NUTRACEUTICALS AND THE FUTURE OF MEDICAL SCIENCE

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The physician strengthens nature, and employs food and medicine, of which nature makes use for the intended end.
Thomas Aquinas, [1225-1274]

The concept of food as medicine is an ancient one, noticeably strengthened by reports from contemporary medical research and practice. The Greek physician Hippocrates, often known as the "father of medicine" enunciated this belief several centuries ago, as "let food be your medicine". While traditional cultures effectively integrated this concept with their lifestyles, modern medical science sought magic bullets from the chemist's bench, and more recently from the biotechnologist's apothecary, to combat disease.

Although the end of the twentieth century saw a rise in life expectancy to 80 years in the developed countries, largely through improved healthcare, it also witnessed an increasing awareness of the side effects of drugs and their contraindications, particularly with regard to long- term use. With improved quality of life, the general population also became susceptible to obesity and its related complications such as diabetes and heart disease. A growing interest in preventive medicine led to scientific research on alternative therapies, with particular emphasis on nutritional approaches to health and wellness.

The final decade of the last century saw renewed interest in traditional therapies (alternative medicine) and the concept of "integrated medicine" wherein several Allopathic medical practitioners also offered some form of complementary therapy. These included herbal remedies (phytonutrients), other nutritional interventions (for example, supranutritional levels of vitamins/minerals and specialized diets), techniques such as acupuncture, relaxation regimens, and homeopathic medicines. A focus on prevention rather than cure summarizes the changing attitude of the average consumer in the West towards modern medicine.

A recent study reports that 70% of patients typically saw a medical doctor before or at the same time as an alternative practitioner[1]. Most of this interest is attributed to the growing population of aging baby boomers, often referred to as the 'me generation', a group that looks to personalized healthcare to counter the effects of aging. As researchers rightly concluded at the turn of the century, the popularity of alternative therapies is not because of dissatisfaction with conventional therapies but because patients view physicians and alternative practitioners as a larger group of their healthcare team.[1] Simultaneously, greater access to knowledge databases on preventive approaches to health and wellness, the desire to "look and feel good", higher disposable incomes and a media focus on fitness, have all played significant roles in the increased popularity of complementary therapies with the younger generation. The buzz words in this context are "dietary supplements", "nutraceuticals" and "functional foods" serving to address the convenience nutritional needs of a mobile population.

An increased general awareness of the role of lifestyle choices in human wellness and disease prevention has generated the desire to exert greater individual control over

health care. Until the early 1900s, herbal remedies were perhaps the only therapeutic modalities known to medical practitioners and pharmacists. However, with the popularity of sulfa drugs and penicillin in the 1930s, herbal remedies receded into obscurity. In several universities in North America, the study of pharmacognosy or drugs of plant origin was excluded from curricula. However the resurging consumer interest in herbs has prompted serious consideration from mainstream physicians, pharmacologists and basic researchers on aspects of their safety, efficacy, contraindications and interactions with conventional drugs.. The annual retail sales of botanical supplements in North America in 2001, was valued at $3.9 billion.[2]

Unlike in North America, treatment with herbal medicines in Europe has become a well established part of healthcare. Extensive research in the European countries, particularly Germany, has generated a wealth of supportive information for various phytotherapies.[3] Colleges and Universities in Europe include phytotherapy in most pharmacy and medical curricula. In Germany, more than 80 percent of physicians regularly prescribe herbal therapies. However, according to a recent report, more than one-half the adult population in the United States consumes dietary supplements including vitamins.[4] An increased interest in nutritional approaches to the management of behavioral problems such as Attention Deficit Disorder (ADD), obesity, digestive problems and allergies in children, also exists.

Dietary Supplements, Nutraceuticals, Functional Foods:

The term "Dietary Supplement" was defined by the DSHEA (Dietary Supplement Health and Regulation Act) passed by the US Congress in 1994 as, "a product (other than tobacco) that is intended to supplement the diet and that bears or contains one or more of the following dietary ingredients: a vitamin, a mineral, an herb or other botanical, an amino acid, a dietary substance for human use to supplement the diet by increasing the total daily intake, or a concentrate, metabolite, constituent, extract or combination of these ingredients." Furthermore, a dietary supplement is intended for ingestion in pill, capsule, tablet or liquid form, is not represented for use as a conventional food or as the sole item of a meal or diet, and is labeled as a dietary supplement.[5] Dietary supplements can claim effects on the structure or function of the body, but they cannot claim to diagnose, treat, cure or prevent a disease. Common health conditions addressed by supplements include joint health, digestive problems, cholesterol levels, skeletal strength, hormonal imbalance, body fat, optimal vision, emotional problems, breast and prostate health and gender specific problems.

Stephen DeFelice, M.D., chairman and founder of the Foundation for Innovation in Medicine (FIM), Cranford, NJ. coined the term 'nutraceutical' in 1989, anticipating that food and food related substances in totality, would be used to improve health. The FIM advocated using the term "nutraceutical" with the following definition:[6]

"A nutraceutical is any substance considered a food, or part of a food, with medical or health benefits, including the prevention, treatment or cure of disease." This term is not recognized by the US Food and Drug Administration (FDA). Dr. DeFelice proposed the NREA (Nutraceuticals Research and Education Act) which is based on the principles of the successful Orphan Drug Act, with a view to spur companies to invest in the clinical research necessary to demonstrate the safety and effectiveness of nutraceuticals marketed.

A recent working definition of "nutraceutical" from a "Science" forum reads[7] "a diet supplement that delivers a concentrated form of a biologically active component of food in a non-food matrix to enhance health." This distinguishes nutraceuticals from Functional Foods defined in the forum as "are consumed as part of a normal diet and deliver one or more active ingredients (that have physiologic effects and may enhance health) within the food matrix."[7]

Health claims approved by the FDA in labeling the benefits of functional food products, include:[8]

- Sugar alcohols and dental caries
- Foods that contain fiber from whole oat products and coronary heart disease
- Foods that contain fiber from psyllium and coronary heart disease
- Soy protein and coronary heart disease
- Plant sterol/stanol esters and coronary heart disease
- Potassium, blood pressure, stroke
- Whole grains heart disease and cancer.

The following is a list of *qualified health claims* permitted for dietary supplements/functional foods. These appear on labels, with appropriate disclaimers mandated by the FDA:[8a]

- *Qualified Claims About Cancer Risk*
  Selenium & Cancer
  Antioxidant Vitamins & Cancer
- *Qualified Claims About Cardiovascular Disease Risk*
  Nuts & Heart Disease
  Walnuts & Heart Disease
  Omega-3 Fatty Acids & Coronary Heart Disease
  B Vitamins & Vascular Disease
- *Qualified Claims About Cognitive Function*
  Phosphatidylserine & Cognitive Dysfunction and Dementia
- *Qualified Claims About Neural Tube Birth Defects*
  0.8 mg Folic Acid & Neural Tube Birth Defects

Other countries have their own definitions for functional foods, dietary supplements, and nutraceuticals. In Japan, functional foods are regulated as FOSHU "Foods for Specified Health Use" a world-first policy initiated by the Ministry of Health in 1991 for legally approving the commercialization of selected functional foods.[9] Within the EU, nutraceuticals can be sold freely as food in most countries, provided they comply with occasionally very strict national rules. In the US, only 3% of botanicals are marketed as OTC drug products but more than 80% are marketed as dietary supplements. In contrast to the US, most herbs with documented pharmacological functions are considered medicinal in Europe.[2]

Garnering Credibility:

The fact that dietary supplements are not subject to the stringent regulations mandated for conventional drugs, leads to warranted concerns about their standards, safety and efficacy. Industry groups as well as organizations such as the US Pharmacopeia are working towards remedying this situation. The 2004 edition of the US Pharmacopeia USP 27–NF 22, for instance, includes 65 official monographs for botanical

dietary supplements, and 125 monographs for non-botanical dietary supplements. Additionally 27 proposed monographs for botanicals and 9 proposed monographs for non-botanical supplements have been published in the Pharmacopeial forum. The USP also has a program to verify and provide a stamp of approval to marketed dietary supplements. The organization also provides certified reference standards to enable analysis of supplements for active ingredient authenticity and potency. On another note, the USFDA proposed draft guidelines for the industry on Botanical Drug Products in August 2000 to evaluate their quality and efficacy. Comments from the industry experts reflected that these guidelines should consider the synergistic action of herbal components as well, in efficacy and toxicity estimations.[10]

Epidemiological data and laboratory studies provide increasing evidence of the role of phytonutrients in the diet in healthy aging and longevity. For instance, researchers in the late 1970s noted that residents in certain areas of France who avidly consumed red wine, had lower incidence of heart disease than other Western populations, even though their diets were high in fat. This is the well known French Paradox which led to the discovery of the healthful role of antioxidant polyphenols in red wine.[11] Similarly, low incidence of breast cancer and prostate cancer in certain populations of oriental origin was linked to the consumption of a diet rich in soy isoflavones.[12]

In recent years, research focus on the molecular biology of aging facilitated the identification and description of the process at the cellular level. The aging process is essentially a cumulative damage to tissues, (influenced by genetics, lifestyle environmental and other factors), that overwhelms the body's natural ability to repair them. Eventually, essential organs and systems begin to degenerate, resulting in chronic diseases and break down of normal body functions.

Oxidative stress resulting from free radical pathology is believed to accelerate aging. Vital components of the cell such as the mitochondria (the energy centers), functional proteins, lipids and DNA are damaged by free radicals. Cross linking and glycation of proteins, such as collagen, results in the formation of advanced glycation end products (AGE) which accumulate with age, and induce stiffening of cartilage and extracellular matrix, resulting in cataracts in the eyes and arthritis in the joints. In the cardiovascular system, aging is associated with a decrease in elasticity and an increase in stiffness of the arteries. Glucose tolerance progressively declines with age, and there is a high prevalence of type 2 diabetes in the aging population. Kidney functions, liver functions and sensory perception also deteriorate with age. Malabsorption of vital nutrients in the elderly, results in a compromised immune system and lowered resistance to infection. Hormonal imbalances associated with menopause and aging, affect bone turnover, muscle mass, strength and mental capabilities. In males, aging is often associated with impaired prostate functions.

Biomarkers or physiological indices of aging include lean body mass, bone density, strength, BMR (basal metabolic rate), body fat percentage, aerobic capacity, blood pressure, insulin sensitivity, cholesterol/HDL ratio, memory / cognitive functions, immune functions and body temperature regulation. While earlier generations accepted a decline in these functions as a certainty of life, the rapidly increasing population of aging baby boomers seeks lifestyle, nutritional and cosmetic interventions to slow down or mask the aging process.

It is unfortunate that in the context of antiaging products, media reports on dubious offerings that advertise the fountain of youth, tarnish the image of other potentially beneficial botanical and nutritional approaches to healthy aging. Nutritional approaches supported by an increasing body of scientific research include, traditional herbal products known for their adaptogenic benefits, and micronutrients that supplement dietary sources. Such interventions potentially improve cellular resistance to oxidative stress, and enhance the quality of life during aging.

For instance, supranutritional levels of the micronutrient selenium, known to be a component of the natural antioxidant defense in the body (the enzymes glutathione peroxidase and thioredoxin reductase) are beneficial in several forms of cancer, as evidenced by laboratory and clinical studies. Selenium in bioavailable organic forms (such as L(+) Selenomethionine found in cereals and other plant foods, and Methylselenocysteine, found in selenium enriched garlic and broccoli) is reported to support immune functions, manifest antiviral effects and inhibit tumor proliferation. The largest ever prostate cancer prevention clinical trial with 32,000 subjects, The **Sel**enium and Vitamin **E** **C**ancer Prevention **T**rial (SELECT) sponsored by the National Cancer Institute in the U.S. is currently underway, and seeks to study the health benefits of Selenium (as Selenomethionine) and vitamin E, in this context.[13] An associated trial **Pre**vention of **A**lzheimer's **D**isease by **vi**tamin E and **Se**lenium (PREADVISE) is also in progress.[14]

There is an increasing amount of scientific evidence to support the beneficial effects of several other nutraceuticals at the molecular level. Preclinical and clinical studies published in reputed journals across the world continually add to the growing body of scientific evidence in the field. Furthermore, i*n vitro* and cellular assays validate the direct effect of several nutraceuticals on human gene expression. An interesting case is Alpha-lipoic (thioctic) acid valued as an antioxidant nutraceutical, particularly in diabetes care and in neurological problems, which was recently shown to modulate redox-gene expression in animal models.[15]

Strengthening the Evidence-Nutrigenomics:

The human genome project which aims at mapping over 100,000 genes, signified the first step in understanding humans at the molecular level. This set the trend for the development of the next generation of novel therapeutics, wherein an individual's genetic profile could be used to generate personalized medical treatment. Individualized medicine is an ancient concept, well established in traditional systems such as Ayurveda, Traditional Chinese Medicine and Homeopathy. In Ayurveda, for example, personalized lifestyle interventions are a major preventive and therapeutic approach. Each patient is prescribed an individualized dietary, eating, sleeping, herbal therapy and exercise regimen depending on his or her constitutional type and the nature of the underlying *dosha* imbalance, at the source of the illness.

Biotechnological advances have revolutionized the areas of drug discovery[16] and development and made individualized medicine a not so distant reality. In summary, a biological mechanism, for example a malfunctioning gene, or the aberrant protein product of such a gene critical to a specific disease process is identified. This becomes the potential drug target which is then proven to be relevant in the laboratory. Potential drug candidates have then to be created and screened for safety and efficacy. *In vitro*, preclinical and finally clinical trials need to be performed to validate efficacy and safety.

Pharmacogenetics is essentially the convergence of the fields of pharmacology and genetics in relation to genetically determined responses to drugs. For instance, a patient administered a "safe" muscle relaxant during surgery could suddenly develop breathing difficulties, sometimes with a fatal outcome, due to inherent genetically determined differences in the way one metabolizes the drug. Pharmacogenomics has emerged as a sub-discipline that would help to develop new drugs to target a particular disease or provide the desired pharmacological action, while simultaneously reducing the likelihood of such adverse effects.

Proteomics is the technological field that elucidates the functions of proteins expressed by genes, for application to drug discovery and pharmaceutical product development. The research tools used in proteomics include model organisms that are used to understand the role of specific genes and their products in disease onset and progression. The model organisms used include microorganisms, insects and animal models in which the effects of gene mutations (transgenesis) on normal development and health, and the expression of proteins can be determined. The study of protein expression, as well as protein structure and function, provides a broader perspective to understanding biology than the study of gene sequence or gene expression alone. Recent advances in the study of protein-protein interactions, quantification and comparisons of protein expression, the creation of proteomic databases for human and other cells, and the elucidation of protein functions, promise to accelerate the development of effective diagnostic and therapeutic products.

Single nucleotide polymorphisms (SNPs), a direct outcome of the Human Genome Project, are instrumental in the development of "smart drugs". More than 85% of genetic variability is estimated to occur due to single nucleotide base substitutions in gene sequences. These variants are known as single nucleotide polymorphisms, or SNPs. Pharmacogenomics assesses the link between SNPs and the therapeutic response in individuals, thereby leading to a better understanding of pharmacokinetics and pharmacodynamics, a reduction in adverse events related to pharmacotherapy and enabling the design of appropriate dose regimens.

According to researchers, pharmacogenomics technology could begin to benefit patients as early as in the next five to six years. A newly developed technology helps to identify unique haplotypes (patterns of SNPs present in the DNA of every patient). A "genetic bar code" is produced by 13 to 15 of these haplotypes. This technology was validated in a recent study of asthma patients, in which the researchers found a clear correlation between clinical response to albuterol and haplotypes associated with the beta-2-adrenergic receptors expressed in bronchial smooth muscle.[16] In another study, markers in multiple genes were shown to be responsible for 50% of the variability in drug response to commonly prescribed statins (HMG-CoA reductase inhibitors), which are used to lower elevated blood cholesterol levels. Genetic information which has much more predictive capabilities than conventional medical information, would therefore permit the development of a patient's response profile to a particular statin drug.[16]

In the futuristic context of medical science, traditional herbal remedies (phytonutrients), and nutritional interventions, currently marketed as dietary supplements, nutraceuticals or functional foods need to adopt approaches linked to pharmacogenomics and proteomics. The evolving science of Nutrigenomics that investigates the interaction between diet and development of diseases based on an

individual's genetic profile would provide scientific validity to such approaches. "Smart nutraceuticals" of the future could be custom-made to provide personalized benefits.

Unraveling molecular mechanisms of action:

Over the last two decades, a phenomenal amount of published research on nutraceuticals and their role in the prevention of chronic disease conditions, has appeared in literature. A few examples are presented here.

Gugulipid (a phytonutrient from the Ayurvedic tradition, a gum resin extract of *Commiphora mukul* from the Burseraceae family to which the myrrh of Biblical renown also belongs) presents an interesting case study in this context. Scientific studies on guggul began almost 40 years ago when an Indian researcher, G.V. Satyavati was intrigued by the strong parallels between modern concepts on the etiology of atherosclerosis and obesity, and descriptions in the Sushruta Samhita written in the 5th to 4th century B.C. Traditionally, guggul is used in formulations for the treatment of inflammation, arthritis, cardiovascular conditions and obesity. Supported by scientific research, it has now been rediscovered as a hypolipidemic agent, with its mechanism of action validated at the molecular level.

A landmark research paper published in the May 31st, 2002 issue of "Science",[17] corroborated observations made by Ayurvedic physicians in India, 3000 years ago. Medical researchers led by Dr. David D. Moore of Baylor College of Medicine, Texas, USA, demonstrated that the gum resin extract of Guggul, has beneficial effects on cholesterol metabolism at the molecular level. These US researchers unraveled the potential mechanism of action of guggulsterones, the biologically active components of the resin. Guggulsterones were shown to be antagonist ligands for the bile acid receptor FXR, which is an important regulator of cholesterol homeostasis in the body.

The chemopreventive roles of several dietary antioxidant phytonutrients are well researched. These include antioxidants such as curcumin, resveratrol, ellagic acid, green tea catechins, quercetin and others. Many of these compounds are reported to provide health benefits through their molecular roles in the hepatic cytochrome P450 monooxygenase system of enzymes responsible for a major portion of drug metabolism in humans. At the fundamental level, phytonutrients such as quercetin and curcumin have been shown to up regulate antioxidant gene expression in animal models.[18] Interestingly, curcumin is reported to inhibit the expression of inflammatory enzymes, as well. Cyclooxygenase (COX-2) gene expression is reported to be characteristic of colon cancer and several high grade tumors. A non-toxic concentration of curcumin was found to significantly inhibit the expression of the COX-2 gene, suggesting its beneficial role against colon cancer.[19] The National Cancer Institute in the United States, is currently in the advanced stages of evaluating Curcumin as a potential anticancer drug.

Another interesting area is the possibility of pharmacological manipulation in weight management through modulation of expression of the enzyme, acetyl –CoA carboxylase 2. Malonyl-Coenzyme A, generated by acetyl-Coenzyme A carboxylases ACC1 and ACC2, is reported to be a key metabolite in the control of fatty acid synthesis and oxidation in response to dietary changes. In a recent study, mutant mice deficient in ACC2 were found to have a normal lifespan, higher fatty acid oxidation rate and to accumulate less fat, as compared to normal mice, when the two groups were fed high fat/ high carbohydrate diets.[20]

A study on Mexican –Americans revealed that the presence of specific variations in one gene resulted in a three fold increase in the risk of diabetes. Calpain-10 a protein associated with this gene has been shown to be involved in glucose regulation.[21] A new therapeutic approach to insulin resistance involves administration of thiazolidinediones that potentially regulate the relevant gene expression.[22] Perhaps certain nutraceuticals would facilitate similar effects?

More recent studies provide the link between obesity and the development of Type 2 diabetes. Researchers identified a mechanism that helps explain how the hormone leptin (originally termed the "satiety signal"), is involved in the metabolism of fatty acids in muscle.[24] A novel molecular link between obesity and diabetes is thus indicated, suggesting the possibility of a new target for the development of drugs that would help manage both conditions. The potential applications of nutraceuticals in this context cannot be ruled out. For instance, recent studies suggest that *Garcinia cambogia* (Malabar tamarind, brindall berry) extract efficiently improved glucose metabolism and displayed leptin-like activity in mice.[25] *Garcinia cambogia* extract (more accurately, its active compound (-) hydroxycitric acid) is a well known dietary supplement that supports weight loss and healthy body composition.

Yet another potential application is in the area of anti-atherogenic nutraceuticals. The citrus flavonoids, naringin and naringenin, were found to significantly lower the expression levels of vascular cell adhesion molecule-1 (VCAM-1) and monocyte chemotactic protein-1 (MCP-1), with potential applications in the prevention of atherosclerosis.[26] Similarly, MMP-8 (matrix-metalloprotein 8) a collagenase enzyme expressed in atherosclerotic plaques, is being researched as a likely target for the treatment of cardiovascular disease[23]. Nutraceuticals that inhibit the expression of this enzyme would therefore be potentially useful in preventing cardiovascular problems.

Envisioning the Future:

The 21st century is often referred to as "the century of Biotechnology". Using biotechnological tools, the physician of the future would be better equipped to offer personalized approaches to preventive medicine. Advances in Nutrigenomics would facilitate individualized diets customized to a person's DNA profile to maximize health and well being. Nutraceuticals supplied through sophisticated oral or transdermal delivery systems would provide well targeted health benefits with optimal bioavailability. With the evolution of "smart nutraceuticals", a futuristic "Physician's Desk Reference" would contain information on individual genetic profiles to be matched with specific nutritional interventions, as well. This would be a vast improvement over current nutritional recommendations which being too generalized are reported to benefit only 60% of the population.[27] Simultaneously, allergic reactions to specific ingredients would be minimal, as recommendations would be based on individual genetic profiles and susceptibility data. Other important areas would be in correcting metabolic insufficiency, in providing adequate nutrition for high energy activities, and as ammunition for survival under stressful conditions, for example in people participating in strenuous sports activities, astronauts in space programs or in military personnel in combat zones. Predictably, "smart nutraceuticals" as adjuncts to "smart drug" therapy would be the norm in cases of chronic diseases.

Do nutraceuticals hold the key to the fountain of youth? Calorie restriction is reported to prolong life span in laboratory animals. A study on yeast showed that increasing the activity of a single gene, SIR2 could extend their life span. An analogous gene, SIRT1 was located in humans. Polyphenols such as quercetin found in apples and tea, and resveratrol (found in grapes and red wine) were found to increase SRT1 activity in a laboratory screening. Interestingly, resveratrol was found to increase SRT1 activity 13-fold.[28]

As research efforts across the world continue to unravel the links between diet and health, the role of nutraceuticals in health and disease, becomes increasingly significant. "Medicine and food have a common origin" says an old Chinese proverb. Armed with a cornucopia of nutraceuticals, and a dazzling array of genomic evidence, modern medical science is all set to trace the footprints of ancient wisdom.

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