HEALTH AND STRESS

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SORTING OUT SUPPLEMENT SUPERIORITY AND SAFETY

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"A desire to take medications is, perhaps, the greatest feature which distinguishes man from other animals." Sir William Osler, considered by many the greatest physician who ever lived, wrote this a decade before the advent of aspirin, which sparked the birth of drug companies and the pharmaceutical industry.

Popular patent medicines promising miraculous results were readily available at general stores, chemists' shops and even from seed merchants. Some were also sold by traveling salesmen out of the backs of wagons with claims of instant cures backed up by convincing testimonials from paid performers. The contents of these concoctions were jealously guarded secrets and often included hefty concentrations of alcohol. Opium, cocaine and other addictive substances were not uncommon components so it's not too surprising that many customers not only experienced relief of their pain and other complaints but also had an urge to keep taking the magical potion.

Patent medicines were cheap and plentiful and if one didn't work there was always another to try. A doctor's visit could cost ten times as much and often ended by a prescription for some particular patent medicine anyway. While some countries like Britain had regulations to protect the public from injurious and falsely represented food and drugs, the U.S. made no attempt to establish such safeguards until well into the 20th century. The FDA essentially did not start to function until 1940 and was primarily concerned with food safety.

It seems clear that patent medicines were mostly quackery and provided little lasting benefit. Indeed, with the exception of purgatives like Ex-Lax and Phillips Milk of Magnesia, few have persisted. It is doubtful if Osler ever envisaged that a gigantic drug industry would emerge with ready made pills advertised directly to patients in an effort to influence prescribing habits. Nor could he have foreseen that it would be rare to find a physician able to write a prescription listing the amounts of various ingredients tailored to a patient's specific needs, the manner in which they should be compounded and the correct dosage of the final product.

ALSO INCLUDED IN THIS ISSUE

The public's fascination with pharmaceuticals has faded due to the withdrawal of numerous drugs because of serious side effects and fatalities. It is not surprising, therefore, that they are eager to find nutritional supplements that are satisfactory alternatives since these are presumed to be completely safe.

21st Century Patent Medicines?

Many feel that some nutritional supplements are essentially the equivalent of patent medicines promoted 100 - 150 years ago because there is nothing to guarantee that they are either effective or safe. With respect to efficacy, supplements may not make claims for curing or treating any disease but there are ways to get around this. Safety has never been viewed as a concern since "natural" supplements are assumed to be harmless when taken as indicated. Recent reports suggest otherwise and many feel that changes in current regulations are urgently needed.

Congress has distinguished between what the Food and Drug Administration considers to be a drug as opposed to a dietary or nutritional supplement. Unfortunately, this categorization is not based on biological effects but how the product is promoted or labeled. It is approved as a drug when it claims that it can "treat, prevent, cure, mitigate, or diagnose" a specific disease and satisfies FDA requirements for safety and efficacy. While nutritional supplements can make only "structure/function" claims, such as "maintains a healthy circulatory system" or "promotes comfort", they are not required to prove either safety or efficacy and enjoy other exemptions.

How this distinction evolved has an interesting history. In 1937, 107 people died after taking elixir sulfanilamide because of the diethylene glycol solvent that was used in its formulation. In response to this, Congress enacted the Food, Drug and Cosmetic Act of 1938, which, for the first time, required proof that a drug was safe before it could be marketed. Several decades later, an epidemic of birth defects associated with thalidomide led to the 1962 Kefauver-Harris Amendment requiring manufacturers to report all adverse events to the FDA and proof of efficacy was now also necessary to receive FDA approval.

Efficacy can be established in randomized trials that might require only a few hundred patients to establish the validity of a claim. Safety is much more difficult to prove and usually necessitates exposing thousands to a new drug, doing tests to insure there are no adverse hematological, kidney or liver abnormalities and demonstrating that there are no contraindications during pregnancy or for patients with other disorders, taking other medications, etc. Dietary supplements are not held to similar standards for the following reason.

The 1990 Nutrition Labeling and Education Act (NLEA) limited health claims that could be made about the relationship between a nutrient or food and a disease or health-related condition, to these seven categories:

- Calcium and osteoporosis
- Sodium and hypertension
- Dietary saturated fat and cholesterol and risk of heart disease
- Dietary fat and cancer
- Fiber-containing grain products, fruits, vegetables and cancer
- Fruits and vegetables and cancer
- Fruits, vegetables and grain products containing fiber, particularly soluble fiber and coronary heart disease

Supplement manufacturers complained that these restrictions would severely limit their ability to develop new products. They mounted a very aggressive and successful advertising campaign to convince Congress that there was a growing public demand for nutritional supplements, legislators were besieged by constituents, and the rest is history.

DSHEA & Supplement Safety Concerns

Since supplements were perceived as being completely safe, passing favorable legislation was not difficult. The Dietary Supplement Act of 1992 exempted supplements from the NLEA restrictions so that essentially they could claim anything they wanted to. However, that was not enough for supplement manufacturers who realized they had enough muscle to gain

other advantages that would bring in billions of dollars. The Dietary Supplement Health and Education Act (DSHEA) of 1994 was a bonanza allegedly designed to further empower people to actively participate in improving their own health care by providing greater access to dietary supplements. According to DSHEA, a dietary supplement was now defined as any product intended to supplement the diet that bears or contains one or more of the following ingredients:

- a vitamin
- a mineral
- an herb or other botanical
- an amino acid
- a dietary substance used to supplement the diet by increasing total daily intake
- any concentrate, metabolite, constituent, extract or combination of these ingredients

Nutraceutical is a term that applies to foods that provide some health benefits as well as products that have medicinal value. Foods and medicines are regulated differently and under DSHEA, a firm has the sole responsibility for determining that the nutraceuticals it manufactures or distributes are safe. A firm also bears the responsibility to insure that any representations or claims made about its products are substantiated by adequate evidence showing that these are not false or misleading.

Critics point out that this is like asking the fox to guard the chicken coop. Under DSHEA provisions, dietary supplements do not need FDA approval before they are marketed nor does a manufacturer have to provide the evidence it relies on to substantiate either safety or effectiveness. Even when new ingredients are added to the formulation the only requirement is evidence that the product is "reasonably expected to be safe".

Drug manufacturers must notify the FDA when they learn of any adverse reaction that is potentially related to their product. Data on adverse reactions to drugs are collected via direct contact with health care providers, patients and manufacturers or from MedWatch, the FDA's voluntary reporting system. Many drug reactions are not recognized as such because they are attributed to something else. In addition, surveys show that probably more than 90 percent of those that are correctly identified are never reported to either the manufacturer or the FDA. Even when such reports are received it may be difficult to prove that a specific drug is the cause of the problem when multiple medications are being taken.

Adverse reactions to nutritional supplements don't have to be reported to the FDA or anyone else no matter how severe they are or how compelling the evidence is. Yet, the FDA is obligated to prove that a nutritional supplement is unsafe before it can even request that its use be restricted, much less attempt to have it banned. Most individuals take more than one supplement and possibly prescription and non-prescription drugs as well, which makes the source of a possible drug reaction difficult to pin down. How can the agency possibly prove that a supplement is harmful or potentially dangerous under such circumstances?

In some instances the problem may have nothing to do with the supplement itself but rather contamination during its production. There were numerous disabilities and more than three dozen deaths in 1989 due to L-tryptophan, a popular supplement used to treat insomnia and depression. After a lot of detective work these were traced to a contaminant introduced in the manufacturing process which resulted in a rare disorder known as eosinophilic myalgia. Authorities have banned certain calcium supplements derived from animal bones because of high lead concentrations. Other supplements have been withdrawn due to possible contamination with salmonella. Such complications take a long time to trace because nutraceuticals are considered to be quite safe when taken as directed. Recent developments suggest otherwise.

PC SPES, SPES, GHB And Lipokinetix

PC SPES is a supplement that contains eight herbs and has been found to benefit certain patients with prostate cancer but is sold to "promote prostate health". SPES is another popular herbal that "strengthens" the immune system. Earlier this year, the FDA warned consumers to stop using these supplements because they contained

prescription drugs that could cause severe side effects. Laboratory analysis of the products by the California Department of Health Services found that PC SPES contained warfarin (Coumadin), a blood thinner, and that SPES had alprazolam (Xanax), a tranquilizer. Both are patented products manufactured by the same company, who voluntarily issued a nationwide recall.

Nobody knows how many other supplements may be contaminated since even routine quality-assurance testing would not necessarily detect the presence of impurities. California investigators reported that nearly one-third of 260 imported Asian herbals were either spiked with drugs not listed on the label or contained lead, arsenic or mercury. Five Chinese herbals had significant amounts of potent drugs used to treat diabetes. A pediatrician reported on children from wealthy California families who were actually malnourished from eating snack food spiked with supplements.

Dietary supplement companies have begun aggressively targeting children and parents with potent nutraceuticals designed to help kids gain strength, lose weight, or treat colds and flu, depression and attention deficit disorder. As a result, increasing numbers of kids are swallowing supplements, often with the knowledge, urging and even insistence of parents in search of "natural" remedies or "healthy" alternatives for youngsters who eat too many cupcakes or drink too much soda. One survey recently found that almost 20 percent of parents were giving their children supplements. In Long Island, a mother gave her 18-month-old baby a teaspoon of eucalyptus oil last year because a store clerk told her it was good for a fever. The child suffered permanent neurological damage and almost died

Supplements designed to improve athletic performance or lose weight are particularly likely to be associated with adverse reactions. The FDA's lack of awareness of the extent of such problems or their severity is disturbing, even though there is little they can do about it. Gamma-hydroxybutyrate (GHB) and its precursors are popular body building supplements but may cause coma and death. The FDA was aware of only 14 episodes and one death from 1993-1998 whereas Florida had recorded 549 in 1998 alone. Because of mounting problems Congress intervened two years later and overrode DSHEA by banning GHB after evidence that it had caused 60 deaths.

A recent article in *Annals of Internal Medicine* described five patients admitted to the same hospital within a six month period for liver failure after taking Lipokinetix, a weight loss supplement. No other drugs were involved, all tests for viral and other forms of hepatitis were negative and jaundice or other manifestations appeared after a few weeks of taking the supplement as directed. Analysis of the product revealed appropriate amounts of norphedrine (phenylpropanolamine), caffeine, yohimbin, diiodothyronine and sodium usinate as listed on the label. **None of these alone is associated with liver toxicity but the authors convincingly demonstrated how their combination could cause problems.** Further investigation revealed two other cases of liver failure due to Lipokinetix (also sold as Syntrax) reported on MedWatch and it is likely that there are numerous others that have not been diagnosed correctly or reported.

This is just the tip of the iceberg with respect to safety problems associated with weight loss supplements and lack of awareness. The FDA's monitoring system implicated dietary supplements in 2,621 adverse events between 1993 and 1998 with 184 deaths. In contrast, the Association of Poison Control Centers received almost 7,000 adverse reports on supplements in 1998 alone. These did not include ephedra products for weight loss, which accounted for the biggest chunk of the FDA's cases, and deserves further discussion.

Should Ephedra Be Banned?

A recent review of hospital records suggested that almost one in four admissions was due to some complication from a medication. **It is estimated that for each statin safety complaint received by the FDA there are probably over ten times as many that are not recorded.** The situation is probably much worse with respect to nutritional supplements and it is impossible to accurately estimate how prevalent safety problems are.

The FDA received 1400 complaints about ephedra between January 1993 and February 2000, most of which were for elevated blood pressure, palpitations or rapid heart rate. However, ephedra containing products were also associated with more deaths, heart attacks, cardiac arrhythmias, hypertension, strokes and seizures than all other dietary supplements combined. Victims tended to range in age from 18 to 45 years old who followed dosage recommendations. Ephedra is believed to have been responsible for the deaths of three football players last year and although it has been banned by the National Football League, National Collegiate Athletic Association, International Olympic Committee and severely restricted in 15 states, sales continue to soar.

The FDA took action against drugs containing ephedrine about twenty years ago listing contraindications and dosage warnings. However, it has little if any control over supplements other than to make recommendations or give warnings that manufacturers can accept or ignore. In 1997, because of mounting criticism, the FDA proposed to limit the dose of ephedra in dietary supplements containing caffeine, prohibit unwarranted label claims and require a warning label limiting daily doses as well as duration of treatment. These were all very reasonable suggestions designed to protect the public based on numerous mishaps that had been voluntarily reported. However, industry pressure has been so powerful that several of these suggestions have already been withdrawn. The last report from the agency indicated that nothing will be done until a more thorough investigation is completed later this year or some time in 2003.

Ephedra supplements in widely varying doses are being taken by millions to lose weight, increase energy or improve performance in sports and athletic activities. Most contain caffeine, guarana or other botanical products to increase stimulant effects but there is no guarantee that the label identifies all the ingredients or the correct amount of those that are listed. One pharmacologist who has analyzed 150 such weight loss and sport supplements noted **"You really don't know what you're getting in these products, or how much."**

Many consumers are not even aware they're ingesting ephedra because it is listed as Ma Huang or *sida cordifolia*. Products also often include B vitamins or green tea extract to imply they promote health and have suggestive names like Metabolift, Thermadrol, Quadraburn, Ripperfuel, Zone Fat Buster and Lipofuel. Convincing promotional material with glowing testimonials that include impressive before and after pictures emphasizing safety as well as efficacy increase their appeal. Data obtained from Poison Control Centers reveals that adverse ephedra supplement reports increased from 211 in 1997 to 407 in 1999 but the numbers are probably much much higher since such facilities would capture only a fraction of those affected.

Last September, the Public Citizens health advocacy group petitioned the FDA to ban all ephedra supplements complaining that the safety problems were much more serious and widespread than appreciated. They pointed out that **Texas reported 500 adverse ephedra events in less than two years or over a third more than the FDA had gathered in 7 years and "the fact that a single state could do this speaks to the pitiful inadequacy of reports to the current FDA system."** The petition was signed by Dr. Raymond Woosley, a cardiovascular pharmacologist and FDA consultant on ephedra's cardiac toxicity. He emphasized that **"Just adding warnings to the product labels is not enough because there have been too many patients who followed the instructions, read the warnings and still suffered strokes or heart attacks."** There has been no response nor is any likely.

And Now Some Good Supplement News

Some supplements like Coenzyme Q10 are not only completely safe, but have been proven to benefit a variety of disorders in rigorous scientific studies. A double-blind placebo controlled study has again confirmed the benefits of Co Q10 in congestive heart failure at a dosage of 200 mg. daily. Based on the experience of others, doubling this amount in divided doses would likely have improved these

results. The ability of Co Q10 to improve immune system responses was shown in another double blind study where subjects vaccinated for Hepatitis B received either placebo, 90 mg. Co Q10 or 180 mg. Co Q10 daily. Antibody titers one month later were significantly higher in the Co Q10 recipients (especially at higher doses) indicating better protection.

A chronic fatigue syndrome cross over study measuring recovery time after a standard bicycle exercise challenge found 90% improvement with 300 mg. Co Q10 daily as opposed to 50% on 100 mg. daily, and a return to pretreatment values after the cross over to placebo. This clear dose-response relationship strongly supports Co Q10's therapeutic efficacy as opposed to a placebo response. Co Q10 has no adverse side or long term effects and there was no evidence of toxicity in one promising study in recurrent prostate cancer where patients received 600 mg./day for a year. In fact, the NIH has funded a study of Parkinson's disease based on very encouraging preliminary results in which **patients will receive 300, 600 or 1200 mg. of Co Q10 daily for up to 17 months!**

Huntington's disease is a debilitating disorder that also causes uncontrolled movements and dementia and usually strikes at an early age. A recent study in *Neurology* found that giving 300 mg. of Co Q10 twice a day for 30 months resulted in significant improvement and for the first time reversed a biochemical abnormality seen in this disorder. Another paper in the same issue reported that 200 to 300 mg. of Co Q10 daily cured two teenagers with a rare inherited muscle disease. The manufacturer has applied for FDA approval of its product as a prescription drug for this disorder .

The stress of an acute heart attack is associated with a disturbance in glucose metabolism that increases blood insulin levels. This hyperinsulinemia can cause further damage by promoting clotting tendencies over the next four weeks. This period is the time of greatest risk for a repeat heart attack and as one cardiologist noted, "The greater the reduction in excess insulin the better off a patient should be." In one study, heart attack patients who received 120 mg. of Co Q10 daily experienced more than 10% reduction in fasting and postprandial insulin levels, significantly less angina and rhythm disturbances and a lower rate of recurrent heart attacks and fatalities.

Probably the most dramatic effects of Co Q10 are seen in patients with periodontal disease that has failed to respond to conventional therapies and antibiotics. A cream containing Co Q10 has been shown to reduce wrinkles and age spots because of its antioxidant effects. In a study of patients with skin wrinkles in the corners of the eyes, "crows feet", Co Q10 cream was applied once daily for six weeks to one eye and a placebo cream to the other. To measure wrinkle depth, silflo replicas were applied, removed and measured for depth by laser at baseline and after six weeks. Wrinkle depth was reduced by 27% in the treated group compared to controls and at 10 weeks there was a 43% reduction in wrinkles.

The reason Co Q10 is effective in heart disease, malignancy and so many other different disorders is that it increases the production of ATP (adenosine triphosphate), which is the source of energy for all cells. As can be seen from the above studies, dosage recommendations can vary widely. When taken for preventive purposes, daily doses range between 60 and 200 mg. either as a single or twice daily dose. Co Q10 should be taken with food, preferably containing fat, since it is not soluble in water. Various preparations are available but gelatin capsules containing Co Q10 dissolved in oil seem to attain higher blood levels. Prices can vary tremendously and do not reflect quality. Cut rate capsules may have little active ingredient but one of the best products is also one of the least expensive.

Omega-3 - Another "Super Supplement"

The claim that fish is "brain food" may be more than an old wives' tale based on recent research. More than 60% of the brain is composed of fatty tissue derived primarily from the omega-3 fatty acids

found in fish. Blood tests show that most Americans are deficient in omega-3 fatty acids and 20% have no detectable amounts. There is good reason to believe that these individuals are at increased risk for behavioral, memory and learning problems as well as depression and even suicide.

Rates of depression are low in countries like Japan where the average consumption of seafood per person is around 150 lbs. a year. The incidence of major depression is nearly 60 times greater in New Zealand, where seafood consumption is about 40 pounds a year. Post-partum depression, the disorder that caused Andrea Yates to drown her five children, is 50 times more common in countries with low seafood intake levels. Scientists have found abnormally low levels of omega-3 fatty acids in the brains of depressed patients and many suspect there may be a link between the decrease of omega-3 fatty acids in the American diet during the past century and our increasing incidence of depression. Omega-3 levels are lower because we are eating less fish and the saturated fats in meats and dairy products, omega-6 fatty acids in vegetable oils, and trans-fats interfere with the ability to utilize omega-3. Through most of human existence the ratio of omega-6 to omega-3 fatty acids in our diet was 1:1 or 2:1. The ratio in the current U.S. diet is estimated to be between ten and twenty times higher.

The importance of this was underscored in a Harvard study in which researchers separated recently hospitalized depressed patients into two groups matched for severity of symptoms. One was placed on a diet high in omega-3 fatty acids and the other received a high omega-6 diet. After three months, the improvement in the omega-3 group was so dramatic that in an unusual move, the University oversight committee ordered the study to be stopped so that all the patients could benefit from omega-3 supplementation.

Another University study found that kids low in omega-3 fatty acids were significantly more likely to have learning disorders, hyperactivity and other behavioral problems. To investigate effects on learning ability, rats were raised on either a diet deficient in omega-3 fatty acids or one containing normal amounts. Both groups initially had similar numbers of synaptic connections in the brain but after four weeks of a learning program, the omega-3 group had considerably more and also scored much higher on tests to measure learning skills.

The well known cardioprotective benefits of fish and omega-3 were confirmed in a recent report from the ongoing Physicians' Health Study showing that participants with the highest omega-3 levels were 81 percent less likely to die suddenly. Another Italian study of heart attack survivors found that those who took fish-oil supplements had only half the incidence of sudden cardiac death within the first four years of treatment compared to controls on the same diet who took vitamin E. The long-term Nurses' Health Study also reported that women who ate fish regularly had nearly one-third fewer deaths from heart disease compared to women who rarely ate fish.

Over 2000 other studies have linked omega-3 deficiencies to memory problems, dyslexia and a host of diseases ranging from arthritis, allergies and childhood asthma to diabetes, breast and colorectal cancer, eczema and other skin disorders. The most beneficial omega-3 acids are EPA (eicosapentanoic acid) and DHA (docosahexanoic acid) which are found in fatty fish like salmon, swordfish, sardines tuna, bluefish, and mackerel.

People who don't like fish or are concerned about mercury contamination can take cold liver oil but it's not very palatable and large amounts are required. Fish oil supplements rich in omega-3 fatty acids are a much better choice but it is important to be certain that the product you choose has both EPA and DHA in significant amounts and lists an expiration date. Supplements containing omega-6 and/or omega-9 fatty acids should be avoided since these are readily available from foods and can reduce omega-3 utilization.

Weight Loss Supplement Scams And The Need For Greater Regulatory Powers

Americans shell out $33 billion yearly in what is usually a futile attempt to shed some extra pounds and keep them off. It is generally recognized that the only way to lose weight is to ingest fewer calories than are expended, which means eating less, exercising more and usually both. What most people seem to be looking for, however, is some magic pill that will do the trick. Pharmaceuticals have been a disaster with the recall of Redux and the imminent demise of Meridia because of severe health hazards. A significant portion of the $4 billion spent annually on nutritional supplements is for weight loss products and programs and the number and types that are available are mind boggling, as are their claims. An Internet search on "weight loss" turned up well over 2 million hits in a tenth of a second, all of which are presumably safe when taken as directed. It is clear that they are not, and ephedra and Lipokinetix are not the only offenders.

Efficacy is another problem and Body Solutions is one example of the numerous scams that abound. No need to worry about diet or exercise, you can "lose while you snooze". The hook is "You simply drink a tablespoon of the formula before bed, sleep well and lose weight." When you receive the product the directions are to drink that tablespoon on an empty stomach so that you can't eat for three hours before you take it, and not again until you wake up the next day. Their Phase 1 program costs $180 for a 90 day supply and then jumps to $48 every two weeks. The primary ingredient is a hydrolyzed cow collagen protein popularized in *The Last Chance Diet* that caused a national uproar 25 years ago because it resulted in numerous deaths. The company does not offer a money back guarantee and despite numerous law suits, is extremely profitable.

The Enforma System claims that its "Fat Trapper" and "Exercise in a Bottle" products increase the body's capacity to burn fat and help it burn more calories while sleeping, at a cost of about $70/month. Their infomercials, claiming that consumers could enjoy fried chicken, pizza, etc., and still lose weight, that were shown 23,000 times over eight months, resulted in sales of $35 million. The Federal Trade Commission sued charging that the claims were not supported and although the company was ordered to pay a $10 million fine and refrain from making false claims, they are still flourishing with slightly different advertising wording. There are numerous other scams ranging from magic mushrooms, wonder bark from Brazil, cellulite pills, pyruvate, creatine, *garcinia cambogia* and green algae to "Slimming Insoles" worn in each shoe that massage certain reflex zones causing the body to burn stored fat and the "Fat-Be Gone Ring" that can help you lose weight in certain body locations by wearing it on a specific finger. It is hard to believe that people fall for scams that only slim their wallets and that the government is powerless to stop them.

There are some promising and safe supplements on the horizon that do have potential for weight loss as well as stress reduction that will be discussed in a future Newsletter - so stay tuned!

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