the use of plant materials as drugs and as drug precursors. In the second article[2] we examined the role of traditional medicine in global human health care and the need for standards to be developed regarding the safety and efficacy of both traditional medicines and phytotherapeuticals. In this the third and final article, we will look onto the broad horizon and try to peer into the future and envisage what the role must be for natural products in global health care. In this sense, we must also examine the role of natural products in restoring and enhancing the health of the Earth.

In the past 150 years we have dramatically accelerated the erasure of entire ecosystems. If we believe that what remains at any given point in time is finite, and cannot be regenerated, then at the beginning of this new century we, the population of the world, must create a new ideology, one that does not assume unlimited resources. One that must be based on finite numbers of people and on finite resources. In 1978, Earth passed though the ceiling of sustainable capacity. At this point, the global population exceeded the capacity to be sustained by the known resources on Earth. Twenty-six years later, it should be quite apparent that a rebalancing of that equation is called for. Yet, as we have seen, UN estimates indicate that global population could be 10.7 billion by 2050[3]. One of the great challenges for humankind in the next 30-40 years will be to find creative ways to restore this balance.

It is time to do the mathematical calculations to establish what will be necessary to provide an increasingly satisfying, sustainable life for the population of Earth for the very long term future. What is the balance of renewable *vs.* non-renewable resources to support a successive population of 7, 8, 10 billion people on Earth? As we saw in the first article, to reach the levels of profligacy of the US for everyone presently on Earth would require the resources of four more earths! We humans are the leading biological force, and at this point a very negative one, on the planet. To not see that is to deny the impact that the deleterious aspects of our science and technology are inflicting on our precious environment. We have now to focus on the positive capacities of our very best science and technology, and use them for bioremediation, to re-establish, restore, and replenish our environment. It is only through the steadied and very environmentally conscious application of science and technology that we *may*, and I really mean *MAY*, be able to survive the next 50 years. We may not. We may run out of water to irrigate blighted croplands, cook foods, and sate savage thirsts. We may run out of usable land to house people and grow those crops. We may have too many drug resistant organisms, or too many new, virulent diseases, and no new, widely affordable drugs. Nature may take charge and do the rebalancing for us, as she has done throughout human history. It would, after all, be perfectly within Gaia to do so. The choices we make in the next ten years regarding our natural resources, including plants, may well decide our long-term viability as a thriving species.

The relationship between humans and plants remains inexorably delicate, one where the balance is constantly shifting towards depletion of the natural resources while the human population expands. All indications are that the number of plant species on the planet is declining at an increasing rate. Tragically, our knowledge of the potential utility of those plants being made extinct is zero. It will require quite different strategies for the exploration and development of biologically active natural products than those employed previously. It will require visionary scientists who can lead their colleagues towards more socially relevant, highly targeted efforts. And it will require a completely new approach to medicinal agents

in the developing world. These ideas are not being presented here for the first time[4-14]. But as the clock ticks and the time runs out, the urgency for change has become obligatory. There are no viable alternatives.

As briefly discussed in Part I in this series[1], the decline in the involvement of the global pharmaceutical industry in natural products research, either as compounds or as extracts, is a very serious issue for a number of reasons. Many developing countries feel that they have within their territorial sovereignty a vast storehouse of biological (and hence chemical) diversity which companies are highly desirous to investigate. At the present time, these pharmaceutical companies are actively disposing of their natural product libraries as they turn to other strategies which are currently deemed more effective for the identification of compounds as drug leads. Consequently, the global 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 any significance for their discovery efforts[1,10,13,14]. They *are* interested in natural products, but the conditions for such compounds to be drug candidates primarily focus on high potency, extremely selective activity, unique mechanism of action, and substantial availability before optimization through medicinal chemistry can be applied. It would be inappropriate to anticipate that this situation will change in the near (10 - 20 years) future. Thus, while it is certainly within the rights of a country under the Convention on Biological Diversity (CBD) to develop regulations monitoring who and how groups and individuals can access their biodiversity, the fact is that the demand for such access from direct commercial interests has declined substantially. As a result, the economic arguments for maintaining biodiversity[15,16], compared with a quick financial return for oil, gas, timber, range land, or mineral development, may well becoming less valid. Thus, biodiversity-rich countries will need to adopt new strategies in order to potentiate the breadth of utility of their assets through either internal or external investment. Only the most innovative strategies will lead to discoveries based on natural wealth which will serve the health of the community and be significant export products. These strategies require the creation of value.

In lectures and in writing, I have frequently quoted Emerson on this topic, and his wisdom is quoted again at the head of this paper. The context which he was describing was different. He was considering the development of commercial plants both as crops and as ornamentals, not medicinals, since, at that time, there was no organic chemistry which could serve as an alternative to plants as a source of drugs. However, he did understand then what we are re-discovering today, that establishing the virtues of a plant, or of a marine organism, or of a particularly rich ecological environment, adds value, enhances the quality of life, and therefore is, inherently, an argument for protection and preservation of existing biodiversity. That a particular area has not been botanically, chemically, or biologically evaluated is not a rationale to destroy it.

When medicinal plants, whether those used in traditional medicine or those developed for single agent drugs, have entered commerce, their value has steadily increased, both intellectually and economically. One needs only look at the number of citations concerning the genus *Taxus* in the years before the discovery of paclitaxel (taxol) and those today to see that paclitaxel, as vincristine did 20 years before, has inspired enormous amount of chemical and biological scientific interest, in addition to being a critical anticancer drug whose sales are approaching $2 billion/year. These plants (*Taxus* spp. and *Catharanthus roseus*) have followed the lines established for digitalis, opium, and cinchona, and for the perfumery and spice plants of commerce. Demonstrating value in plants and in marine organisms, for medicinal and health purposes is therefore a critical aspect of the rationale for conserving the remaining biodiversity for future generations. Ecological impact assessments are essential in most countries before any new commercial development in an untouched, forested area. In the future, botanical investigations should also have to presage rain forest destruction. This would parallel the archeological work that precedes building construction in many of the «old» cities of the world, where construction is underway over the ruins of previous civilizations. We should never again be faced with the situation where possibly the last member of a valuable medicinal plant species is lost to the construction of a parking lot[17].

In the first paper, we saw how, although we have accumulated substantial knowledge regarding the diversity of the plant biota of planet Earth, we know very little about the potential of that biota to be an integral and sustainable aspect of maintaining human health. However, very few of the estimated diversity of fungi of the world have been catalogued; similarly, for the many forms of marine animal and organism[3,18]. 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. While there are well-established germ-plasm banks for essential crops, there appear to be no major depositories

of the medicinal plants in the world. In the event of a catastrophic disaster, natural or otherwise, this could be a critical omission.

As natural product scientists, it is our responsibility to propose and initiate the conduct of the diverse investigations on all types of natural products, globally and locally. Such broad-based research activities must begin locally, not in a far-flung laboratory in a developed country, and be conducted by local scientists who have the health and welfare of their people and their country at heart. An exploration of this type, for new, biologically significant plants or other natural products will require two fundamental areas of excellence: places and people. For success to be achieved in such an endeavor, it is necessary that these two facets are brought together at the same time.

Creating value in places requires the determined linking of conservation, research, and agro-industrial development in a way that enhances the real and the perceived value of an existing, biologically diverse environment. Various suggestions of how to achieve this have been offered[3,18], including creating value in previously cleared land to cultivate fast-growing woods to serve as building materials, so that the need to threaten the biodiversity represented by hard woods in rain forest areas is reduced.

There are very few countries in the world which have a vertically integrated pharmaceutical industry, where a drug discovery program (natural or synthetic based) can take a compound or a concentrate through the complex chemical and biological stages 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 noted in the second paper[2], most of the world uses plant materials (largely in an unregulated and uncontrolled manner) as a primary source of health care, as well as for other personal hygiene products. Health ministries in countries around the world should therefore be asking whether there is long-term economic benefit to maintaining the *status quo* of the continued importation for these refined natural products (including essential oils, perfumery and flavoring components), as well as synthetic drug compounds, or whether there is the possibility to grow, extract, and standardize any of these materials for local consumption, using local expertise and technology, with the expectation of an export market as the long term goal. What are the local issues which prevent or hinder such developments? How can countries elaborate programs for the production of their medicinal plants of commerce and at the same time devise a rational base for the standardization of their traditional medicines?

For this vision of primary health care through the use of medicinal plants and their products to become a reality, establishment of local research centers of excellence is needed where the infrastructure to pursue selected areas of the natural product sciences can be located. Such centers may take several years to evolve and mature, because they include the buildings, the laboratories, and the offices, as well as the sophisticated equipment for compound isolation, characterization, and biological evaluation, and the information systems to support the collection and analysis of the acquired data. 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. Specialized technology training programs in collaborating academic and industrial laboratories in developed countries, as well as on-site, demonstration workshops are needed to enhance the background required to establish such programs. Some Pacific Rim countries are beginning to embark on such strategies.

What research studies will be conducted in these new centers of excellence? How will the technology be transferred to benefit society? When we indicate research on terrestrial plants here, it should be understood that, in principle, many of the same comments apply to studies of the marine and animal environments. But before there can be any vision of substantial program development, there is serious ground work which needs to be done on a global basis.

It is important to recognize that relatively few of the known plants (ca. 5.2%)[2] (there is an error in ref. 2 regarding this percentage) have been used in ethnomedical practices around the world, and of those only 60% have been studied chemically and/or biologically. Clearly, these are important plant materials for preliminary investigation as potential commercial entities, locally and internationally. This requires that the knowledge (ethnobotanical, chemical, and biological) relating to these plants is available for consideration. Consequently, the development of both local and global databases for the collection and analysis of the information on plants that is already in the public domain is essential. If the local knowledge is not published previously, it may be subject to state regulations enacted since the CBD regarding the accumulation, use, and development of indigenous knowledge. As we have seen

previously[1], the 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.

Herbal pharmacopeias also provide significant information on many plants used, and probably at some level approved for commerce in various countries. As pointed out, these pharmacopeias, as well as many new and ancient herbals, are an excellent source of potential new agents and products[19]. However, the need remains to see enhanced global harmonization of botanical, chemical, and biological standards of safety and efficacy of pharmaceutical products, so that international commerce in these products can be simplified and enhanced.

A second tier of plants for potential investigation are those that are being used currently in traditional medical practice, but for which the uses have not been recorded. That raises intellectual property issues as described in the CBD. Knowledge of the biota and its uses rests with the sovereignty of the territorial limits of each country under the CBD. As a result, 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 for biological samples within their international borders. The application procedures to be granted permission to collect, and to reach a negotiated settlement within 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 between an institution and several different countries, as 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* mutually supportive relationships between developed and developing countries so that indigenous resources could be investigated primarily for the benefit of the developing country concerned. Unfortunately, that is simply not happening. The capacity building efforts which occur through collaboration and the development of the centers of research excellence described above are not occurring because countries are promulgating onerous regulatory policies and procedures.

Is there a reasonable vision for the many 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 fully and effectively. There must be a willingness on both sides, those who have the resources and those who wish to assist in the exploration and potential development of 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[20]. In addition, as Cox has recently pointed out[21,22], there is also ample opportunity to go beyond the minimum requirements and address broader social and economic issues, if the local community so desires.

As indicated above, one aspect of the intellectual property issue also relates to information systems and to 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 substantial 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 through the NAPRALERT system[23]. Nevertheless, it is extremely important that such data is both accumulated to the extent possible, and made universally available. Only then can there be adequate data from which good decision making can lead to truly worthwhile research projects, without the unnecessary duplication of effort.

The future impact of natural products

Having examined briefly the resources and background needed to develop the research programs, let us now turn our attention to a vision for the natural products themselves. In the first paper[1], we saw 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. There are about 135,000 natural products known and characterized. They represent approximately 5,750 different skeleta. Of great significance from the perspective of interactions with enzymes and receptors is that even this limited number

of natural product structures represents substantially greater chemical diversity space and is more reflective of the chemical diversity space of drugs compared with the known range of combinatorial compounds[24].

Compared with the number of synthetic organic compounds available, there are relatively few natural products, and that number is increasing at a comparatively slow rate. Therefore, 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 or investigating previously unexplored sources for new structure types? Fortunately, there are several, all of which remain to be explored in depth (Table 1).

Table 1. Some Strategies to Diversify Natural Product Structures

- Combinatorial chemistry on strategic natural products
- Combinatorial biosynthesis (shifting the gene sequence)
- Move the gene sequence to faster growing organisms
- Chemistry on plant extracts
- Microbial transformation
- Potentiating the genes of biosynthesis to realize full metabolic capability
- Solid phase stable enzymes for structure modification and synthesis
- Plant associated and difficult to grow fungi and bacteria
- Use engineered hairy root cultures for valuable natural products
- Examine the 80% of plants which have not been tested chemically or biologically

The first potential strategy is combinatorial chemistry. There are several available approaches, but fundamentally the idea is to take a compound, which may or may not be active and modify it successively with several different types of functional groups. Surprisingly, relatively few studies have been conducted on the combinatorial chemistry of natural products, in spite of the availability of a number of very good candidate molecules[25-27]. Combinatorial biosynthesis is receiving substantial attention. This strategy for molecular diversification is based on the ability to move biosynthetic sequences either around in a single biosynthetic pathway, or between biosynthetic pathways. Depending on substrate specificity, it should be able to offer a myriad of potential new compounds for biological screening, and offers one important advantage: that they are readily available for additional study should any of them prove to be of biological interest[28]. A third, as yet untried, strategy is to conduct chemistry on plant extracts. A methanolic plant extract may contain 300-500 compounds, probably in at least half a dozen or so structural classes (alkaloids, flavonoids, coumarins, lignans, various terpenoids, etc.). These metabolites are likely to contain the full diversity of functional groups (alcohols, ketones, esters, double bonds, amides, amines, etc.) and many heterocyclic nuclei. Activity may have been observed in the extract, or, in the particular assay(s) being used, no activity may have been observed. It doesn't matter. The approach is to do solution-based chemistry on the crude 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[10,13]. There are also two alternative natural 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[29]. 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[30].

Yet another approach to enhancing the number of known natural products is to determine the full biosynthetic potential of a particular organism. When a plant is collected in its natural habitat, it is usually done at one instant in time in the life of a plant which may span several years or more. Thus, the metabolites noted in the plant are those which have been produced and are being stored at that time for various reasons (e.g. protection from predators), or for which the next step in a biosynthetic pathway is slower than the previous one. However, we know that when a plant is challenged with a microbial infection, it often produces compounds, phytoalexins, to combat the infection. These compounds are not normally seen in the chemical profile of the plant; for unchallenged by the infection, these inducible biosynthetic pathways remain dormant. Random elicitors (such as jasmonic acid) have also been used to induce biosynthetic pathways in plants and produce a hitherto unseen range of secondary metabolites[31].

It is not yet possible to control these biosynthetic systems to produce either specific metabolites or a full metabolic profile, as desired. There have been numerous advances in understanding the precursors and the pathways for the biosynthesis of natural products of plant and fungal origin. Yet 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 complex, multistep pathway, and the nature of the molecular "switches", the transcription factors, which turn on and off the gene systems responsible for making those enzymes available.

One interesting illustration of this phenomenon of biosynthetic pathway control is the propensity for plants in tissue culture to produce groups of metabolites that are not observed in the field-grown plant[32]. In addition, when media conditions are changed fungi, bacteria, and plants frequently produce a different set of metabolites in cultured systems. There is no single plant for which the full biosynthetic capacity to produce a diversity of chemical structures is known. Until we can characterize the genes associated with particular biosynthetic pathways and screen for them in the DNA of the plant, we will not be aware of the potential biosynthetic capacity of the organism. Thus, for several reasons, including chemical diversity and optimum productivity reasons, if plants are to be effective and reproducible «factories» for drug production, the molecular switches which control the overall pathway and the specific enzymes involved in secondary metabolite formation must be profoundly understood[33].

Biocatalysis, the use of isolated enzyme systems to conduct a diverse array of chemical transformations, is another approach to enhance natural product structural diversity. Formerly, the materials used in these reactions were quite crude enzyme preparations with limited and somewhat unpredictable reaction outcomes. Increasingly, these systems are preparations expressed in heterologous hosts which can carry out a very specific reaction to achieve a targeted goal in good yield, and which can be used in commercially significant synthetic sequences. The substantial advantage is that reactions which have no parallel using synthetic organic reagents can be conducted in high yield[34].

Less than 20% of all plant species have been evaluated chemically or biologically[2]. And what of the biological evaluation of those natural products derived from the studied plants? We have already mentioned some of the issues related to extracts and compound libraries. But there is another facet which has arisen because of the long-time separation of chemistry and biology. Of the approximately 21,200 alkaloids, 76% have never been evaluated in a single bioassay[35]. This startling statistic was discovered as we were examining how many of the known alkaloid drugs had been tested in a broad array of bioassays. It is quite possible, although as yet it is not established, that this lack of biological evaluation may be quite general across the range of natural products. Some pharmaceutical companies do have collections of 1000-2000 natural products which they screen as a part of their compound library when a new bioassay is brought on-line, but of course these data are never published. Consequently, in general terms there is a very substantial opportunity to evaluate almost any natural product against a new assay in the search for new potent compounds or new mechanisms of action.

It is well-established that drug discovery for a single agent drug is a very inefficient and extremely expensive process. The costs of going from discovery to market and beyond are probably in the region of $800 million to $1 billion. 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. Even at the clinical trial stage, only one compound in ten will be marketed[36] and productivity, in terms of FDA approved drugs, is decreasing steadily. For example, whereas 34 New Molecular Entities were approved as drugs by the US Food and Drug Association in 1999, only 21 were approved in 2003[37]. This is extremely wasteful of both human and fiscal resources. As we have seen, the companies are screening millions of samples from their compound libraries, yet there are nowhere near even a million natural products characterized So against these odds what can be our vision for natural products in the area of drug discovery for the future? One of the industry complaints about natural product extracts in drug discovery screening programs is that many plant materials, when recollected, do not confirm the original observed activity. Another significant problem is that many of the active extracts on bioactivity-directed fractionation afford only known active compounds. How can the natural product sciences respond to these challenges?

Initially, compounds from natural sources will only be of interest to pharmaceutical industry if they are operating by novel mechanisms, because synthetic modification is necessary in order to achieve molecular uniqueness for patent protection. To overcome this obstacle, there is the need to determine the active principle(s) in an extract without fractionation. Several years ago we developed an approach to this issue using a dereplication protocol[38,39]. The technique has involved a HPLC/electrospray mass spectral/bioassay/database system using the NAPRALERT database to assess biologically active extracts for known compounds. Only those extracts which indicate the presence of new active compounds are typically fractionated. Other procedures which are being applied include HPLC/ESMS/NMR systems[40].

How will we strategize the biological evaluation of the thousands of plants for which there isn't even a single bioassay data point or a compound isolated? We must begin in the field. 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[4,7,10,13]. 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 and robust (in reproducible reporting capability), proteomics-based tests for plant extracts. Then, when activity is observed in an extract obtained on-site, collection of the same plant population can take place. In such a program, only those plants which show activity in a particular bioassay 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 botanical, chemical and biological database systems, such as NAPRALERT, in real time, to assess prior knowledge regarding the plant in question.

Three trends, automation, nanotechnology and proteomics, will have an increasingly important impact on drug discovery in the next ten years, and thus natural product scientists must be prepared to use them appropriately[41,42]. Microarray assay systems based on the enhanced knowledge of the human genome will be brought to the level of routine screening of extracts and compounds in order to assess genetic impact. 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 to those with the discovery resources. Natural products screening will almost certainly have no place in this scenario, unless it can provide (probably from external sources) discrete molecular entities of high potency and/or unique structure and mechanism. In addition, the diseases/conditions being studied will not be those affecting mortality in most of the world[2]. We should see this as *the* challenge, the development of drugs for the majority of the world. It is only one of numerous ways in which the natural product sciences can, indeed *must*, contribute very substantially to the global health care enterprise.

In paper II[2], the almost complete absence of consumer assurances with respect to plant materials, traditional medicines, and phytotherapeuticals, used in primary health care and prevention on a global basis was discussed. For the traditional medicinal plants which are being brought to market all over the world as phytotherapeuticals at a steady pace, the quality control is typically very poor or non-existent. It was mentioned how consumers need to be assured of the authenticity, safety, efficacy, and shelf-life of any phytotherapeutical or traditional medicine being sold. It is the responsibility of the natural product sciences to challenge the *status quo* and effect that change.

Our vision for the future of plants in primary health care must substantially 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 routine standardization. There is a very substantial need to collate the incidence, and rationalize the potential, for drug-herb interactions, and to make the patient and the diverse health professions involved fully aware of these risks. As we learn more about the effects of traditional medicinal plants on the human genome through microarray analysis, both the positive and negative attributes will be clarifies. Also, it will become clearer the difference in effectiveness between the pure active compounds and the whole or selected plant extracts. Finally, the plant material(s) in a product must be made available on a sustainable basis, and not wild-crafted[2].

Beginning in the early 1990s, a very substantial interest in the production of drugs, proteinaceous materials, and vaccines in secondary metabolic sites, such as fast growing plants or animals, developed[43,44]. Recently, the successful production of the chloroplast expression of a tetanus vaccine antigen, Tet C, was described, and its effectiveness in confering resistance to Tetanus infection in mice was demonstrated[45]. 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[46]. 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[47,48]. Two enzymes, trypsin and aprotinin, both from bioengineered corn, have been scaled up in production[46]. Issues and legitimate scientific concerns regarding genetically altered crops would need resolution.

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. This strategy also has the advantage (like that of fungal and bacterial 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[33]. 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[49]. 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 targeted towards drugs. One can imagine multistep reaction sequences using a selection of renewable enzyme systems integrated with wet chemical steps in a single reactor format.

We have presented several of the critical challenges which lie ahead for the future of the natural product sciences, and a selection of these is summarized in Table 2. However, there is a missing component: how will these goals be achieved? An essential vision, one 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 international foundations (Ford, Gates, MacArthur, Rockefeller, etc.). It will be an important component in the development of natural product based drugs for health care.

Table 2. 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 natural product drug discovery technology in the areas of automation, proteomics, and bioassay targets
- Evaluate the known natural products in diverse bioassays
- Develop proteomics-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 the personnel to conduct the above programs

Conclusions

"In wilderness is the preservation of the world" *Henry David Thoreau*

The thin mantle of the biosphere that covers the Earth and supports our survival is the largely unappreciated miracle in all of our lives. That we are destroying it before we can fully savor it and learn its uses, is the ultimate, unforgivable folly. It was Ralph Waldo Emerson who 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. Is it one which represents our folly, or is it one of thoughtful caretaking? We must continually envision the natural product 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 the creative growth of individuals and societies. We must reconnect with the deep obligation that we have to the food supply and to the health care of those future generations. We must create innovative strategies employing

all of the associated sciences and technologies in order that the natural product sciences can assist in the development, in a sustainable manner, of the foods and the health care products, including drugs, for a dramatically expanding global population.

Finally, we must foster the development of multidisciplinary, international, collaborative research programs which will support global scientific development and which are essential for the future health of the Earth.

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