HEALTH AND STRESS

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DIETARY SUPPLEMENTS AND RELATED CONTROVERSIES

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The odds are overwhelming that you and most adults you know take one or more vitamins or other nutritional supplements daily. Sales have skyrocketed over the past decade, particularly for herbal products, which increased 350 percent between 1966 and 1999. The supplement market generated $15.4 billion in the U.S. in 1999 and has undoubtedly grown since then.

There are a variety of reasons for this, including increased wariness of the side effects and long term adverse consequences of prescription medications presumed to be safe. **Phenylpropanolamine, a common ingredient in cold and weight loss products available without a prescription for over fifty years was recently withdrawn because it was linked to hemorrhagic stroke.** At least eight drugs approved since 1993 have now been banned because of serious health hazards and deaths despite being certified as safe. Small wonder that consumer confidence has declined.

Supplements are also riding the crest of a tidal wave of popularity in alternative medicine, which is viewed as much safer and just as effective as mainstream approaches for certain indications. There is also the recognition that many widely used drugs, including aspirin, quinine, digitalis and morphine were derived from botanical sources, providing some herbals with a scientific patina that is not deserved.

However, the majority of people take nutritional supplements not to treat symptoms, but because they believe they will help delay the stigmata of aging, make them "feel better", provide more energy, strength and stamina for sports activities or will help them lose weight. There are no studies to support any of these claims but the promotional hype is pervasive and can be very persuasive. **The problem is that most people assume that since herbals are "natural" and don't require a prescription, they are harmless.** There is little concern about interactions with prescription drugs or taking more than suggested, and many take megadoses of some in the belief that more must be better.

ALSO INCLUDED IN THIS ISSUE

This can create problems for senior citizens who often take multiple medications in addition to over-the-counter drugs and supplements that may interfere with each other. Adverse effects can be exaggerated because of poor liver and kidney function. Even healthy young individuals have died or suffered serious damage from weight loss and body building products. Problems with others are just starting to surface.

Are "Stress Reducing" Herbals Safe?

Valerian allegedly alleviates insomnia and has a "soothing" effect, passionflower is reported to have sedative, hypnotic and antispasmodic properties, Siberian ginseng is reported to increase stamina and endurance and omega-3 fatty acids are reputed to have beneficial effects on mood and cognition. Most of these claims are based on anecdotal reports that are difficult to evaluate. Some herbals do have supportive double blind studies including St. John's wort (depression), ginkgo biloba (improved memory), adaptogens (increased resistance to stress) and kava kava (anxiety).

Kava, a member of the pepper family that has been used for centuries in the South Pacific for its tranquilizing effects is approved in some European countries for treating anxiety and insomnia. In one study of fifty-two people suffering from anxiety, 81% of those taking a kava preparation rated the results as "very good" or "good". Other studies suggest that kava can reduce annoying premenstrual and postmenopausal complaints. In menopausal females taking estrogen replacement therapy, those who were experiencing anxiety and took kava supplements had a greater reduction in anxiety scores than controls treated with hormones and a placebo. A lengthy article on page 1 of the Feb. 26, 1998 *Wall Street Journal* Marketplace section entitled "The Making of an Herbal Superstar" predicted that **"kava is poised to become the next blockbuster herbal remedy"** noting that **"Never mind that no clinical trials have been conducted on it in the U.S.** or that promoting it as a cure for anxiety disorder would be illegal – the vast industry that sells herbal remedies is convinced it has another super-seller in kava." It went on to ask **"How does an herb rise from obscurity to star status, despite a lack of scientific proof and puny advertising budgets? Here's how: zealous proselytizers, regulatory gamesmanship, shoestring marketing and doctor endorsements. It also helps to be the subject of a glowing book or two, not to mention magazine and newspaper articles and radio and TV shows."**

The article went on to explain that the kava promoters already had all those items in place. There was a forthcoming book by a California psychiatrist claiming that kava was preferable to Valium and Xanax for treating mild to moderate anxiety. His previous best seller, along with prominent media presentations including a 20/20 interview, had put St. John's wort over the top the previous year. A media blitz was planned and he assured the reporter that "In 1998, you're going to see kava just go through the roof" and he was right.

Two months later, a Medical College of Virginia double blind study of kava's anxiolytic effects found statistically significant decreases in stress levels in the treated group compared to placebo controls. **The company whose product was used in the study had spent $2 million on promotional ads the previous year.** Kava's fortune was further bolstered by a double blind study showing it could decrease harmful cardiovascular responses to stress that can cause sudden death. It's not clear how kava works but some of its ingredients produce muscle relaxation and animal studies suggest that it acts on the limbic system – a primitive part of the brain that controls emotions and survival instincts. Kava has also been used to reduce muscle spasm, relieve insomnia and improve memory.

Herbals Are Not Always Harmless

As predicted, kava sales soared to $17 million in 1998. However, it is important to reemphasize that herbals and other nutritional supplements are not required to demonstrate either efficacy or safety, nor is there any incentive to do so since few are proprietary or protected by patents. Little regulation also means there is no guarantee that the information on a label accurately

reflects the contents of the container. In some instances, little or no trace of the active ingredient can be found or the dose can be dangerously high. This together with the lack of long term safety studies and the increasing inclusion of herbals like kava and ephedra in beverages and functional foods for sedative or stimulant effects has raised serious safety concerns.

Supplements are considered safe because they are "natural" but adverse side effects in some herbal products may not surface until they have been in widespread use for years. All of the kava studies commented on its safety and that unlike prescription tranquilizers there was no tendency to develop addiction or tolerance with prolonged use. In the Virginia study, the kava treated group showed progressive improvement on weekly evaluations. Kava has been known to cause dizziness, hair and hearing loss and a flaky, dry, yellowish skin discoloration when taken in high doses for prolonged periods. This condition, called kavaism, is seen only in South Pacific people who regularly take amounts 100 times or more higher than suggested and is reversible when kava is discontinued. Kava effects are potentiated by alcohol and sedatives and can cause impaired or loss of consciousness when combined with either.

Kava was recently banned in several European countries and Australia because it was linked to severe liver disease requiring liver transplantation and one death. The FDA is now considering similar action here although some believe that other factors may be involved. **Herbals are generally harmless when taken as directed but several do interfere with prescription drugs and can cause other unanticipated problems.**

Germander, chaparral leaf, comfrey, jin bu huan, maHuang, valerian, mistletoe and pennyroyal can also cause liver problems, especially with high doses. Niacin and Vitamin A may have similar toxic effects and other very popular supplements are also not as harmless as generally believed. **Ginseng can have side effects** ranging from insomnia, diarrhea, vaginal bleeding and fibrocystic breast disease to severe headache, schizophrenia and the Stevens-Johnson syndrome – a serious hypersensitivity disorder involving the skin and mucous membranes that can be fatal. Ginseng can also interfere with anticoagulant therapy.

Gingko adverse effects are usually mild, transient, and reversible but serious bleeding (subdural hematoma) has been reported as well as seizures in children taking excessive amounts and elderly epileptics who took normal doses for only a few days. It may also interfere with anticoagulants because of effects on platelets. **Echinacea** is thought to prevent upper respiratory infections because it stimulates the immune system. While adverse effects are uncommon there have been reports of hepatitis, asthma and rashes.

Except for rare cases of photosensitization and mania in predisposed patients, **St. John's wort** is quite safe. However, its effect on liver enzyme systems can significantly reduce the action of anticoagulants, oral contraceptives and antiviral agents and when taken with certain antidepressant drugs can cause a serotonin overload syndrome that can prove fatal, particularly in elderly patients. **Saw palmetto**, used to treat prostatic enlargement because of its anti-androgen actions, has been reported to cause constipation, decreased libido, diarrhea and headache and might interact with certain hormonal medications or cause false-negative PSA tests that could conceivably mask the presence of prostate cancer.

Garlic seems to be the safest supplement although one recent article claimed it could interfere with drugs given for AIDS. **Adverse reactions can also be caused by contaminants. L-tryptophan deaths from eosinophilic myalgia were due to faulty manufacturing practices abroad over which there was no control.**

Should Supplements Be Regulated?

Almost everyone agrees that some sort of standardization for dietary supplements is needed to insure that the amount of each active ingredient is listed accurately on the container and that the product has safe amounts of any contaminants. Additional concerns are that nutrients are listed but their level is not

sufficient to provide any benefits or, as in the case of calcium and magnesium, they are in a form that is not readily bioavailable. **There are a variety of organizations composed largely of manufacturers that ostensibly provide such guarantees for products that carry their own seal of approval but some fear this is like having the fox guard the chicken coop.**

At the other end of the scale, there is also the Codex Alimentarius Commission, which operates in conjunction with the United Nations and the World Health Organization (WHO). Established in 1962 for the purpose of setting international standards and codes for all foods and food additives, the Codex Commission committee of 146 nations is largely composed of German and international pharmaceutical corporations. As might be expected, **their goal seems to be making all nutritional supplements available by prescription only.**

Some of the proposed provisions are that no vitamin, mineral or herb could be sold for prophylactic or therapeutic purposes and that their dosage should not exceed the levels set by the commission. This might mean that consumers would be limited to the RDA for vitamins, (e.g. 60 mg. for vitamin C) and that **supplements without a RDA, such as coenzyme Q10, would be illegal to sell since they would all now be classified as drugs**. **All new supplements would be banned unless they satisfied the Codex approval requirements.** These regulations would become binding and eliminate the current escape clause within the General Agreement of Tariffs and Trade that allows a nation to set its own standards. **Any United Nations member country that refused or failed to accept these new standards would face heavy fines from the World Trade Organization and possibly other sanctions**

Such Draconian restrictions could cripple the nutritional supplement industry and efforts are underway to find satisfactory alternatives. The U.S. Pharmacopoeia plans to launch its Dietary Supplement Verification Program (DSVP) certification program for dietary supplements later this year and all U.S. dietary supplement manufacturers have been invited to participate. The DSVP would include:

1. Quality control and manufacturing data review.
2. Laboratory evaluation of product samples.
3. Evaluation of manufacturers' quality control systems through periodic audits.
4. Granting of a USP verification mark.
5. Ongoing surveillance of products that bear the USP verification mark.

There will be periodic monitoring of manufacturing facilities and extensive document review to insure that good manufacturing practices and appropriate quality control systems are in place prior to issuing the USP mark. To further guarantee that USP verified products meet their label declaration, products bearing the USP verification mark will be randomly tested to insure that the contents are correctly labeled. The program is voluntary and testing would be performed only on products submitted to the USP program for review. Manufacturers who do not wish to participate in the USP program would still be free to market their wares under present regulations.

Consumers can determine if a dietary supplement satisfies this program by the distinctive USP mark with the words "USP Verified" on the label. This means that the label accurately reflects the content and dosage of all ingredients, the product meets the requirements for limits on contaminants and that the manufacturer is in compliance with quality controls consistent with USP, National Formulary and FDA requirements for good manufacturing practices. **How successful the USP program will be remains to be seen. It is not clear how it will be funded, how overseas manufacturing practices will be inspected and how many manufacturers participate and also sign up for each one of their products.**

How Things Now Stand Under DSHEA

The 1994 Dietary Supplement and Health Education Act (DSHEA) was backed by a powerful industry lobby and pushed through by Sen. Orrin Hatch of Utah, home to many supplement makers. DSHEA established a new class of product, the

dietary supplement, which is considered neither food nor drug and not subject to the regulations that prescription and over-the-counter medicines as well as food additives must obey. **It essentially ruled that herbal products didn't have to be proven safe or effective or even guarantee that the label accurately reflected what was in the container.** The FDA was prohibited from banning any herbal product unless it proved that it caused a medical problem. FDA approval was not required for packaging or marketing statements so various health claims could be made without providing scientific support. The label was required to state that such claims had not been reviewed or approved by the FDA but this is usually in small print. Supplements did not have to be manufactured according to any standards and there was no control over their harvesting or processing.

Some of these deficiencies were addressed in a February 2000 revision that clarified the types of claims that could be made for dietary supplements without prior FDA review. The label can carry claims that a product may affect the "structure or function" of the body, such as "maintains a healthy circulatory system'', "for muscle enhancement'' or "for hot flashes". Companies are prohibited from claiming or implying that the product can be used to treat, diagnose, cure or prevent any disease without prior FDA review. This would apply to statements such as "prevents osteoporosis" or "prevents bone fragility in postmenopausal women" and they must notify the FDA 30 days in advance of any claims they intend to make.

However, there are ways to get around this. Implied disease claims can be made through the product's name (Carpaltun, CircuCure), through a statement about its formulation (contains aspirin), or through the use of pictures, vignettes, or symbols such as an electrocardiogram tracing.

The new rules require all dietary supplements to carry a "Supplement Facts" panel with information similar to the "Nutrition Facts" panels that appear on most processed foods. The "Supplement Facts" panel must include information on 14 nutrients such as vitamin A, vitamin C, sodium, calcium and iron if they are present in significant amounts as well as any other vitamins and minerals that are added or are part of a nutritional claim on the label. The labels of products containing botanical ingredients must also identify the part of the plant that was used.

The updated regulations also set parameters for use of the terms "high potency" and "antioxidant". "High potency" may be used to describe a nutrient when it is at 100 percent or more of the Reference Daily Intake (RDI) established for that vitamin or mineral and for multi-ingredient products if two-thirds of the nutrients are present at levels that are more than 100 percent of the RDI. Statements such as "Good source of antioxidant" and "High antioxidant" can be used only when scientific evidence shows that absorption of a sufficient quantity of a nutrient such as vitamin C will inactivate free radicals or prevent free radical-initiated chemical reactions in the body. **Trade groups representing supplement makers, such as the Council for Responsible Nutrition, don't want any changes. They claim that the present regulations are just fine.** According to their spokesperson, "The problem is that they are not enforced, particularly with respect to supplements spiked with prescription medications or contaminated with pesticides and heavy metals like lead and mercury and it is not fair to blame the entire industry because of a few bad apples."

But the FDA has limited powers and cannot possibly monitor the thousands of products being sold. Despite deaths and lawsuits related to ephedra and aristolochia, another weight loss supplement that has been banned in many countries, they are still available here even though the FDA has stopped imports and asked for a voluntary recall. **Supplement makers say the public is very satisfied with product safety and that they can prove it.**

The Public's Perception Of Supplements

The Dietary Supplement Education Alliance (DSEA) is an interdisciplinary alliance of manufacturers and relevant health professionals dedicated to promoting the

responsible use of dietary supplements. As part of their activities, they commissioned the Dietary Supplement Barometer survey of over 1000 American adults last June to evaluate consumer attitudes and beliefs about vitamins, minerals, herbals and other nutritional supplements.

The survey revealed that the majority of respondents believe that such supplements do provide a range of benefits and take them on a regular basis for the following reasons:

- 72% to "feel better"
- 67% to help prevent illness
- 51% to help get better when ill
- 50% to live longer or delay aging
- 37% to build muscle and increase strength
- 24% to improve athletic performance
- 12% for weight management

More than half the participants were convinced that certain supplements offered benefits that were comparable to prescription drugs but with fewer side effects. Although 95 percent said they were satisfied with the supplements they took, there were misconceptions about their indications or how they functioned. Calcium was viewed by 58% as being important primarily for postmenopausal females although it is needed throughout life. Over 40% were not aware that although iron supplements could increase red blood cell production if there was a deficiency they did not increase energy levels. **Many did not know that it often takes several weeks for supplements to produce their desired effects**.

The need for better public education was evident from the lack of appreciation of potential prescription drug interactions with supplements and the importance of heeding dosage recommendations. **Over 90% said it was important to adhere to doses of prescribed drugs but less than 75% felt that this applied to nutritional supplements**. Most also failed to inform their doctor about supplements or other over-the-counter drugs they were taking and were seldom asked about this.

Some felt the survey did not ask questions that would have highlighted ignorance about functional foods or why such supplements differ from food additives, which are regulated the same as prescription drugs. The FDA did stop the sale of Benecol, a cholesterol-lowering functional food. The manufacturer claimed it was a dietary supplement and did not require any approval. However, the FDA cited a law saying dietary supplements may not masquerade as a food. Although Benecol was made from a natural ingredient found in trees, it looked and tasted like regular margarine, would be sold in stores next to butter, and therefore required FDA approval, which could take years. The agency subsequently granted it as well as Take Control, a competitive product, GRAS "generally recognized as safe" status that allows temporary marketing.

This DSEA consortium designed to educate the public about dietary supplements is a strategic alliance between the National Nutritional Foods Association, which represents the interests of manufacturers and retailers of a wide variety of natural foods and supplements, and the National Sanitation Foundation, an organization primarily involved in assuring water safety. Its steering committee includes the American Herbal Products Association, Corporate Alliance for Integrative Medicine, and various media and public relations representatives and is supported by over 100 supplement manufacturers and distributors.

Senator Tom Harkin, who helped Orrin Hatch get DSHEA approved in 1994, enthusiastically endorsed the DSEA alliance last July. Harkin also announced that, as Chair of the U.S. Senate panel that funds health care and education, he would be working to expand NIH funding for supplement research and legislation to provide consumers tax deductibility for healthful dietary supplements and push for coverage under health plans. The "Dietary Supplement Tax Fairness Act of 2001" was introduced the next month by Harkin and Hatch **giving certain supplements parity with drugs as medical expenses for IRS purposes. Who will decide which ones?** That's just the beginning of an upcoming battle.

Other Non-Prescription Problems

That's not the only complicated issue looming for over-the-counter products. **Under existing laws, any drug that can safely be used without physician management should be available without a prescription.** The 1951 Durham-Humphrey Amendment to the Food, Drug and Cosmetic Act established the criteria for prescription and non-prescription drugs. In 1972 the FDA began an extensive investigation of all over-the-counter drugs and eventually published a series of monographs that established standards for allowable ingredients and appropriate labeling and recommended 40 prescription drugs or dosage strengths for transfer to non-prescription status. It is estimated that more than 200 products no longer require a prescription and that 80 ingredients, dosages, or indications have achieved over-the-counter status since 1976.

Such switches can have powerful positive and negative consequences for pharmaceutical manufacturers and can be accomplished via several administrative mechanisms: **(a**) if one of the FDA monographs describes their ingredients as safe and effective for a specified indication. Many analgesics, antihistamines, decongestants, sleep aids, antipruritics, and vaginal antifungal preparations have used this approach over the past 2 decades; **(b)** applications to switch are reviewed by the FDA on a case-by-case basis using a new-drug application (NDA) process similar to that used for new prescription drugs; **(c)** publishing a new regulation that reclassifies a drug. The FDA used this for the antifungal agent tolnaftate and dextromethorphan, to suppress coughing. However, **any interested party may initiate this process** and during the past decade, reclassification has resulted in non-prescription H2-receptor antagonists for heartburn, nicotine gum and patches, pediatric analgesics, and various hair-growth formulations.

Only products used to treat acute or episodic complaints were granted non-prescription status. Drugs for chronic conditions that might require laboratory tests or examination by a physician to make a diagnosis were usually excluded but this is also likely to change.

One argument for expanding over-the-counter drug availability is that chronic but "silent" health problems like hypertension and high cholesterol are largely under-treated because many Americans lack health insurance and those who do often seek medical care only when they have symptoms. If drugs to treat such conditions were available without prescription they might be used more widely. There are numerous flaws in this reasoning and the FDA commonly requires drug makers to conduct additional studies to demonstrate that switching to over-the-counter availability will yield a public health benefit.

However, **it is economics that drives drug manufacturers to ask for a switch, often because a drug patent is about to expire in the hope that brand recognition and loyalty will provide an edge over generics. Astra Zeneca's patent for Prilosec (omeprazole), the world's best selling drug with 2000 sales of $6.2 billion expired last October.** The company has filed lawsuits claiming that several additional patents should extend its rights to exclusive marketing of the drug through 2007. A Florida company has already received an exclusive 6-month approval to market a less expensive generic Prilosec pending resolution of this litigation. This could be the biggest switch since generic Prozac was approved last August.

The 1984 Waxman-Hatch Act grants 3 additional years of market exclusivity if drug makers perform the extra clinical trials required to gain non-prescription approval. If an over-the-counter request is for the same indication at the same or a lower dose, the FDA demands proof that physician guidance is not needed by determining if the patient can read and understand the label, follow its instructions properly and achieve the desired outcome. Satisfying this requirement is not easy.

To protect their position, the company has introduced and aggressively promoted Nexium (the purple pill), a second-generation proton pump inhibitor. They also requested FDA approval of a non-prescription Prilosec at half the usual dosage for Procter & Gamble to sell. Although denied, the stakes are so high that further attempts will surely be made.

A Non-Prescription Product Battle Is Looming — Who Will The Winners Be?

Health plans have petitioned the FDA to switch the nonsedating antihistamines Allegra, Claritin, and Zyrtec to over-the-counter status so they would no longer have to cover them as prescription drugs. Women's health advocates want emergency contraceptives to be over-the-counter. Drug companies are seeking nonprescription status for statins and topical drugs for herpes. The Codex commission wants all nutritional supplements to be regulated like pharmaceuticals but manufacturers and distributors don't want any changes in the current lax legislation. **They say that supplements currently being sold are generally quite safe but that was disputed in a *New England Journal of Medicine* study commissioned by the FDA**. It reported that ephedra, taken by about 12 million Americans a year for weight-loss, bodybuilding and energy was linked to high blood pressure, heart attack, stroke, seizure and death in otherwise healthy people. Most cases were settled out of court but $13.3 million was awarded to an Alaskan woman who had a stroke after taking a weight-loss supplement that contained a synthetic version of the herb marketed by a Utah company. Another study in the same prestigious publication linked the Chinese weight-loss herb aristolochia to kidney failure and urinary tract cancer. In an accompanying editorial, former FDA commissioner David Kessler said the fact that U.S. consumers could buy aristolochia is another reason why Congress should amend DSHEA, a law that he fought hard against when in office. Following the report, the FDA did stop importation of aristolochia and asked for it to be voluntarily recalled but that's no guarantee that it is still not on some shelves.

Supplement manufacturers say that what is needed is simply more enforcement by the FDA although they are well aware that the agency is severely understaffed and cannot even fulfill their present obligations to insure food and drug safety. Nobody knows the extent of adverse reactions to supplements or drugs since physicians and hospitals are not required to report them and there is little incentive to do so. Most supplements are safe when taken as directed but there is a confusing array of concoctions available with claims that are difficult to evaluate and promising new supplements supported by double blind studies are likely to be drowned out by a plethora of worthless wares. Policosanol, made from sugar cane, has been taken by millions of people in other countries and shown to be as effective as statins in lowering LDL and cholesterol without any side effects or drug interactions. It also prevents LDL oxidation, reduces inflammation and foam cells, inhibits clot formation and provides other cardiac benefits. Relora™ is a new stress-reducing product derived from Chinese herbs used for centuries that appears safe and effective based on double blind studies. How can these gain entry into this fiercely competitive market?

The public is caught between conflicting powerful drug and supplement manufacturers, both of whom have considerable clout on Congress and the FDA. The outcome is likely to be determined by economic rather than public health concerns. Stay tuned to see what happens next!

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