POLICY FORUM: HEALTH

Regulation of "Nutraceuticals"

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We constantly search for new substances that can improve biological function or make us fitter and healthier. Recently Western society has turned to foods as sources of these enhancers. These products are called, variously, vitamins, dietary supplements, functional foods, "nutraceuticals," phytochemicals, biochemopreventatives, and designer foods. These terms vary in meaning from country to country, as does regulation of these agents. Dietary supplements are ingredients extracted from foods, herbs, and plants that are taken without further modification outside of foods for their presumed health-enhancing benefits. The term dietary supplements was formally defined for U.S. Government offices in 1994 as a product (other than tobacco) intended to supplement the diet to enhance health that bears or contains one or more of the following dietary ingredients: a vitamin, mineral, amino acid, herb, or other botanical or is a dietary substance for use to supplement the diet by increasing the total dietary intake, and is intended for ingestion in the form of a capsule, powder, softgel, or gelcap, and not represented as a conventional food or as a sole item of a meal or the diet (*1*). The dosage to be administered is not included as part of the definition. I propose to define nutraceuticals as those diet supplements that deliver a concentrated form of a presumed bioactive agent from a food, presented in a nonfood matrix, and used to enhance health in dosages that exceed those that could be obtained from normal foods. (A good example is genistein purified from soybeans and delivered in a pill in dosages greater than could be consumed in soy). "Functional foods" are similar in appearance to conventional foods and are consumed as part of a normal diet. They deliver one or more active ingredients (that have physiological effects and perhaps enhance health) within the matrix of a food (for example, a bread or breakfast cereal with added high-dose folic acid). Diet supplements, nutraceuticals, and functional foods are designed to supplement the human diet by increasing the intake of bioactive agents that are thought to enhance health and fitness.

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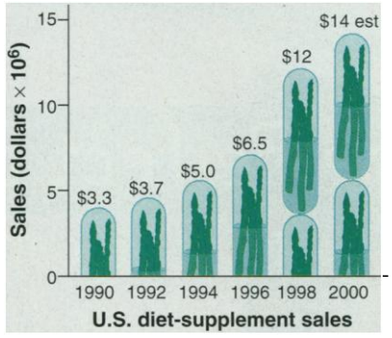
A growing industry exists to commercialize these discoveries. In 1996, U.S. consumers spent more than $6.5 billion on dietary supplements (*2*). By 1998, this market had almost doubled to $12 billion. It is projected to increase to more than $14 billion by 2000 (*3*). The American Pharmaceutical Association estimates that 80% of pharmacies in the United States sell these products (*4*). Until a few years ago, most companies in this field were relatively small, but now multibillion-dollar companies (like Monsanto, Bristol-Myers Squibb, Lipton, Johnson & Johnson, DuPont, Procter & Gamble, and Novartis) commit major resources to discover health-enhancing activities within the foods we eat and to change traditional foods so they contain more of these active ingredients. The National Institutes of Health (NIH), acting on directives from the U.S. Congress, set up the Office of Dietary Supplements within the Office of the Director of the NIH in 1995 to accelerate basic research to identify effective dietary supplements.



It is often difficult to distinguish among nutrients, food additives, and drugs. Independent of the matrix (food or pill) in which it is delivered, a dietary supplement can sometimes be foodlike and other times druglike. Nutrients are defined as having nutritive value (they participate in metabolism or are used to build the structures of our cells) and are presumed to be safe. Food additives enhance the aroma, color, structure, or taste of foods but are not nutritive. Under present conceptualizations, the boundary at which a food ingredient becomes a drug is not well defined; often the health claims made for the substance are used to make the determination (*5*). Should a nutrient used as part of a treatment for a defined disease be considered a drug, whereas the same nutrient used to enhance health (reduce the risk of disease) be considered a functional food or dietary supplement? This approach could result in classifying a naturally occurring cholesterol-lowering agent as a drug when it is used to reverse atherosclerosis and as a dietary supplement when it is used to prevent atherosclerosis.

One way to differentiate between foods and drugs is to examine how people are exposed to them. Drugs can sometimes be found naturally in foods, and they can participate in metabolism. However, they are substances that humans are not normally exposed to at the dosages at which they exert their beneficial effects. In contrast, a nutrient exerts its effects at dosages that correspond to reasonably expected exposures for a given population. Some supplements are druglike when ingested in amounts that could never be achieved in the diet, even though they are essential nutrients when ingested in smaller amounts. At low dosages tryptophan is a necessary amino acid required for metabolism and incorporation into proteins. At high doses it (or the currently used 5-hydroxy-L-trytophan) increases brain serotonin synthesis and thus acts as a drug that treats insomnia. In this case a substance normally part of most foods was administered in dosages that exceeded dietary requirements in order to obtain a pharmacological response and so was druglike in this circumstance. Another case is a substance that is not usually consumed by humans. Some plant constituents (for example, ephedra and digitalis glycosides) are biologically active at even small concentrations and have toxicity relative to this activity at higher concentrations. Even small doses of these constituents are beyond common human experience. Foods are presumed to be safe because we can extrapolate from a known history of exposure to them, whereas a drug that has no such widespread exposure history cannot be presumed to be safe. Thus, we must weigh the risk/benefit ratio before large populations of humans are encouraged to ingest drugs.

In 1994 the U.S. Congress passed the Dietary Supplement Health and Education Act (DSHEA) (*1*), which established a new framework for regulation of dietary supplements by the U.S. Food and Drug Administration (FDA). Legislators recognized that people believed that dietary supplements offer significant health benefits. The U.S. Congress wanted to facilitate access to these so-called "natural" medicines so that the public could be empowered to take some measure of control of their own health care. DSHEA gave manufacturers of dietary supplements freedom to sell these supplements and to provide information

about product benefits on labels, with significantly reduced requirements (compared with those for drugs and food additives) for premarket review by the FDA. Dietary supplements on the market before October 1994, when DSHEA was passed, were exempted (that is, presumed to be safe). For these supplements, the FDA must show they are unsafe before it can restrict marketing of the products containing them. For new ingredients in dietary supplements, the manufacturers (not the FDA) are responsible for determining that the products they market are safe. The FDA must be notified of a new ingredient in a supplement, and this notice must provide information that supports the manufacturer's conclusion that the ingredient is safe. This is a less rigorous process than is required for review of food additives (used to enhance the aroma, color, structure, or taste of a food), for which there is a formal process for evaluation of safety. A manufacturer wishing to use a new food additive or a drug must conduct safety studies in a manner defined by the FDA and must submit the results to the FDA for review and approval before the ingredient or drug can used in marketed products. This is not the case for dietary supplements in the United States, because they are legally in a class by themselves; they can be marketed without the manufacturer's satisfying the FDA that they are safe.

Is this a reasonable approach? DSHEA ensures rapid access to products that are taken by half of all Americans. This legislation makes it easy for a relatively small enterprise to create and market a product without investing the time and money typically needed to prove safety and efficacy. However, DSHEA modifies the regulatory environment so that it becomes possible, even likely, that products will be marketed that inadvertently harm people. To date, the FDA has asked for the voluntary recall of a product containing the herbal ingredient plantain contaminated with *Digitalis lanata* after an individual consuming the product suffered a complete heart block. The FDA proposed a regulation to limit the amount of ephedrine alkaloids in dietary supplements (ephedra, Ma Huang) after serious side effects, including death, were observed (*6*). Recently, the FDA asked for the voluntary recall of supplements containing γ-butyrolactone, because this agent was associated with serious side effects, including coma and death (*7*).

The concept that dietary supplements are natural and therefore must be safe is fallacious. A presumption of safety derives from a history of exposure to the agent as part of normal diet (or as part of long-term practice); when the dosage is in excess of historical exposure, there can be no presumption of safety. Normal metabolism of nutrients includes many physiological regulatory protective mechanisms (for example, activation of hepatic enzymes that metabolize or store excess nutrient) that make adjustments for modest changes in intake of the nutrient. When a nutrient or chemical is eaten in amounts that greatly exceed normal exposures, these safeguards can be overwhelmed. Similar considerations apply to substances derived from plants. As long as supplements do not appreciably increase exposure to plant-derived substances, it is reasonable to think of these as food ingredients. When the dosage of food components, botanicals, or their extracts exceeds levels achievable in normal diets, their bioactivity can be drug-like. Although the determination of normal dietary exposure for an individual is complex, it may be possible to implement policy based on the highest common dietary intake for some human population (for example, to use the Japanese population's intake of soy products to set the upper bounds for soy components like genistein).

As discussed above, I propose that we create the category of nutraceuticals for dietary supplements administered in large dosages in order to obtain pharmacological effects. The benefits and risks of nutraceuticals should be considered much more carefully than those for foods. For the smaller health effects usually seen after administration of nutraceuticals (compared with drug effects like those of penicillin, which completely eliminate a disease pathogen) the cost of demonstrating efficacy (required of all drugs) may be prohibitive. Thus, it may be inappropriate to classify all nutraceuticals as drugs, but clearly we should require more rigorous safety evaluation than we do for foods. The FDA should be empowered to ask for this evidence before—and not after—humans are exposed to potential risk. Perhaps the FDA could regulate nutraceuticals by requiring safety data similar to those required for over-the-counter (OTC) medications (like cold remedies).

There is further reason to regulate the preparation of dietary supplements, nutraceuticals, and functional foods, no matter what the dosage. Some plants contain a wide variety of toxic chemicals that help them to survive in their environmental niche and to defend themselves against bacteria, insects, and herbivores. Manufacturers may inadvertently add toxic constituents during the manufacturing process; the recent experience with eosinophilia myalgia syndrome and impurities in tryptophan preparations is an example (*8*). Natural ingredients, stored improperly, can be substrates for molds that make highly dangerous mycotoxins—mold on peanuts forms the potent carcinogen aflatoxin. There is as much reason for oversight of natural supplements as there is for oversight of synthetic drugs and foods. The FDA proposed reasonable rules for Current Good Manufacturing Practices for dietary supplement ingredients in 1997 (*9*), a public meeting was held in July 1999 (*10*), and further action is expected shortly. These rules are an essential first step toward a rational oversight of dietary supplements. They should be implemented as soon as possible for supplements administered at any dosage.

The increased review and regulation of dietary supplements will decrease the access of the public to some beneficial products. For supplements administered at dosages that can be found in foods, the adoption of Good Manufacturing Practices should not significantly alter availability. For nutraceuticals that expose humans to ingredients at dosages they would normally not be exposed to, demonstration of safety may mean it will take years rather than weeks to introduce a new product, and some products may never be introduced. This seems a reasonable cost to protect the public health. The proposed schema for regulation also is in the interest of supplement manufacturers. In a manner similar to the experience of the pharmaceutical industry after the thalidomide debacle, a dietary supplement harming a large number of individuals, with ensuing publicity, could result in public reaction that would damage the marketplace for all dietary supplements. In addition, with no requirement to show efficacy or safety, corporate investments in research and development of better nutraceuticals are unlikely because competitors can jump in without having to amortize the costs of such research.

Although DSHEA has fostered a situation that encourages continued market growth, it has not fully protected the public or fostered an atmosphere conducive to continuous quality improvement through an investment in research.

References and Notes

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