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Natural Products and Traditional Medicine: Turning on a Paradigm

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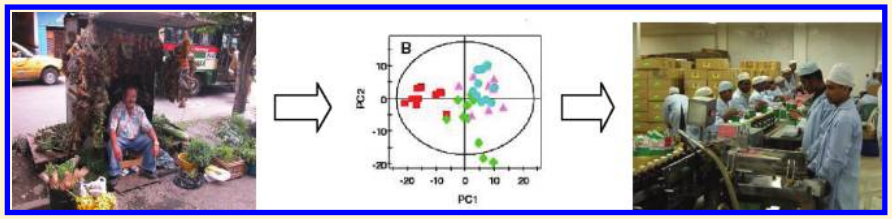

ABSTRACT: Paradigm shifts in the strategies and the sciences that would enhance the quality, safety, and efficacy of traditional medicines and dietary supplements in global health care are discussed. Some of the challenges facing traditional medicine in health care are described, and the importance of defining clear goals and directions for the information systems, botany, chemistry, and biology related to plants and health care, including for drug discovery and quality control, is indicated.

INTRODUCTION

There is the Zen story told by the Nobel Peace Prize nominee Thich Nhât Hạnh about a peasant who is carefully planting rice in his field.[1] He hears a horse and rider approaching rapidly along the path and sees that it is the King with his entourage stretched behind him trying to keep up. "Sire, Sire!" exclaims the peasant. "Where are you going at such a pace?" "I don't know", cried out the King, "Ask the horse". In the relationships of natural products, traditional medicine, and health care, that tale seems to describe the contemporary situation.

If the "horse" is burgeoning information, science, and technology related to natural products and health care, and we are the "peasants" seeking quality health care, and NIH, NCI, NCCAM, WHO, international funding agencies and governments, and philanthropic foundations are the "King", then where are we headed at such a pace and for what, and whose, purpose with respect to traditional medicine and dietary supplements? Is someone directing the "horse" to do the right thing for the health care of the "peasants"? Does the "King" have a strategic direction for health care? At this time, it seems not to be the case. So the question remains pertinent: "Where are we going at such a fast pace?" This review will not (indeed cannot) answer that question. All it can do is to acknowledge the pace of the "horse" and offer some paradigm shifts that might attract the "King" to rein in the "horse" and perhaps follow a more mindful and considered direction toward the greater involvement of natural products as a future partner for global health.

In a recent article,[2] one of us discussed the importance of the development of plant medicines as a key to global health and presented an overview of some aspects of the possible future role of chemistry in traditional medicine. The present article is an expansion of some of those ideas, with a focus on the development of new strategies for traditional medicine in the future. Several other recent articles have examined aspects of the sustainability of traditional medicines and the integration of various new technologies into traditional medicine research.[3−7] Global health in this context means both the health of the planet and the health of the people on the planet. These are not separate issues, since we are one large, deeply interwoven, totally vulnerable organism.[8,9]

Globally, over one billion people lack access to health care systems, and HIV/AIDS, tuberculosis, malaria, and typhoid kill about 4.8 million people each year.[10] It has been recognized for many years that there are vast "gaps" in numerous parameters of worldwide health care.[11] Examples include the tremendous "gaps" that are reflected in the per capita expenditures by countries on health care as indicated by the UN Development Program (Table 1),[12] the number of trained physicians per thousand population in various countries,[13] and the overall global access to medicinal agents,[14−16] including those for rare diseases.[17,18]

"Access" in this context may have several interpretations, including (i) Are there prevalent diseases in a country for which drugs are not available at all? (ii) What are the diseases for which drugs are available globally, but are either too costly or not available locally? (iii) What are the diseases for which there is known drug resistance to existing treatments? (iv) Finally, there is the facet of access relating to the global sourcing of medicinal plant materials and the long-term sustainability of a disappearing forest as a source of medicinal agents. Individually or collectively, these factors can form the basis for rationalizing

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Table 1. Government Expenditures on Health per Capita (2006) in US $[12]

Norway	3780	Iran	406
United States	3074	Brazil	367
United Kingdom	2434	South Africa	364
Australia	2097	Peru	171
Czech Republic	1309	China	144
Republic of Korea	819	Philippines	88
Argentina	758	India	21
Costa Rica	565	Nigeria	15
Turkey	461	Myanmar	7

the intense need for highly targeted new drug discovery programs and for placing that rationalization in a conservation and sustainable development framework. Access to health care, and to medications in particular, is consequently a global concern for all, with the possible exception of the very wealthy. However, even in the United States in 2011, the Food and Drug Administration (FDA) has reported record supply shortages of critical anticancer drugs, such as doxorubicin, cytarabine, and cisplatin, and the atrial fibrilation drug digoxin, threatening access and patient care.[19]

An economic chasm exists between the health care offered by the developed and developing economies, as well as in the health care system between rich and poor within developed nations such as the United States. Indeed, a study of the countries with the widest income gaps between rich and poor rated the worst five countries as Hong Kong, Singapore, the United States, Israel, and Portugal.[20] In the Philippines, 27 million of the 90 million people live on less than a dollar a day. Health care accounts for only 3% of the Gross Domestic Product (GDP), 2% less than the WHO-recommended level, and the situation is deteriorating as privatization of rural health care facilities continues.[21]

In a recent article,[22] a number of projections for global health outcomes were offered for the period 2005 to 2060. Deaths from communicable diseases are anticipated to decline by 50%, while deaths from noncommunicable diseases (NCDs) are projected to nearly double. If there are only one billion additional people on Earth by 2060 (an improbable scenario), then the GDP per capita could rise by 20%. Dramatic changes in life-expectancy for both males and females are anticipated, particularly in sub-Saharan Africa and Southern Asia, with the former change from about 52 years currently to 68 years in 2060, being attributed to a significant decline in HIV/AIDS-related mortality. The demand for drugs for this expanding and aging population was not addressed, but clearly it is a very significant factor, with respect to both the volume required for noncommunicable diseases (NCDs) and access.

Medical research is a very big business, and global spending is probably around US $110 billion at the present time. However, 90% of this spending is for the health problems of 10% of the global population,[23] and, as WHO noted in 2003, less than 1% of new drugs in the previous 25 years were developed for the diseases of the poor. True innovation in drug development is also lacking, with studies in the United States, France, and Canada showing that over 75% of the approved drugs showed no added therapeutic benefit, and only 5% were "breakthrough" drugs. In addition, there is a well-known and widening "gap" between research investment and approved drugs in the major pharmaceutical companies.[23] Yet, over the past 25 years, and in spite of their historical importance in drug discovery, the role of natural products has diminished significantly in the early stages of the discovery process in the pharmaceutical industry. Ironically, several recent articles have highlighted the importance of natural products in the drug discovery process[24−27] and described their continued success in contributing important molecules to the drug development pipeline.[24−31] As pointed out several years ago,[32] the alkaloids that are prescription products provide (with classic exceptions such as vincristine and paclitaxel) an excellent fit to the Lipinski "rules of five".[33] More recently, this strategy has been inverted, and natural product-likeness scores have been developed for the prioritization of large compound libraries for preliminary drug screening.[34]

Fundamental to the future of the availability of appropriate medicinal agents in global health care is another of the medicine-related "gaps". This "gap" relates to two important questions: What are the global health care needs for medicinal agents? And what is contemporary drug discovery in the pharmaceutical industry targeting? The "gap" between these two responses is significant philosophically and practically for what it says about products 10−15 years from now, and is expanding. This is reflected, in part, in the area of the neglected diseases that have such a dramatic effect on disability adjusted life years (DALYs) and on economic development.[35] Although it causes no deaths, according to the WHO, lymphatic filariasis has a global burden of over 5.6 million DALYs,[36] while malaria has a major negative economic impact on economic productivity and growth.[37]

The global health needs for over 1 billion people on Earth include treatments for trypanosomiasis, dengue fever, leishmaniasis, malaria, schistosomiasis, tuberculosis, Chagas' disease, leprosy, lymphatic filariasis, onchocerciasis, HIV-AIDS, hepatitis C, diarrheal diseases, ascariasis, rabies, yaws, and necatoriasis. However, contemporary drug discovery areas in the major pharmaceutical companies have been winnowed to antivirals, oncology, metabolism, central nervous system ailments, and inflammatory diseases.[38] Except for HIV-AIDS, which also impacts developed country populations, the disconnection between global drug needs and the application of discovery resources is staggering.

The 2006 WHO Commission on Intellectual Property, Innovation and Public Health (CIPIH) demonstrated that drug innovation has declined in both quantity and quality and that patent protection in developing countries did not boost innovation.[39] The Commission called for new models to encourage research and development to respond to real health care needs (as opposed to developing lifestyle or "me-too" drugs) and suggested a plan of action for funding drug discovery for diseases of the developing world. Medicins Sans Frontieres through its Campaign for Access to Essential Medicines has also called for a "shake-up of the way that health research and development is funded and prioritized" including a "new global framework to support needs-driven research...that prioritizes the greatest medical needs, and ensures that innovation does not happen at the expense of access to medicines".[23] WHO's Intergovernmental Working Group on Public Health, Innovation and Intellectual Property has proposed a Medical Research and Development Treaty, similar in construct to the Kyoto Protocol, based on a credit trading system. However, this idea has been severely criticized as being impractical at many different levels of bureaucracy, implementation, and enforcement, and too cumbersome and

complex to meet contemporary needs in an appropriately simple and direct manner.[40]

Partnering between drug companies and nonprofit agencies and foundations has been one of the responses to addressing the global issues of neglected diseases.[41,42] The Gates Foundation, the Rockefeller Foundation, the Wellcome Trust, and companies such as Novartis, GlaxoSmithKline, Merck, and Johnson and Johnson have all developed various forms of partnerships with groups around the world, and, as a result, over 65 drugs and vaccines are in various stages of phase I and phase II clinical trials at a cost that is a small fraction needed for normal drug development.[42] These initiatives have led to some investment in facilities in several parts of the world, including Singapore, Bangalore, India, and South Africa.[41] However, who will pay for large phase III trials is not always clear and may be a stumbling block to an actual product. Perhaps more significant, though, is the issue of whether a model for drug discovery and development such as this, which is based over 80% on philanthropy, is sustainable.

There are two other significant issues with these partnership developments, namely, the significant costs of the final products (single-agent synthetic drugs and vaccines) and their overall sustainability. More disturbingly, they follow a discovery model that has voided natural products from consideration, and the basic model of placing and maintaining a drug on the truly global market is probably not realistic and is unlikely to be sustainable in the long term. One only has to recall that the world's most widely administered drug, aspirin, is not globally available. Plants, in many forms and with many advantages and disadvantages associated with them (*vide infra*), are available and are a potentially sustainable, local drug resource.[3−5,7]

"Mind the Gap" is the sign on the platform and the verbal admonition all over the London Underground system, the "Tube". In this way, passengers are advised to avoid falling into the space between the train and the platform. "To mind" has three clear meanings however: to take care, to take care of, and to be caring about. One of our responsibilities, as natural product scientists, is *to care about* that global "gap" for medicinal agents. Many aspects of that "gap" are not related to science directly. Yet, as discussed subsequently, there are many opportunities for natural product scientists to have a profound impact in some of the areas relating to the issues of access indicated above. For this to occur, some paradigm shifts are needed, both within the natural sciences and outside. Only the former will be discussed in this article.

Pharmacognosy is defined as "the study of biologically active natural products".[43] A paradigm is defined as "a set of assumptions, concepts, values, and practices that constitutes a way of viewing reality for the community that shares them, especially in an intellectual discipline". So what is being discussed here is changing the very core, the raison d'être, of pharmacognosy, the assumptions, concepts, values, and practices in the community of natural product sciences, and, as a result, positively impacting global health in a more direct and practical manner. We discuss this in the context of rapidly declining forests in the most biodiverse areas of the world, which are the main source of traditional medicines, and the rapidly rising global population of 7.14 billion now, possibly rising to 10 billion by 2035.[44]

The top killer diseases in the middle- and low-income countries are HIV/AIDS, lower respiratory infections, diarrhea, hepatitis C, childhood diseases, malaria, and tuberculosis.[10,23,45] With the exception of the HIV/AIDS initiatives within these countries,[23,46] traditional, plant-based medicines are typically the only treatments available. However, for any one of several reasons, these medicines lack the quality and the scientific evidence for safety and efficacy. The earlier article[2] questioned the moral compass of the sciences of chemistry and biology for the forthcoming years; does the "King" have a appropriate and ethical science-based direction for global health care? These sciences are the basis for drug discovery and development and, with botany, constitute three of the four "pillars" for the quality control of traditional medicine and of dietary supplements, and for natural product drug discovery.[4−7] Pragmatically, one paradigm shift is not going to occur, since the pharmaceutical industry will not focus on developing medicinal agents for the whole world. Developing countries need to grasp and fully comprehend the implications of that message very clearly and act accordingly to secure effective medicinal agents for the long-term health care of their populations.

So who are the stakeholders, the "Kings", who will lead the endeavor and participate financially and scientifically in discovering and developing drugs for the majority of the world over the next 10−20 years? Before we address that question, it is important to explore some paradigms that need to be shifted. There are several: in this article we will discuss five.

THE SHIFT TO SUSTAINABILITY

Earth's resources are limited. Even though there are certainly adequate resources for the contemporary provision of synthetic and natural drugs, it would be false to presume that 20 or 30 years from now those resources will still be available, at an affordable price, for a markedly enhanced global population. Already a number of cancer treatments (e.g., brentuximab vedotin, sipuleucel-T, and ipilimumab) are marketed at a cost of more than $100,000 for a treatment regimen.[47] Strategies are needed that will encourage rethinking the responsibilities we have to use our resources wisely and to consider how drugs will be derived synthetically, semisynthetically, and naturally in the future. Hence the first paradigm to be shifted is the assumption that resources will be available in the future to provide access to needed medicines, synthetic or natural, will be enhanced globally, and will not decrease. This involves bringing to drug discovery, drug development, and drug production the concept of sustainability.[2−5,7]

Medicines that have gone through the long (10−20 year) approval, registration, and postmarketing surveillance process, as well as traditional medicines and dietary supplements that have been evaluated in an appropriate manner clinically for safety and effectiveness, should be regarded as a sustainable commodity. Prescription products, over-the-counter medicines, or plant-based drugs should be synthesized or resourced in as sustainable a manner as possible. Efforts are already ongoing to re-examine the processes for the production of synthetic drugs and to make those processes more "green".[48−50] Long-term, this approach probably will not be adequate, but it is a philosophical start to change the way people are thinking about medicinal agent resourcing. Synthetic organic chemistry will need to rethink its strategies and focus more sustained efforts toward the use of renewable systems for key synthetic procedures and, eventually, for a complete reaction sequence. The challenge will be how many enzyme modules can operate sequentially toward a product without the requirement for isolation and purification of intermediates. Considerations toward production will undoubtedly demand the use of

multiple enzyme systems as key reagents, and such strategic considerations may control the nature of the initial products that are screened in synthetic compound libraries.

Nature, through the use of exquisite enzyme reaction sequences, conducts many chemical transformations with high regio- and stereospecificity in the formation of secondary metabolites. An understanding of these processes in plants is in its infancy at this time, but one can imagine that fifteen or so years from now plant enzyme systems, as well as those from microbial sources, will be within the chemical armamentarium of synthetic chemists. The key element, as with many enzyme systems, will be the observed substrate specificity.

It may not always be necessary to isolate the enzymes responsible. In a recent review, we discussed the progress that has been made toward the use of whole plant systems for conducting synthetic organic chemical reactions.[51] One of the areas studied is for the reduction of aldehydes, prochiral ketones, and unsaturated ester systems. Whereas traditionally heavy metal chiral catalysts or expensive chiral reagents are typically used, the same transformations can be achieved with cheap, renewable reagents from common vegetables, such as cassava, coconut juice, sugar cane, and carrots. More research is needed, and correlation with the biosynthetic transformations known to occur within a given plant material would permit the consideration of a broader range of reductions, oxidations, acylations, alkylations, aminations, etc. The question of a natural "Diels-Alderase" has been pursued for many years.[52−55] Such an enzyme system would also be a useful synthetic, renewable, and low-energy alternative to many Diels−Alder reaction procedures.

The concept and practices of sustainability must also be applied to various aspects of the study of traditional medicine. Approximately 85% of medicinal plants sold are collected indiscriminately from the field; many essential medicinal plants are consequently under threat or, in some cases, are no longer available.[56] Thus, it is important to evaluate how changing ecosystems are modulating the availability of plant-based medicines, particularly at a time when changes in climate are occurring in many parts of the world. Overharvesting of medicinal plants may have a profound and deleterious effect on critically needed resources.

Medicinal plant sustainability is an essential component of thoughtful long-term health care strategies and should be on the agenda for discussion of many countries at this time. Several other aspects of the study of traditional medicines also have an impact on sustainability from the perspective of reducing the use of unnecessary plant materials, since reducing plant usage, while maintaining health benefits, is an important strategic direction.[4−7] Sustainability considerations are evident in three main areas of traditional medicine usage: (i) Are all of the plants absolutely needed in a multicomponent system, and has this been established experimentally? (ii) Are extraction techniques as efficient as they can be to make optimal use of the active principles of traditional medicine plant materials? and (iii) What is the correlation between the age of the plant material and its biological activity? Some would indicate that an older plant has reduced biological activity, but in very few cases has this been determined through experimentation. The possibility also exists that for a number of reasons the activity of a plant could increase with age.

THE SHIFT OF DRUG DISCOVERY TO GLOBAL DISEASE NEEDS

Earlier, discussion focused on the "gaps" that have occurred between drug discovery programs and global disease needs and how, while some research partnerships are under way to bridge those "gaps", these efforts remain inadequate to meet the needs. A reminder that only 20 of the 1556 new chemical entities marketed globally in the period 1975−2004 were for either tropical diseases or tuberculosis may be made here.[23,24] Natural product chemistry has played a minimal role in providing or improving the medicinal agents for the majority in the world, whether one is considering single-agent drugs or traditional medicines. The outcome is that many major diseases in the world desperately need a drug pipeline. However, it is well recognized that funding for discovery research on these diseases is inadequate by at least several billion dollars per year. As mentioned, there have been some partnerships developed; however, these are typically between pharmaceutical companies and nonprofit organizations in the developed world, and, with rare exception, the research is conducted mostly there. That does not help the middle- and low-income countries develop their infrastructure to be able to address their local disease issues. Yet a number of countries would appear to be ready to participate in a global commitment to become part of the drug discovery research process, if afforded the opportunity.

New international initiatives for natural product drug discovery are needed to develop a more structured, well-funded, broader-based approach based on evidence-based traditional medicines. Innovative collaborations and partnerships must form across the developed−developing world divide and between developing countries. Such collaborations can provide local infrastructure, information systems, people, and, most importantly, funding and long-term commitments in order to promote local and regional drug discovery initiatives using indigenous knowledge. Programs must also build commercial capacity and develop appropriate protections for intellectual property rights. A high priority will be resolving the conflicts centered on intellectual property rights between the Trade-Related Aspects of Intellectual Property Rights (TRIPS) Agreement and the U.N. Convention on Biological Diversity (CBD) (which remains unratified only by the U.S., Andorra, and the Holy See). Who owns the intellectual property rights, the sovereign country of origin (usually a low- or middle-income country) or the developer of the invention (often in the developed world)? Can sharing rights to the invention be a "win-win" situation? The impact of the CBD, and the relationship to TRIPS, as well as the experiences in several countries around the world with implementation of the CBD and the effects that has had on natural product research have been reviewed by one of us.[57]

On October 29, 2010, the "Nagoya Protocol on Access to Genetic Resources and the Fair and Equitable Sharing of Benefits Arising from Their Utilization to the Convention on Biological Diversity" was adopted under the auspices of the CBD.[58] It is an instrument for the implementation of the access and benefit-sharing provisions of the CBD. Only those countries that have signed and ratified the CBD are eligible to sign or ratify the Nagoya Protocol. As of December 29, 2011, 72 countries had signed the Nagoya Protocol, but none had ratified it as yet.

The primary focus is on the equitable sharing of benefits and the requirements of signatory nations to develop procedures for

implementation and regulation of the CBD, with a specific requirement for the issuance of permits with respect to permission granted for access to either genetic resources or indigenous knowledge. The Protocol establishes an international Clearing House under the CBD secretariat to assist countries with respect to developing various aspects of their implementation process. It also requires countries to deposit appropriate records and information from their country with the Clearing House for common availability. Specific issues relating to trans-boundary situations must be discussed in instances where indigenous groups overseeing knowledge or resources are not located in a single country.

Ratifying countries are now required to ensure legal certainty, clarity, and transparency, both legislatively and in the implementation of regulatory requirements, such as applications for prior informed consent. Countries must also provide effective communication systems during periods of application evaluation. Permits that are recognized internationally will be issued by the recognized national authority for approved programs in a country based on prior informed consent and mutually agreed terms. This information will be provided to the newly established CBD Access and Benefit-Sharing Clearing House. One can imagine that the permits will be needed internally at various points in the process, at the collection site, at the exportation site for genetic material, and probably for publications by major international journals in the field, to ensure compliance with international standards for published articles.

Contentious issues related to patents are not discussed in the Nagoya Protocol, even though it is an essential aspect for many research groups and institutions seeking access to genetic resources and traditional knowledge, and an anticipated constituent aspect of any prior negotiated agreement between parties. Directly related to the concerns regarding patents and nonobviousness of inventions is the issue of "derivatives", which the Protocol defines as "a naturally occurring biochemical compound resulting from the genetic expression or metabolism of biological or genetic resources". This is not a robust definition of a derivative, and it is easy to imagine how a corporate entity could develop derivatives of an active natural product, be in accordance with mandates of the Nagoya Protocol, and be the sole recipient of patent rights. Another significant omission from the Nagoya Protocol is the absence of mandatory checkpoints or benchmarks that a certificate holder should be required to reach during the application and experimental processes. Individual countries may, however, include benchmarks of performance and reporting as they deem necessary. Clearly, the protocol will have a significant impact, as the CBD did, on natural product research all over the world.

THE SHIFT TO IMPROVE TRADITIONAL MEDICINE QUALITY CONTROL

Until 1899, when Bayer introduced aspirin, ethnomedicine was the basis of health care for humankind. Through a slow throughput process of clinical trial and error each culture developed a local, natural resources-based tradition of healing. These systems of traditional medicine, today, provide the basic drug supply for an estimated 4.6 billion people worldwide.[59]

For many patients, this system, including its mode of delivery and its quality control, has not changed significantly in 4000 years. Their access to medicinal agents is still the local street market, a shaman, a hakim, or other herbal practitioner. In the 21st century, our goals, as natural product scientists, should be substantially higher than this for the sake of our fellow human beings.

All patients have the right to expect that a medicine will "work", i.e., that it will be safe, effective, and consistent. Ethically, it should not matter whether the medicine is an approved prescription product, over-the-counter medication, dietary supplement, phytotherapeutical, or traditional medicine; human health is at stake. To diminish that right is to diminish the value of one human life over another. Global implementation of a solid, evidence-based regulatory foundation for traditional medicines and dietary supplements would transform health care for all.

In some middle-income countries, governments, academic institutions, and corporations are working together, with little external support, to examine local resources and indigenous knowledge in order to discover new drugs for both global and local diseases and to develop processes for the validation of the safety and efficacy of traditional medicines. In the People's Republic of China, very significant government investments in the diverse aspects of examining quality, safety, and efficacy are a central component of national health care policy. Major efforts are under way to enhance research and industrial production facilities and to close those not meeting GMP standards. Dedicated ultraperformance liquid chromatography systems examine each batch of each traditional medicine product in one major company visited (GAC) in 2010. This company is also responsible for the first phase III clinical trial to be approved by the United States Food and Drug Administration based on a standardized traditional medicine. The product consists of the root of *Salvia miltiorrhiza* Bunge (*Dan-shen*) and includes *Panax notoginseng* (Burkill) F.H. Chen ex C.Y. Wu & K.M. Feng (*Sanchi*) and borneol.[60] Chinese government and corporate expectations are that tight quality control will ensure regulatory acceptance and enhance the future global marketing of evidence-based traditional Chinese medicine products.

Whether it is the United States, Europe, Japan, the People's Republic of China, Brazil, or South Africa, the quality control of plant-based medicines is a global issue. Early in the 21st century, it should not be. All of the technologies and expertise are present for there to be a very high level of quality assurance. Clearly, political, economic, and marketing factors, which will not be discussed here, are involved and have been mentioned elsewhere.[2,4−7] As a result of these factors in the United States, it is estimated that there is only a 50:50 chance of selecting an authentic product containing both the correct species and correct plant component at an appropriate strength.[61] No regulatory body in the United States assures the quality, safety, or efficacy of dietary supplements, although the Office of Dietary Supplements at NIH was directed to initiate methods validation processes.[61] Unfortunately, at the present time, the fundamental sciences of botany, chemistry, and biology behind the marketed products that could protect the patient, who rightfully expects safety, efficacy, and consistency in dietary supplements as a result of a strong evidence base, remain essentially absent. The major sciences supporting traditional medicine and dietary supplements are currently in the midst of dynamic change, so opportunities to improve this appalling health care situation are certainly available. Adequate funding, as well as corporate and regulatory commitment to a significantly higher ethical standard for dietary supplements, is missing, however.

In considering the continued and evolving use of traditional medicines and dietary supplements, the importance of sustainability and accessibility has been demonstrated. These elements are the solid foundation upon which the four "pillars" of traditional medicine can be built.[3−7] These pillars are (i) information systems, (ii) botany, (iii) chemistry, and (iv) biology and also include the application of appropriate biotechnology tools and well-designed and reported clinical studies. Thus, the quality control of traditional medicines is not about a single science or technique. Pharmacognosy, with its breadth and depth of allied and associated sciences, is uniquely positioned to bring the necessary, fully integrated, highly collaborative focus to these studies.

Quality control of traditional medicines begins, as any research project begins, with information, and the management of information is a critical facet in this paradigm shift. There are many aspects of prior information relating to a traditional medicine: the basic botanical information on the plant material(s), the chemical and biological information on the plant material(s), and reports of any clinical studies that have been conducted. Gathering this information is not a trivial task, and the result is very similar to an herbal monograph, with a thorough and very detailed analysis of previous work. More importantly, these contemporary data (as opposed to a published monograph) should be used to frame the nature of the subsequent research steps. Literature acquisition is an ongoing and active process, as subsequent literature may modulate ongoing experiments.

Unfortunately, ethnomedical information is exceptionally scattered in databases, books, review articles, herbarium records, etc., making it impossible to evaluate completely the global use of a particular plant, even if that information is in the public domain. Monitoring research results on a particular plant is somewhat easier, although it should be recognized that papers dedicated to the screening of plants are not fully abstracted, so that it may be very difficult to assess whether a particular plant has been evaluated in a certain assay. This is one of many reasons that a fully accessible, *global* compilation of traditional medicine, which embraces the contemporary botanical, chemical, biological, and clinical aspects of individual plants, their extracts, and their compounds, would be an exceptionally valuable resource for government agencies, scientists, industry, practitioners, and patients and would probably cost less than $10 million per year to operate.

The other pillars of quality control are botany, chemistry, and biology. Paradigms to be shifted exist within each of these areas, as the technologies associated with them change and evolve; DNA barcoding, Raman-based remote sensing, and gene profiling are individually and collectively transforming the fundamental nature of what might be possible for the quality control of a medicinal plant material in the next few years.

Merely using the correct part of the correct plant is not an adequate botanical standard for scientific studies on traditional medicines or dietary supplements. Considering otherwise may be a fatal and fundamental flaw. It is a prime reason that variable results arise from the repeated testing of extracts of the same plant in the same or in different laboratories. Since the metabolism of a plant, in content and spectrum of secondary metabolite production, changes—with age, time of year, watering pattern, or location—its chemical profile is modulated. As a result, the biological and therapeutic effects associated with that plant sample will change in a non-predictable, nonreproducible manner.

It is important to consider that only when plant-based medicines and dietary supplements are defined in a botanically and chemically consistent manner, does it become appropriate to explore the *in vivo* and *in vitro* effects, the pharmacokinetics, the formulation, the mechanism of action of metabolites, and the efficacy of traditional medicines and dietary supplements. It is scientifically important that the same criteria of botanical and chemical investigation be applied to *all* natural product samples being subjected to *in vitro*, *in vivo*, and clinical evaluation.[62]

The strategies for the validation of traditional Chinese medicines are evolving rapidly through a combination of vastly enhanced fiscal and physical resources and the application of new technologies. One of the major advances has been to show correlations between chemistry and biology for quality control purposes, and this area of research is growing rapidly. Zeng and co-workers[63] reviewed the "component-based" and "pattern-based" approaches to the quality control of traditional medicines as proposed by Mok and Chau.[64] While the former looks only at the secondary metabolite content, the latter examines both the chemical fingerprints and biological activities.[65] They emphasize the importance of a multipatterned approach of comprehensive chemical fingerprinting, the application of chemometrics, and correlation with biological assessment. Liu and co-workers have provided an overview of the quality control of TCMs based on a combination of microscopic and molecular identification, qualitative and quantitative analysis, fingerprinting of selective extracts, quantification of a combination of fingerprint and multi-component analysis, and activity-integrated fingerprinting.[66] They also discussed the combination of biological fingerprinting and chemometrics for quality control. Jiang and colleagues[67] reviewed recent applications of bioautography to the quality control of TCMs and the importance of various hyphenated analytical techniques, as well as the combination of chemical and biological methods taking TCMs into an integrative and comprehensive analytical direction, while still recognizing the holistic nature of the preparation. Gao and co-workers[68] looked at the validity of the ancient (1247 A.D.) remedy *Danggui Buxue Tang*, comprising *Radix Astragali* and *Radix Angelicae Sinensis* in a 5:1 ratio. After examining six other ratios, it was concluded that the immunomodulatory, osteogenic, and estrogenic effects were optimally manifested with this established ratio. Correlations were made between several constituents and four different biomarkers.

Dietary supplements and traditional medicines are frequently defined in a regulatory manner by a botanical name, a plant part, and several nonchemical, nonbiological, macro- and microscopic parameters.[69] But what is a "plant"? What are the parameters that should now define that plant? More particularly and importantly, how should a medicinal "plant" be defined? If, instead of being morphologically based, the criteria for the definition of a medicinal plant are safety and efficacy, then a new regulatory definition, one not based on a 260-year-old concept of a Latin binomial, is needed. The paradigm of medicinal plant definition has now shifted. *Instead of looking at a medicinal plant as a botanical entity, it should be viewed as a clinical entity in which botany, chemistry, and biology are all contributing factors to the validation of its identity.* This being the case, those three sciences will become essential factors in the quality control of a medicinal plant product, whether the product is a single plant component or a mixture of several plants. Importantly, they will constitute a part of the evidence

base upon which traditional medicine and dietary supplements can provide assurance to the patient of safety and efficacy.

The botanical and chemical sciences associated with defining a plant are changing rapidly through the application of two technologies, DNA barcoding and metabolomics.[5−7] For traditional medicines, it is anticipated that these techniques will become the standard parameters for determining botanical quality control standards for most processed medicinal plants and an integral aspect of traditional medicine and dietary supplement regulatory control within the next 5−10 years.

DNA barcoding is one facet of the Consortium for the Barcoding of Life (CBOL).[70] The technique enables the rapid and reliable distinction to be made between species based on one or two short genetic sequences. In the past two years, the "barcoding" of a number of medicinal plant genera has become a very active research area, particularly in mainland China.[5−7] For example, Chen and co-workers[71] studied over 6600 plant samples from 753 genera and 4800 species using seven DNA barcodes (psbA-trnH, matK, rbcL, rpoC1, ycf5, ITS2, and ITS). It was found that the ITS2 barcode gave a 92.7% successful identification rate and, thus, could potentially be useful for medicinal plant identification. Other DNA fragments that are being considered for species identification include the matK and trnH-pasbA genes. An important future development may be the incorporation of barcoding technology into highly automated, hand-held devices, which could provide extremely rapid, in-field identification of plants.[72] Another critical aspect for future exploration is the correlative relationship between the genes used for botanical identification and those important for initiating secondary metabolite production, therefore providing the compounds essential for a reproducible biological activity.

Metabolomics, defined as "both the qualitative and quantitative analysis of all the metabolites in an organism", offers a completely new perspective on secondary metabolite profiling.[73−76] Multivariate analysis of the proton NMR spectra of crude extracts and principal component analysis (PCA) of the low molecular weight secondary metabolites is the common technique used.[74] This technique has allowed distinctions to be made between *Panax* species,[77] *Ephedra* species,[78] and *Echinacea* species[79] and has permitted distinction to be made between samples of *Rhodiola rosea* from different locations.[80] A correlation of the multisite collection of the Mexican plant *Galphimia glauca* with an active principle through *in vivo* testing has been reported,[81] and the maturity of a particular plant part can be determined.[82] Within a plant "species", well-defined "chemical races" occur, wherein plants grown under slightly different conditions cluster into groups.[83] These "chemical races" will result in a different biological profile, with possibly only one providing the anticipated pharmacological effect.

Combining the technologies of DNA barcoding and metabolomics has the potential to dramatically transform the fundamental definition of a plant as a traditional medicine or dietary supplement and assist in assuring safety, efficacy, and product consistency for patients.[5−7] However, the situation is made more complex by the observation that individual clones of plants may display significant differences in concentration of a major medicinal metabolite, such as galanthamine, during a yearly growth cycle, even under controlled culture conditions.[84] The same could be true for potential toxic metabolites. Safety and efficacy will probably be modulated also from a defined "standard" during a year of plant development. Consequently, quantitative phytochemical analysis on a lot-to-lot basis will be needed to ensure a therapeutic outcome based on a flexibly prescribed measure of dried plant material or extract.

The next phases of these investigations will examine the correlations between DNA barcoding, the chemical profile (including active metabolites), and the biological activity of the plant material. Such an integrated strategy will provide the first evidence for the ability to determine, comprehensively and with some assurance, that a particular plant sample will have a desired clinical outcome. It will also provide an indication of the minimum analytical and biological techniques that will be necessary to provide the assurance of safety and efficacy. If successful, these techniques will begin to address the most fundamental question in the use of traditional medicines worldwide: what is the dose of a traditional medicine? The development of regulatory standards based on such an approach will likely follow.

The application of various technologies, terrestrial and aerial, for the detection of medicinal plant locations and for providing preliminary indications of the quality of a medicinal plant *in situ* has been discussed.[3−6,85,86] Among these are techniques for hyperspectral imaging, surface-enhanced Raman spectroscopy, and ATR/FT-IR and FT-Raman spectroscopy. Hand-held, directed energy and laser-based technologies continue to evolve with rapid advancements in power, emission distance, and reflectance capability, requiring that safe practices be established for all fields of research.[87] Laser and Raman technologies[4] in hand-held manifestations will amplify and expand ethnomedical diagnostic research, the biometric barcoding of medicinal plants, and the field-based analysis of secondary metabolic profiles.

Strategies relating to the concept of conducting the quality assessment of medicinal plants (botany, chemistry, and biology) in the field rather than in a laboratory have also been presented. This approach, which can be applied to both quality control and medicinal plant drug discovery programs, would use nanoscale determination of the identity (e.g., DNA barcoding), preliminary mass spectrometric analysis, and biological determination of plant extracts at the point of collection, the so-called "pharmacognosy in a suitcase" approach.[3−6,85,86]

In addition to the secondary metabolite profiling of medicinal plants, protection of patients from untoward toxic hazards associated with traditional medicines is an important role for natural product analytical chemists.[88] Medicinal plants are often grown commercially in polluted environments or for which no pollution assessment has been made, including for radiation. Accidental contamination and deliberate adulteration of traditional medicines and dietary supplements have become very serious global problems. Contaminants may include pesticides, heavy metals, microbial species, and radiation, while adulterants may include other plant materials with similar biological effects or a range of synthetic drugs (e.g., prednisone, chloramphenicol, hydrochlorthiazide, cortisone, diethylstilbestrol, and diazepam). A study of traditional Chinese medicines collected from eight hospitals in Taiwan found that 23.7% were adulterated with synthetic drugs, and most of the samples (52.8%) contained two or more adulterants.[89] Both natural and artificial radioactivity levels are also a concern.[90]

Recommendations for heavy metal standards (arsenic, cadmium, lead, and mercury) are available from WHO.[91,92] A recent study of the heavy metal content of eight metals (Cd, Cr, Cu, Pb, Fe, Mn, Ni, and Zn) in 24 commonly used medicinal plants in Pakistan[93] showed that the greatest concern was for

cadmium levels, since 10 of the sampled plants had levels of Cd up to 40 times higher than the WHO recommended level of 0.30 μg/g. Similar results have been reported previously for plant samples from Thailand, Egypt, Turkey, Mexico, the United States, and India.[93] Four commonly used Ayurvedic plants had heavy metal and pesticide levels below detection.[94] On the other hand, a study of heavy metals from different cultivation areas in Hebei Province in China showed significant variations in four heavy metals and established a concern for careful monitoring of pollution indices in plant samples.[95] In a more detailed study, 294 samples of 126 species of Chinese herbal medicines were examined for five heavy metals (As, Cd, Cr, Pb, and Hg) and 162 pesticides.[96] At least one heavy metal was found in every plant sample, and 34% of the samples contained all five metals. Forty-two different pesticides were detected in 108 samples, with up to nine pesticides being detected in a given sample. The authors cautioned that while 95% of the samples were safe, monitoring of all samples for heavy metals and pesticides was needed to protect patients from the remaining 5% of plant samples.

Some medicinal plants seem to naturally accrue certain heavy metals and have become a cause for concern.[97,98] At least one company in Asia is applying sophisticated analytical chemistry to analyze for over 180 potential contaminants and adulterants in their traditional medicine products. At the same time, a burgeoning threat to the integrity of traditional medicine and dietary supplements is the uncontrolled sale of products on the Internet. Copies of traditional Chinese, Japanese, and Korean medicines, as well as various supplements and newly developed products, are available. The origin of these products remains for the most part unknown, and their contents are an even more significant concern in terms of quality control.

The biological evaluation of traditional medicine extracts using well-established standard protocols for *in vitro* and *in vivo* techniques will remain the core of validation for many years to come. However, the application of gene-based technologies to understand how medicinal plants act biologically, as individual entities and as holistic entities as integral parts of complex matrixes of several plants, is a very important paradigm shift toward a deeper understanding of the comprehensive nature of traditional medicine mechanistic behaviors and interactions. These techniques are delineating the functions of an individual plant extract and its components. Eventually, this will allow for a more informed rationalization of the use of a medicinal plant and will suggest appropriate, simple, and cheap biological systems to be applied for quality control to augment the botanical and chemical controls. This would further rationalize therapy with medicinal plants, as was discussed previously.[99]

A traditional medicine, like a single-agent drug, contains an active principle, or in some cases, several active principles, possibly acting synergistically or at multiple targets (*vide infra*). Unlike a single-agent drug, the concentration of active ingredient(s) in the plant or plant extract is typically not known. Levels of active ingredients in a plant may vary many-fold over the life of a plant, so correlating chemical content with biological outcome is important for there to be assured efficacy. A "scoop" or a "handful", or even a weighed (100 g) quantity, of a plant may, in reality, represent wild variations in dosing. Linking chemistry and biology to an effective dose, or at a minimum a dose range, is critical to achieve a positive therapeutic outcome. The paradigm of a fixed dose will end, unless extracts can be completely and consistently standardized, and this may not be a realistic expectation. One can imagine that for one batch of product one capsule is taken twice a day, and for another batch containing a lower available dose of active ingredient, but still meeting other minimum specifications, the dose may be two tablets, three times a day.

The evolution of highly personalized plant-based medicines may also evolve from deconstruction of the diverse functional roles of multiple components within complex traditional medicine preparations. The deconstruction process asks a series of important questions relating to safety, effectiveness, sustainability, and risk. Are all of the plants in a 20-plant prescription biologically necessary? Are there strategies that can be applied to improve the concentration of the effective ingredients, standardize the dose, and maintain safety? Can alternative extraction techniques afford higher yields of active ingredients? What happens to toxicity under those circumstances? As mentioned,[2] "traditional medicine, with its heavy investment in contemporary science and technology, is rapidly becoming very non-traditional".

Demonstration of effectiveness also applies to the human situation for which the traditional medicine and dietary supplement is being recommended. It will never be possible to conduct detailed clinical evaluation of every traditional medicine or dietary supplement. Prioritized clinical trials are therefore an essential aspect of traditional medicine validation of safety and efficacy. It is crucial though that, as with *in vitro* and *in vivo* testing, the material being evaluated is well defined for the lifetime of the trial. The NCCAM presentation[62] of some of the parameters for characterizing a clinical trial material is a starting point, with further considerations arising based on the local drug regulatory agency and human subject review board requirements. Also, as with any drug trial, each plant material will bring with it individual challenges for quality control.

The information on the clinical trial must be accessible, transparent, and public. All trials on traditional medicines and dietary supplements should be registered at clinicaltrials.gov and comply with the CONSORT standards, an evidence-based minimum set of recommendations for reporting. There are serious safety and ethical concerns about the failure to report clinical trials of traditional medicines or dietary supplements giving negative results and also the potential that exists for conflict of interest. Clarity is paramount when describing the relationships of all parties to the funding unit for the clinical trial and the material being provided. There is a potential for conflict of interest for a company to sponsor a chair at a university, then fund a clinical trial at that university conducted by the named professor, and then sponsor the publication of the results. If a clinical trial gives a negative result, that is essential information, it should be published in both the scientific literature and the public domain. Ineffective, albeit safe, agents should not be marketed with health claims (or inferences) if these have been clinically disproven; the patient retains the expectation of safety and efficacy. The practitioner/prescriber has a vested interest in a positive outcome also.

Multitarget therapy and synergy are significantly underestimated in terms of therapeutic outcome when considering both the quality control and the drug discovery perspectives of traditional medicines. Therapeutic outcomes have improved significantly for two of the most important disease states, cancer and AIDS, as a result of strategically assembled multicomponent regimens derived from considering a diverse mechanistic targeting system.[100] Ethnomedicine has already established that model of therapy. The chemical factory of a

plant sample, even a hot water extract, will contain a multitude of constituents. A multicomponent plant regimen, in which five, 10, or even 20 plants are used in a prescription, will provide an unprecedented range of highly diverse chemical constituents capable of modulating multiple sites and acting by diverse mechanistic pathways.

The biological effects observed *in vivo* or clinically in an extract may be due to one or more active compounds acting at different sites. Alternatively, two, or more, components in the mixture could be acting in a synergistic or antagonistic manner. In addition, for the most part, the effects when a traditional medicine is taken with a single-agent drug are unknown, resulting in a possible adverse drug reaction or perhaps a synergistic, potentiating one. When combinations of medicinal plants are used, the situation becomes substantially more complex. Williamson[101] and Wagner[102−104] have stimulated discussion in this area.

Significant issues in studying synergy and antagonism in multicomponent traditional medicines have been technique and definition.[100] Berenbaum[105] used a mathematical definition based on an isobole, so that the effects of a combination of agents are independent of the mechanism of action and can be presented graphically. A powerful demonstration of a synergistic interaction between two natural products occurs with mixtures of ginkgolides A and B examining platelet aggregation.[106] Potentiation of the effects of kava-kava and a *Passiflora* extract as a sedative and of a complex preparation of nine plants for dyspepsia, for which the constituent plants demonstrate effects in a range of motility-related disorders, has also shown synergistic results.[102−104] The protocols developed for these studies may be important prototypically as strategies evolve for the evaluation of the quality, safety, and effectiveness of an individual traditional medicine and for the discovery and development of new, more effective combinations of medicinal plants. In addition, such studies may also offer strategies to increase the sustainability of particular medicinal plants, if the synergistic effects can be quantified and reliably reproduced. Critically, these experiments necessitate that the extract is well standardized and the biological mechanisms are clarified prior to synergy experiments being initiated.

THE SHIFT IN VOICE FOR NATURAL PRODUCTS IN HEALTH CARE

In spite of the essential role in global health care that traditional medicine and the natural product sciences has, and must have, for the majority of the foreseeable future, the influence of scientific professional groups in public policy has to date been minimal. To enable progress in medicinal agents, that paradigm also has to change based on content expertise. In Japan, the Japanese Liaison of Oriental Medicine (www.jlom.umin.jp) brings together the major scientific societies involved in traditional medicine and the WHO Collaborating Centers for Traditional Medicine based in Japan. The government uses this expertise directly as a source of advice and opinion, to represent the government at international meetings, and to propose areas for future research development.

In North America and Europe, there is a significant need for similar groups from natural product, chemical, and biological societies to assist government scientists and regulators. Such cooperation would enable scientifically sound choices with respect to establishing an evidence base for the quality, safety, and efficacy of traditional medicines and dietary supplements being sold globally and online.

THE FUNDING OF PARADIGM SHIFTS

How can the proposed paradigm shifts and associated programmatic goals be initiated? Proposals of the scale described in this article and elsewhere[2−5,7] must begin with a commitment to small-scale initiatives, reasonable benchmarks, and an appropriate timetable. Small steps on what will be a long pathway are needed: steps that are not instantaneous "fixes", nor which will necessarily yield rapid results, yet which do reflect a public health concern and a priority for traditional medicine as an integral and integrated aspect in the health care system. New models for research and development funding, for establishing investment incentives, and for intellectual property rights will be required. As discussed earlier, the existing systems of funding, and some under consideration, do not address the question of health care for the majority. Strategic planning at the highest levels is necessary, combining government agencies, industrial enterprises, international agencies and foundations, academic institutions, and private consultants with natural product drug discovery and development experience. Planning and proposal development may take 1−2 years of meetings, discussions, and consultations to evolve. New centers of excellence will be developed, and new international collaborations fostered. Over time, countries, or consortia of countries, will develop the infrastructure to produce their own sustainable medicinal agents from natural sources based on the quality of their natural product sciences. International aid programs will be needed to assist countries to potentiate their infrastructure and resources, including 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, and these initiatives may take 5−10 years to evolve.

As proposed several years ago,[107] what is urgently needed is a Global Alliance for Natural Product Development and Health Care to give new voice and focus to the natural product sciences and their necessary role in health care, which involves traditional medicines, phytotherapeuticals, and dietary supplements. Such an alliance would be composed of international agencies (WHO, UNIDO, UNDP, NATO, EU, WIPO, etc.), government agencies (NIH, NSF, NIE, MRC, DAAD, etc.), global and local pharmaceutical companies, academic institutions, nongovernment organizations (WWF, WRI, CYTED, TRAMIL, IFS, TWAS, etc.), scientific societies (IUPAC, RSC, ACS, ASP, PSE, GA, ISE, JSPS, etc), and major foundations (Ford, Gates, MacArthur, Rockefeller, etc.). It would provide a mechanism to bring representatives together to discuss the global issues and implications in new strategic terms, with a new set of goals, a new agenda, but most importantly, a new vigor, and is vital for the global development of natural product-based medicinal agents for health care.

THE CHALLENGES FOR TRADITIONAL MEDICINE

Historically, the study of traditional medicines has been, and remains, a very neglected aspect of global health care. As a result, a vast array of challenges face all those who venture into this financial backwater of global health, and these have been discussed elsewhere.[7] Some of the challenges are mentioned below, and a few of those based in science have been touched on in this article. Many of these same challenges also apply to the appropriate development of dietary supplements:

- Nations typically have no policies or regulations relating to all of the aspects of traditional medicine as an integral part of their overall health care system. This results in a

minimal commitment to research and development funding.
- The basic information on health care needs, on the economic issues relative to investment and development, and on the cost-effectiveness of health care outcomes is not available for various traditional medicine practices. There is little respect from most Western medicine physicians for traditional medicine in its various forms in the health care system.
- The breadth and depth of the issues related to the quality control of traditional medicine products and practices may not be known to regulators, producers, and scientists.
- Global attention (fiscal and human resources) is insufficient to enhance the basic, applied, and clinical sciences behind traditional medicine. This results in major deficiencies in the scientific evidence regarding the quality, safety, effectiveness, and/or health benefits of traditional medicine. Costs of traditional medicines may increase as investment is made to enhance product validity.
- Formal training programs and associated standards for learning and licensing of practitioners may not be available. Regulations regarding practitioner training are quite different between nations.
- Standards for traditional medicine products and practices, including terminology and philosophical approaches, are highly varied. This limits communication and efforts to harmonize systems between nations.
- Patients may be unaware that the plant-based products they are buying are not regulated for quality, safety, and effectiveness. There may be limited awareness of the results of traditional medicine research with respect to safety and effectiveness.
- Mechanisms may not be in place to report and act on issues related to adverse drug events involving traditional and allopathic medicines within and between nations.
- Conservation of medicinal plants, as a component for assuring long-term access to health care resources, may not be a government priority.
- Intellectual property issues regarding access to indigenous knowledge and to natural resources for research may be complex and highly bureaucratic within a country and are typically different between countries.
- The literature and knowledge regarding traditional medicine are highly scattered, or are in library collections and databases that are not easily accessible.
- Scientific and clinical research on traditional medicines does not always fit the Western model for medical research, which may make publication of results difficult. Health insurance coverage is very difficult to justify if traditional medicine products and practices are not evidence based.

Addressing these challenges in a strategic manner is a critical aspect for the development of traditional medicines as an integral component of validated health care practices and products for the benefit of a global population.

CONCLUSIONS

In most parts of the world, eventually, and with adequate support, an important health outcome of the evidence-based approach to the study of traditional medicines will be that a plethora of new, effective products derived from established traditional medicines will be available. Some of these products will be in direct competition with the single-agent synthetic modalities of the developed world. Beyond the scientific questions, economic and regulatory ones will remain: What are the global implications of the availability of traditional medicines demonstrated to be safe and effective and sustainable? Where will they be marketed, and how will they be regulated? What disease-related health claims, based in science and on standardized clinical trials, will be allowed? Will they provide a reliable source of medication that can bridge the gap in access to drugs for the majority?

Most people on the planet require, and expect, access on a sustainable basis to scientifically demonstrated safe, effective, and consistent traditional medicines. It will take many years to plan, fund, develop, and implement the initiatives described in this overview. Yet for most of the world there is very little choice; relying on access to synthetic drugs is not an option. Wisdom and compassion, and enhanced global collaboration and leadership, are needed to change the contemporary paradigms and develop new strategies for the enhancement of traditional medicines and dietary supplements. Even partial success would be a major transformation in health care for practitioners and patients who would be assured access to products providing beneficial health with minimal risk. The "horse" would be under the direction of the "King", and, more importantly, the "peasants" (the patients) would not be concerned that their access to a higher quality of health care was compromised.

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DEDICATION

Dedicated to Dr. Gordon M. Cragg, formerly of the National Cancer Institute, Frederick, Maryland, for his pioneering work on the development of natural product anticancer agents.

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