

A SCIENTIFIC LOOK AT ALTERNATIVE MEDICINE

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Dietary Supplements; Weight Loss

Dietary Supplements

Estimated annual sales (including herbs): nearly \$20 billion in 2004 (up from \$9 billion in 1994 and \$4 billion in 1990). Major food and pharmaceutical companies are increasingly participating (16 companies control over half the market). Recent trends include soft drinks and candy bars "fortified" with herbs and supplements. Some companies are now combining genetic testing with recommendations for supplements allegedly targeted to individual needs ("nutrigenomics"). Rapid increase in use by children, including products like creatine for high school athletes (a survey found that 1 million 12- to 17-year-olds were taking sports supplements). New terms: "*nutraceuticals*"; "*functional foods*" (or "*phoods*").

I propose to define nutraceuticals as those diet supplements that deliver a concentrated form of a presumed bioactive agent from food, presented in a nonfood matrix, and used to enhance health in dosages that exceed those that could be obtained from normal foods..."Functional foods" are similar in appearance to conventional foods and are consumed as a 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...

(S. Zeisel (1999) *Science* 285, 1853-1855)

Many products are sold via *multilevel marketing*. Successful distributors make most of their money not by direct sales but by recruiting other distributors (whose profits they share). Many individual distributors (who are often lay people) have web sites.

According to Stephen Barrett (Quackwatch article, 2001), "During the past few years, thousands of physicians have begun selling health-related multilevel products to patients in their offices...Doctors are typically recruited with promises that the extra income will replace income lost to managed care."

A 2001 survey of American adults found that 59% used dietary supplements. Main reasons for use were to feel better (72%), prevention of illness (67%), treatment during illness (51%), longer life (50%), strength (37%), weight management (12%). 33% of adults took supplements on the advice of their physician. Another survey (Blendon et al. (2001) *Arch. Intern. Med.* 161, 805-810) found a somewhat lower use (48%). While "a majority...expressed support for increased government regulatory efforts to ensure that dietary supplements are not harmful and are pure, that doses are consistent, and that advertising claims are true," most regular users said they would continue to use products even if scientific evidence showed they were not useful. Many reported that "they do not discuss the use of dietary supplements with their physicians because they believe that the physicians know little or nothing about these products and may be biased against them." 18% of parents gave supplements to their children. A separate survey found that 62% of children with chronic illness used supplements, half of them nonprescription. For the nonprescription supplements, only 20% had been discussed with a health care provider. Another survey found that 60% of heart patients used supplements, many of them ones that could interact with their anticoagulant drugs.

A 2005 review concluded, "Notwithstanding the justification for targeting recommendations for nutrient supplements to certain segments of the population (eg, the elderly), there are insufficient data to justify an alteration in public health policy from one that emphasizes food and diet to one that emphasizes nutrient

supplements." (Lichtenstein and Russell, *JAMA* 294, 351-358)

The following chart lists known nutrients, as well as some components of human metabolism not known to be required in the diet.

Under "Notes," uses referred to as "Promoted for..." or "Marketed..." are generally unsupported by scientific evidence.

In general, small excesses of *water-soluble vitamins* are excreted; larger excesses can be harmful. Excesses of *fat-soluble vitamins* are more likely to be toxic because these accumulate in fatty tissues.

VITAMINS AND MINERALS

Note: new Dietary Reference Intakes are being developed to replace RDAs. EAR = estimated average requirement (adequate for 50% of individuals); AI = adequate intake (when not enough data to calculate EAR); UL = tolerable upper level.

Item	RDA or <i>safe and adequate level</i> (SA) (adult)	Toxic effects of megadoses	Notes
<i>Fat-soluble vitamins</i>			
A (retinol)	700 (women) 900 (men) µg [8400-10,800 µg beta carotene] (UL: 3000 µg vit A)	Birth defects, liver damage, skin problems, headache, fatigue, bone problems, nausea, diarrhea, hair loss. High dietary intake linked to hip fractures in women.	Many diets may be deficient. Promoted as cancer cure, antioxidant (see below, pp. 7-10). Made from beta carotene (much less toxic in large amounts).
D (D ₃ or cholecalciferol)	AI: 5 (age 19-50), 10 (51-70), 15 (over 70) µg (UL: 25 (0-1 yr), 50 (>1 yr) µg)	Hypercalcemia, bone demineralization, hypercalcuria. Also nausea, vomiting, other. Various problems in infants, including retardation and kidney damage.	A 2003 study on calcium absorption suggests that the recommended levels might need to be raised. 2004 studies showed intake inversely related to rheumatoid arthritis and multiple sclerosis.
E (α-tocopherol)	15 mg from food; 22 IU (<i>d</i>) or 33 IU (<i>dl</i>) (UL: 1000 mg, 1500 IU)	Bleeding problems, diarrhea, headache, muscle weakness, other.	Promoted as enhancing sexual performance; as antioxidant (see below, pp. 7-10). Natural (<i>d</i>) appears superior to synthetic (<i>dl</i>). Can increase effect or bioavailability of aspirin, digoxin, warfarin.
K	AI: 90 (women) 120 (men) µg	Could be hazardous if getting anticoagulants	Deficiency rare except in newborns
<i>Water-soluble vitamins</i>			
thiamine (B ₁)	1.1 (women) 1.2 (men) mg	Nausea, vomiting, anorexia	

Item	RDA or <i>safe and adequate level</i> (SA) (adult)	Toxic effects of megadoses	Notes
riboflavin (B ₂)	1.1 (women) 1.3 (men) mg		2004 study supported use in prevention of migraine.
niacin	14 (women) 16 (men) niacin eq. (mg free niacin) (UL 35 mg)	GI upset, abnormal liver function tests, hyperglycemia, atrial fibrillation, flushing of skin, itching, others	Promoted as cure for schizophrenia. Use in controlling high cholesterol (2000 mg doses).
pyridoxal phosphate (B ₆)	1.3 mg (over 51: men, 1.7, women 1.5) (UL 100 mg)	Peripheral neuropathy, depression, headache.	Many diets may be deficient. Marketed to treat PMS, depression, and carpal tunnel syndrome, but lack of evidence for these. *see p. 7
pantothenic acid	AI: 4-7 mg		Made by intestinal bacteria. Deficiency known only in severe malnutrition.
biotin	no RDA AI 30 µg		Made by intestinal bacteria. Deficiency only in unusual situations.
folic acid	400 µg dietary folate equiv. (UL 1000 µg, exc. food)	Increases neurological problems of B ₁₂ deficiency while masking its symptoms. Possible toxic effects of the synthetic form, which at high doses cannot all be converted to the active form.	Grains now supplemented to prevent birth defects. May reduce risk of colon cancer and heart disease. 2005 studies found high intake associated with reduced hypertension and Alzheimer's risk. *see p. 7
vitamin B ₁₂ (cobalamine)	2.4 µg		Deficiencies extremely rare. Several year supply stored in liver. Marketed to provide extra energy. *see p. 7
ascorbic acid (C)	women 75 mg, men 90 mg, (smokers 35 mg extra) (UL 2000 mg)	Diarrhea, interference with test for colon cancer, reduced effectiveness of anti-coagulant therapy, impaired immune function. 2004 study suggests could worsen arthritis. Possibly prooxidant if iron levels high.	Promoted as antioxidant; preventive for heart disease, cancer, etc. (see below, pp. 7-10) Little increase in plasma level at intakes above 200 mg/day.
choline	AI: 425 (women), 550 (men) mg (UL 3.5 g)	Hypotension, sweating, diarrhea, fishy odor	Promoted to improve memory, prevent aging, protect liver, reduce cholesterol; ergogenic aid

Item	RDA or <i>safe and adequate level</i> (SA) (adult)	Toxic effects of megadoses	Notes
<i>Not generally required in diet (can be made in the body)</i>			
inositol			Promoted to prevent baldness, reduce cholesterol, lose weight
betaine			
lipoic acid			Promoted as antioxidant, and for treatment of diabetic neuropathy, cataracts, glaucoma, others. Preliminary studies support benefits in diabetes. **see p. 7
carnitine		Possible deficiency of L-carnitine if D-carnitine also taken.	Promoted to aid weight control and athletic performance, to prevent heart disease and aging. Some evidence for use in treatment of heart disease, and for improved cognitive functioning in elderly. **see p. 7
biopterin			
para-amino-benzoic acid (PABA)			Promoted to prevent or reverse graying of hair
creatine			Ergogenic aid (see below, p. 13)
pyruvate			See below (p. 14)
coenzyme Q-10 (ubiquinone)			See below (p. 13)
<i>Macrominerals</i>			
calcium	1000 (20-50), 1200 (51-70), 1500 mg (>70). (UL 2500 mg)	Constipation, kidney problems	Some supplements found to be contaminated with lead. Can cause decreased absorption of several drugs and minerals.
phosphorus	800-1200 mg		
magnesium	320 (women) 400 (men) mg (UL 350 mg in supplements)	Diarrhea. Kidney failure. Neurological and other metabolic effects. Reported pediatric death.	Can decrease digoxin absorption. Supplements may help bone density in some older adults, and may be useful for coronary artery disease.

Item	RDA or <i>safe and adequate level</i> (SA) (adult)	Toxic effects of megadoses	Notes
sodium	1500 (20-50), 1300 (50-70), 1200 mg (>70) (UL 2300 mg)		
potassium	4700 mg (AI)		
<i>Trace minerals</i>			
iron	8 (men, post-menopausal women), 18 (pre-menopausal), 27 (pregnant) mg (UL 45 mg)	Gastrointestinal distress. Possibly heart damage, cancer.	Can cause decreased absorption of several drugs.
chlorine	1700-5100 mg (SA) (UL 3500 mg)		
fluorine			
iodine	150 µg (UL 1.1 mg)		
zinc	15 mg (UL 40 mg)	Blocks copper absorption. Increases magnesium excretion. Bone marrow depression, anemia, weaken immunity, reduce HDL, other. A 2003 study indicated increased risk of prostate cancer.	Promoted to prevent or treat colds (see p. 15), enhance sex drive, restore taste, help swollen prostate, others. Can decrease absorption of some drugs.
copper	900 µg (UL 10 mg)	Liver damage	
selenium	55 µg (UL 400 µg)	Damage to liver, nervous system, skin, nails, teeth. Gastrointestinal upset.	Functions in glutathione peroxidase and at least 14 other selenoproteins. Promoted as antioxidant and for treatment of many diseases. Recent studies support role in cancer prevention (e.g., prostate and colorectal cancer). (However, supplements appeared to <i>increase</i> skin cancer in high risk individuals.)
sulfur			See p. 17 concerning MSM, an alleged source of sulfur.

Item	RDA or <i>safe and adequate level</i> (SA) (adult)	Toxic effects of megadoses	Notes
manganese	AI 1.8 (women) 2.3 (men) mg (UL 11 mg)	Neurological problems. People with liver disease more sensitive.	Deficiency unknown. Some supplements provide 10-40 mg/day.
molybdenum	45 µg (UL 2 mg)		
cobalt			
chromium	AI 25 (women) 35 (men) µg	One report of kidney and liver damage.	See below (p. 12). Can enhance effects of several drugs.
boron	(UL 20 mg)	Nausea, vomiting, diarrhea, dermatitis, lethargy	Promoted as "ergogenic aid," aphrodisiac, arthritis remedy. No requirement established in humans.
silicon			Marketed to maintain bones, connective tissue, hair, nails
vanadium	(UL 1.8 mg)		Role unknown. See below (p. 19)
nickel	(UL 1 mg)		Role unknown
<i>Other</i>			
fatty acids			Linoleic and linolenic considered essential. Docosahexaenoic acid (DHA) and eicosapenta- enoic acid (EPA) are promoted for infant formula and other uses. See also fish oils (p. 13) and flaxseed oil (p. 16).
lecithin (phosphatidyl choline)			Marketed to lower cholesterol, improve memory, and treat arthritis, and for weight loss.
phosphatidyl serine			Marketed to prevent muscle breakdown and improve memory.
amino acids (general)		Excess of one may interfere with absorption and utilization of others.	See "smart" drinks below (p. 19). Studies of amino acid combina- tions have not supported claims that they increase growth hormone or insulin secretion.
tryptophan		Deaths due to eosinophilia- myalgia syndrome (from contaminant, but tryptophan itself might also cause)	Marketed to treat insomnia, depression, PMS, overweight

Item	RDA or <i>safe and adequate level</i> (SA) (adult)	Toxic effects of megadoses	Notes
valine			Marketed to "combat stress"
glutamate			Marketed to improve memory
cysteine			Marketed as antioxidant
glutamine			Marketed to provide glutamate to brain; build muscle protein
phenylalanine			Marketed for pain relief, alertness, improved mood, appetite suppression
aspartate			Marketed to aid mineral absorption.
lysine			Marketed to treat genital herpes. Studies have given contradictory results.
arginine			Arg is a precursor of NO. Marketed to enhance "vascular health" and sexual function, and to stimulate growth hormone release. Clinical studies for use with coronary artery disease have given conflicting results.
protein	0.8 g/kg body wt. (about 50-60 g)	Kidney damage	Marketed for muscle building.

*The combination of folate, B₆, and B₁₂ is important in maintaining low *homocysteine*, implicated as a risk factor in heart disease. However, a 2004 study reported no vascular benefits from such a combination (Toole et al. (2004) *JAMA* 291, 565-575).

**In 2002 Ames and colleagues reported anti-aging effects in rats from lipoic acid plus a carnitine derivative. Ames (*Arch. Biochem. Biophys.* 423, 227-234 (2004)) also cites clinical studies in support of supplementing with these two compounds, and has formed a company (Juvenon) to market them.

VITAMINS AS ANTIOXIDANTS

During normal metabolism, some dangerous products (hydrogen peroxide, superoxide anion) are made from oxygen. These can damage proteins, DNA, and lipids. Such damage may lead to cancer and/or various effects of aging. Molecules that fight these oxidizing compounds are antioxidants (conversely, molecules that help generate them are prooxidants).

Traditional research on vitamins has dealt with levels needed to prevent deficiency diseases. Increasing attention is being placed on their possible uses, at much higher levels, in preventing other diseases. Of special interest is roles of vitamins E, C, and A as antioxidants. Selenium, which is needed for glutathione peroxidase, is also the focus of attention. Many large clinical trials and retrospective studies have been performed or are in progress.

The leading hypothesis of *atherosclerotic plaque formation* proposes a critical role for oxidation of LDL; thus, antioxidants are proposed to protect against atherosclerosis.

Studies have supported roles (antioxidant and other) for:

- Vitamin E in prevention of heart disease, various types of cancer, cataracts
 - in protecting the heart, during or after heart attack or after bypass surgery
 - (however, a 1999 review notes that not all studies on vitamin E and heart disease are consistent (*Arch. Int. Med.* 159, 1313))
 - in enhancing immunity
 - in treatment of Parkinson's disease
 - in prevention of free radical damage to muscles during exercise
 - in slowing the progression of Alzheimer's
 - in prevention of age-related macular degeneration
 - (conflicting results have been obtained concerning prevention of strokes)
- Vitamin C in prevention of heart disease (also some evidence for improved heart function after heart attacks), some types of cancer (not confirmed in other studies), cataracts, strokes; and in overall reduction of mortality.
- Vitamin A (from beta carotene) in prevention of heart attacks and stroke (*but see below*)
 - in treatment of mouth cancer, prevention of prostate cancer
 - (possible reduction of cancer risk in general)

Note - levels of A and C comparable to those being studied can be obtained from a diet rich in fruits and vegetables.

Other points concerning vitamin E:

- There is stronger evidence for the benefits of *dietary* vitamin E than for supplements. Two studies with vitamin E supplements in high risk cardiovascular patients found no benefits.
- Meta-analyses also concluded that vitamin E supplements provide no benefit for cardiovascular mortality (a 2003 review, Vivekananthan et al. *Lancet* 361, 2017-2023 included 7 trials with 82,000 patients).
- Meagher et al. (*JAMA* 285, 1178-1182 (2001)) found no effect of vitamin E supplements on biochemical markers of lipid peroxidation.
- Taylor et al. (*BMJ* 325, 11-14 (2002)) observed no benefit of vitamin E supplements for macular degeneration.
- One study indicated that γ -tocopherol may also be important, and that too much α -tocopherol could interfere with its actions.
- 2004 study found vitamin E did not reduce onset of Alzheimer's.
- 2004 meta-analysis including more than 135,000 subjects concluded that high doses of vitamin E increased mortality (Miller et al., *Ann. Intern Med.* 143, 37-46). A 2005 paper found that 11% of U.S. adults were taking 400 IU or more per day (Ford et al., *Ann. Intern. Med.* 143, 116-120).
- 2005 secondary prevention study of cancer (Bairati et al., *J. Natl. Canc. Inst.* 97, 481-488) found adverse effects of vitamin E supplements.
- 2005 trial including heart or diabetes patients found no benefit of vitamin E supplements in cancer prevention or cardiovascular events, and possibly increased risk of heart failure (Lonn et al., *JAMA* 293, 1338-1347). Similar findings were reported in a study involving healthy women (Lee et al. (2005), *JAMA* 294, 56-65), although there was a decrease in cardiovascular mortality (but not overall mortality).
- 2005 meta-analysis indicated that dietary vitamin E (but not vitamin C or beta carotene) reduced risk of Parkinson's.

Other points concerning vitamin C:

- Many studies have disputed Linus Pauling's claims that vitamin C can prevent colds. Some studies suggested that it could slightly reduce symptoms; one trial found no effect. It also does not prolong

survival times of cancer patients.

- Some have proposed that vitamin C can act as a prooxidant (especially with high iron levels), but others feel that this activity is negligible under physiological conditions. Also controversial is whether high levels can cause DNA damage.

Other points concerning vitamin A/beta carotene:

- Two large studies (22,000 doctors; 40,000 women health professionals) found *no benefit of beta carotene supplements* in preventing cancer or heart disease. (As with dietary vitamin E, possibly *other compounds* associated with dietary beta carotene are beneficial.)
- The meta-analysis by Vivekananthan et al. (see above) reviewed 8 trials of beta carotene supplementation for heart disease, involving 138,000 patients, and found a small *increase* in mortality.
- In a 2003 study of prevention of colon polyp recurrence, beta carotene supplements were beneficial for non-smoker, non-drinkers, but caused increases in recurrence for those who smoked or drank (Baron et al. *J. Natl. Cancer Inst.* 95, 717-722).

Combinations of the vitamins:

- Plotnick et al. *JAMA* 278, 1682-6 (1997): vitamins E and C protected endothelial function from effects of a high fat meal.
- Masaki et al. *Neurology* 54, 1265-1272 (2000): vitamins E and C in combination protected against vascular dementia (but not Alzheimer's).
- A combination of antioxidant vitamins plus zinc was found to slow the progression of age-related macular degeneration, but not to help with cataracts. [This study prompted marketing of supplements to *prevent* not only macular degeneration, but also other eye problems.]
- A study found that a diet rich in fruits and vegetables did *not* reduce colon and rectal cancer, while a pooled analysis of several large studies found no protection from breast cancer. Another study (van Gils et al. (2005) *JAMA* 293, 13-193) also found no protection against breast cancer.
- Two studies examined effects of *dietary* antioxidant intake on incidence of Alzheimer's disease. One found protective effects of E and C (Engelhart et al. (2002) *JAMA* 287, 3223-3229; the other only for E (Morris et al. (2002) *JAMA* 287, 3230-3237). Neither found a benefit from vitamin *supplements*. A third study found no effect of dietary carotenes, vitamin C, or vitamin E, nor effects of vitamin C or E supplements (Luchsinger et al. (2003) *Arch. Neurol.* 60, 203-208).
- The British Heart Protection Study, following 20,000 subjects for 5 years, found no benefit from a combination of vitamins E and C, and beta carotene, for heart disease, cancer, and several other conditions (*Lancet* 360, 23-33 (2002)).
- Supplementation with vitamin E, C, or multivitamins was not associated with reduced risk of cardiovascular disease (Muntwyler et al. (2002) *Arch. Intern. Med.* 162, 1472-1476).
- Dietary intake of vitamin E was associated with reduced risk of Parkinson's disease, but not dietary vitamin C or carotenoids, or supplementation with vitamin E or vitamin C (Zhang et al. (2002) *Neurology* 59, 1161-1169).
- In women with heart disease, supplementation with vitamins E plus C did not provide benefit, and there was a suggestion of harm (Waters et al. (2002) *JAMA* 288, 2432-2440).
- Zandi et al. (*Arch. Neurol.* 61, 82-88 (2004)) - combination of vitamin E and C supplements reduced risk of Alzheimer's.
- Bjelakovic et al. (*Lancet* 364, 1219-1228 (2004)) - a meta-analysis of 14 trials with more than 170,000 participants found no evidence of protective effects of antioxidant supplements against gastrointestinal cancer (and even a slight increase in mortality). (However, selenium might be protective.)

Potential hazards of these vitamins:

- Study of smokers in Finland (1994) - beta carotene *increased* incidence of lung cancer. Also suggested increased risk of stroke from vitamin E. The beta carotene danger to smokers was confirmed in a National Cancer Institute study (which used beta carotene and vitamin E together).
- Brown et al. (*New Engl. J. Med.* 345, 1583-1592 (2001)) found that a combination of antioxidant vitamins plus selenium interfered with the benefits of cholesterol-lowering drugs.

- Because antioxidant vitamins protect against apoptosis, they may *interfere with chemotherapy or radiation treatment*. (However, some recent papers indicate that antioxidants can be useful when combined with certain types of chemotherapy.) Antioxidants may also interfere in other metabolic situations in which oxidizing conditions are required for desirable effects.
- A review on antioxidants noted, concerning their use in fighting oxidative stress, “Antioxidants can protect or increase injury depending on the situation and therefore their use should always be made with a full appreciation of the situation.” (Azzi et al. (2004) *FEBS Lett.* 558, 3-6)
- An animal study indicated that combinations of vitamins C and E could increase lung cancer in smokers (Fiala et al. (2005) *Carcinogenesis* 26, 605-612).

The Institute of Medicine, which released new dietary recommendations for antioxidants in 2000, concluded that there is not yet sufficient evidence to conclude that megadoses prevent chronic disease.

In 2003, the U.S. Preventive Services Task Force (an independent panel sponsored by the Agency for Healthcare Research and Quality) concluded that “the evidence is insufficient to recommend for or against the use of supplements of vitamins A, C, or E; multivitamins with folic acid; or antioxidant combinations for the prevention of cancer or cardiovascular disease.”

An American Heart Association Science Advisory statement (*Circulation* 110, 637-641 (2004)) concluded, “At this time, the scientific data do not justify the use of antioxidant vitamin supplements for CVD risk reduction.”

PHYTOCHEMICALS

There is great interest in roles (antioxidant and other) of various plant compounds (*phytochemicals*) in preventing cancer and other diseases. These include bioflavonoids (including quercetin and rutin), allicin (in garlic), lutein (in spinach, kale, and other vegetables), lycopene (in tomatoes), genistein (in soybeans), resveratrol (in grapes), anthocyanins (in blueberries), and sulforaphane (in broccoli). Of particular interest are estrogen-like compounds (*phytoestrogens*). Some evidence that phytoestrogens may reduce risk of various forms of cancer. However, a 2004 review found they were ineffective in dealing with menopausal symptoms. Lycopene may also protect against cancer and heart disease, while lutein may protect against atherosclerosis, macular degeneration, and cancer. In 2005 the FDA decided to allow only qualified health claims related to lycopene and cancer. [A 2003 animal study suggested tomato compounds other than lycopene were protective.] See below (pp. 14-15) for discussion of soy products.

Dwyer et al. (*Arterioscler. Thromb. Vasc. Biol.* 24, 313-319 (2004)) - plasma levels of carotenoids (lutein, β -cryptoxanthin, zeaxanthin, α -carotene) associated with lower risk of atherosclerosis.

An alternative view to the antioxidant hypothesis is that some of these compounds are potentially toxic, yet confer advantages by inducing detoxifying enzymes. These in turn help dispose of carcinogens.

DIETARY SUPPLEMENTS: LABELING ISSUES

FDA labeling regulation are governed by the Dietary Supplement Health and Education Act (DSHEA) of 1994. (Note: *herbs* are included in these regulations.)

Definitions:

label - anything on the product

labeling - anything that is written, printed, or graphic which accompanies the purchase of the product. Subject to same rules as label.

health claim - refers to prevention or treatment of a specific disease

structure and function claim - related to general ideas (e.g., bones, energy, immune system) but not to a specific disease

Regulations:

Structure and function claims must have scientific support, but need not be approved by FDA (can even be kept secret!). Consumers do not generally understand this provision, and tend to think that claims have been approved. Because of confusion over allowed claims, clarifications were issued by the FDA in January, 2000. Claims for dealing with minor symptoms associated with life stages (e.g., menopausal symptoms) are allowed. Structure and function claims on the labels must be accompanied by a disclaimer: "This statement has not been evaluated by the FDA. This product is not intended to diagnose, treat, cure, or prevent any disease."

Health claims (see definition above) must be approved by FDA. A 1999 court ruling required that the FDA also issue *qualified health claims*

that would be misleading without such qualification. These qualified claims are based on the weight of the scientific evidence. An example of this type of claim is "supportive but not conclusive research shows that consumption of EPA (eicosapentaenoic acid) and DHA (docosahexaenoic acid) omega-3 fatty acids may reduce the risk of coronary heart disease." (*FDA Consumer*, Jan.-Feb. 2005)

Third party literature making health claims may be disseminated in a store, as long as it is not in direct conjunction with the product (which would be labeling), is not false or misleading, and doesn't promote a particular brand.

Products do not need to be shown to be safe, just have to give "reasonable assurance" that not a significant risk of harm. Burden is on FDA to show unsafe. "To police an industry with 1,000 manufacturers offering 20,000 products, the FDA has a core staff of eight people." (Boston *Globe*, Aug. 22, 1999) (It is now estimated that there are 30,000 products, with 1000 new ones each year.)

In an editorial (*JAMA* 289, 1568-1570 (2003)), Fontanarosa et al. wrote, "...these products nearly always include at least one 'structure/function' claim...Yet the only way such claims can be valid is if the dietary supplement actually promotes or has inherent biological activity...If dietary supplements have or promote such biological activity, they should be considered to be active drugs. On the other hand, if dietary supplements are claimed to be safe because they lack or have minimal biological activity, then their ability to cause physiologic changes to support 'structure/function' claims should be challenged, and their sale and distribution as products to improve health should be curtailed. Manufacturers of dietary supplements are trying to have it both ways. They claim that their products are powerfully beneficial, on the one hand, but harmless on the other. To claim both makes no sense, and to claim either without trials demonstrating efficacy and safety is deceptive. The public should wonder why dietary supplements have effectively been given a free ride."

In a 2002 report, the FDA identified the following as priority areas for enforcement: treatments for life-threatening diseases; weight loss products; autism treatments; treatments for behavioral disorders; treatment for mental retardation and Down's Syndrome; colloidal minerals; supplements for smokers; supplements for drinkers; and colloidal silver products.

In 2003, the FDA proposed manufacturing standards for dietary supplements. These would relate to issues of quality control and handling of customer complaints, not to whether the products are effective.

In 2004, the Institute of Medicine and the National Research Council recommended that DSHEA be modified to give the FDA greater ability to regulate supplement safety. They also concluded that "FDA does not have to find direct evidence of actual harm from use of a supplement ingredient to determine that the product poses an unreasonable risk to consumers' health." (A. Clark, Senate testimony, June 2004)

SOME DUBIOUS PRACTICES OF THE DIETARY SUPPLEMENT INDUSTRY

Invalid diagnostic methods for nutritional deficiencies (questionnaires, applied kinesiology, iridology, live cell analysis, hair analysis, etc.)

Reliance on testimonials and anecdotal evidence

Disparaging claims about quality of food due to poor soils, food processing, pesticides, etc. But plants won't grow properly if they don't have the necessary minerals, and make vitamins themselves.

Promoters may boast of degrees from nonaccredited institutions

Ignorance of principles of digestion and metabolism (e.g., selling enzymes that will be degraded before they can be of use)

Promotion of products that are not needed in the diet (e.g., carnitine) or have no role in human metabolism (e.g., chlorophyll)

Promotion of products for nutrient content (e.g., royal jelly, blue-green algae) that can be obtained much more easily from normal food

Promotion of products that can be dangerous at the levels suggested.

Aggressive marketing techniques, which may involve lay people who are not knowledgeable in nutrition

Gotay and Dumitriu (*Arch. Fam. Med.* 9, 692-698 (2000)) surveyed health food stores, with a researcher pretending to be a daughter of a cancer patient. "Store personnel readily provided information and product recommendations." 18% "directly or indirectly counseled against the use of orthodox cancer therapies."

SOME POPULAR DIETARY SUPPLEMENTS

Antioxidants and phytochemicals - see pp. 7-10.

Androstenedione - precursor of testosterone and estrogen. Studies found no increase in strength or testosterone in men, but rather increases in estrogen and unfavorable changes in blood lipid profiles. Numerous other side effects and potential risks have been reported. In 2004, the FDA ordered companies to stop selling it unless they can prove that it is safe.

Chromium picolinate - Chromium appears to enhance insulin action, but mechanism not clear. Recent research suggests activation of insulin receptor kinase activity. Although dietary requirement not known, it is alleged that 90% of Americans are deficient. However, deficiency is difficult to detect, and thought to be unlikely; the typical American diet meets or exceeds the AI. Picolinate is organic molecule to complex the chromium and aid absorption. Controversial whether toxic. Report from China suggesting value in treating diabetes, though a meta-analysis found no association with glucose or insulin levels in non-diabetic individuals (Althuis et al. (2002) *Am. J. Clin. Nutr.* 76, 148-155). The NIH-ODS has concluded that "the value of chromium supplements for diabetics is inconclusive and controversial." Controlled studies have shown no benefit in increasing muscle mass. In 1996, the FDA acted to stop unsupported claims made by major marketers of chromium picolinate.

Coenzyme Q10 - component of mitochondrial respiratory chain. Made in body, not required in diet. Some evidence that it might be useful in treatment of heart disease, though other studies found no benefit. Also promoted as antioxidant. A study found that it slowed progression of Parkinson's symptoms (Shults et al. (2002) *Arch. Neurol.* 59, 1541-1550). An open-label trial found benefits with migraine. Another rationale for using is to counteract possible decreases in CoQ10 due to use of statin drugs.

Coral calcium - derived from coral of Okinawa. Alleged to be better absorbed than other forms of calcium; to prevent numerous diseases; and be responsible for longevity of Okinawans. In 2003-4 the FTC and FDA took action against leading marketers for making false and unsubstantiated claims.

Creatine - marketed to increase muscle strength and athletic performance. Evidence for benefit in sports requiring short bursts of intense activity, but not for sustained aerobic exercise. Side effects including diarrhea, muscle cramps, and dehydration reported (but not confirmed in blinded studies). Also possible mutagenic effects. Some increase in muscle mass may be water retention. In 2000, the KMA passed a resolution opposing use of creatine for athletic performance, and urging coaches and parents to consult physicians before allowing its use. Two studies (2002, 2003) indicated that prolonged use may produce abnormalities in pancreatic metabolism and glucose homeostasis. A 2003 paper found improved brain performance with supplementation in vegetarians (who have lower creatine intake).

Dehydroepiandrosterone (DHEA) - a natural steroid which declines in age; some evidence that administration may relieve some effects of aging. However, popular claims are exaggerated, and doses sold over-the-counter may be ineffective. Higher doses could cause dangerous side effects. Recent studies support reduction of abdominal fat (2004), reduction of hypertension (2005), and treatment of depression (2005). Lobbying for the supplement industry resulted in DHEA being exempted from being a controlled substance like other steroids.

Fish oils (with the ω -3 fatty acids EPA and DHA) - considerable evidence associating intake of oily fish with reduced incidence of heart disease, cancer, stroke, and Alzheimer's. Proposed mechanisms related to heart disease include antiarrhythmic, antithrombotic, antiatherosclerotic, and anti-inflammatory effects; enhanced endothelial function; reduction in blood pressure; and reduced triglycerides. Less evidence in support of supplements. There is an FDA-allowed qualified health claim that ω -3 fatty acids from fish oil may reduce the risk of heart disease, and the American Heart Association supports the use of supplements for heart patients. Found beneficial in one study of heart attack patients (*Lancet* 354, 447 (1999)). Some studies support prevention of prostate cancer and reduction of menstrual discomfort. Possible side effects: may increase cholesterol; abdominal and intestinal distress; impaired blood clotting; vitamin E deficiency; drug interactions.

Garlic - promoted to lower cholesterol and blood pressure, prevent heart disease, cancer, and other problems. A 2001 review found "possible small short-term benefits of garlic on some lipid and antiplatelet factors" (*Arch. Intern. Med.* 161, 813-824). Another meta-analysis supported a protective effect against colorectal and stomach cancer (*Am. J. Clin. Nutr.* 72, 1047 (2000)). Improved elasticity of aorta (*Circulation* 96, 2649 (1997)) and antiatherosclerotic effects (*Atherosclerosis* 144, 237 (1999)) have been reported. A problem with garlic studies is that adequate blinding requires preparations lacking in distinctive taste and odor, which may remove active ingredients.

Glucosamine - widely used for treatment of arthritis. Rationale: synthesis rate-determining for proteoglycan synthesis, which in turn can help restore cartilage; also suggested to inhibit proteoglycan breakdown. A 2003 paper, using cultured chondrocytes, found that exogenous glucosamine had no ability to increase chondroitin sulfate synthesis, but other effects remain possible. (It has also been proposed that the sulfate is useful, not the glucosamine; the compound is usually sold as the sulfate salt.) *Chondroitin sulfate* is marketed along with glucosamine. This is less plausible, since this large molecule is unlikely to survive digestion, be absorbed, and delivered to a useful site. Conflicting results have been reported concerning the ability of chondroitin sulfate to be taken up in intact form.

A 2003 meta-analysis (Richy et al. *Arch. Intern. Med.* 163, 1514-1522) supported the utility of both glucosamine and chondroitin. However, since then additional negative studies have been reported. It has been noted that positive studies were funded by manufacturers, while negative studies were independent. A 2005 Cochrane review gave mostly negative conclusions. Negative results from a large new trial were announced in November 2005.

Possible allergic reactions with products derived from shellfish.

Juicing - consumption of juices from raw fruits and vegetables. Allegedly provides superior source of nutrients and active enzymes, as well as helping to cure various diseases. Dried juice products are also sold. (See also Noni, p. 16) *Mangosteen* (an Asian fruit) is another currently popular juice, supposedly providing immune and anti-aging benefits.

Melatonin - hormone produced by pineal gland. Promoted in best-selling books, not only for aiding sleep, but also for many other conditions, including cancer, AIDS, and Alzheimer's. Some effects on sleep are well-supported; evidence for other effects is anecdotal or preliminary. An Agency for Healthcare Research and Quality (AHRQ) review (2004) concluded that "there is evidence to suggest that melatonin is not effective in treating most primary and secondary sleep disorders, although there is some evidence to suggest that melatonin is effective in treating delayed sleep phase syndrome. Moreover, there is no evidence to suggest that melatonin is effective in alleviating the sleep disturbance aspect of jet lag and shift-work disorder" and "the effectiveness of melatonin in alleviating jet lag may not involve alleviation of the sleep disturbance, but rather, the daytime fatigue associated with jet lag." Possible side effects, including disturbances in sleep patterns and GI problems. One study found that melatonin levels do *not* decrease with age.

Pyruvate - claimed to aid weight loss, improve endurance, reduce cholesterol, and act as antioxidant. Some research support, but in general studies are almost entirely from one investigator, limited to very special situations (e.g., morbidly obese patients in experimental setting, or preliminary studies of specific types of exercise), and used much larger doses than in marketed products. A review by Pittler and Ernst (*Am. J. Clin. Nutr.* 79, 529-536 (2004)) concluded that "Considering the evidence available from rigorous clinical trials, the case of pyruvate as an aid to body-composition changes and weight loss is weak."

S-Adenosylmethionine ("SAM-e") - promoted for depression and arthritis. Many clinical studies, though mostly from Europe, and some American researchers are skeptical. A 2001 review (*Ann. Pharmacother.* 35, 1414-1425) concluded that "Although there exists significant potential for therapeutic application of SAMe, its uncertain risk profile precludes definitive recommendation at this time." A 2002 report by the AHRQ also indicated that results appeared promising for depression, arthritis, and liver disease. U of L researchers have studied effects on liver disease. Compound is unstable, so supplements can vary widely in quality. Can cause gastrointestinal distress.

Seasilver - liquid supplement containing vitamins, minerals, and amino acids. Allegedly could treat or cure 650 health problems. In 2003 the FTC and FDA took action against the marketers.

Soy products - soybean products are thought to provide some benefits in prevention of heart disease, certain cancers, and osteoporosis. Evidence is mainly epidemiological (lower incidence in Asian populations with diets rich in soy products). Effects may arise from *isoflavones* acting as *phytoestrogens* (see above), but the protein may be important in itself or in allowing proper absorption. An FDA-allowed health claim is that soy protein may help lower cholesterol and reduce the risk of heart disease. Some women are taking soy isoflavone supplements as an alternative to estrogen replacement therapy, but these present potential dangers. Doses are much larger than in Asian diets. Trade-off of estrogenic and anti-estrogenic effects could increase cancer rather than prevent it. Benefits seen in Asian diets might be from taking early in life; large amounts later in life could be harmful. (A report also suggested that high consumption of tofu in midlife was correlated with decreased mental performance in later life.) 2004 study of women age 60-75 found no effect of soy protein on cognitive function, bone mineral density, or plasma lipids, but a 2005 study found decreased risk of bone

fracture. 2005 study of women with breast cancer found no benefit for menopausal symptoms. Another 2005 study found decreased blood pressure. Reviews by the AHRQ (2005) and American Heart Association (2006) concluded that there was not good evidence in favor of various claimed benefits.

Zinc - promoted for treatment of colds. Administered as spray, gel, or lozenges. Contradictory results have been obtained in various studies. Reports of loss of sense of smell after use of nasal products.

OTHER ITEMS MARKETED AS DIETARY SUPPLEMENTS

(Note: herbs are discussed in a separate handout)

"Claimed benefits" are generally unsupported by scientific evidence.

Proteins (e.g., digestive enzymes, superoxide dismutase, catalase), nucleic acids (DNA and RNA), and "glandulars" will be digested and therefore will not provide any special benefits to other parts of the body.

Name	Claimed benefits	Toxicity	Notes
Acidophilus (<i>Lactobacillus acidophilus</i>)	Aid digestion, restore healthy balance of microorganisms to digestive tract		In supplements, milk, yogurt. See "probiotics" below.
"Barley green"	Source of vitamins, amino acids, SOD, chlorophyll (to help anemia). Cure for arthritis, cancer, other diseases. Enhanced athletic performance.		From young barley leaves. Chlorophyll (see below) is chemically similar to heme, but it would not be converted to heme.
bee pollen (see also propolis, royal jelly)	Source of protein, vitamins, minerals. Enhanced athletic performance. Cure for hair loss, faulty memory, alcoholism, diabetes, other.	May cause allergic reactions. May be contaminated with insect and rodent debris.	Protein content small, can be obtained from regular food. Controlled studies show no effect on performance. No evidence for other claimed benefits.
beta-hydroxy beta-methylbutyrate	Decreased protein breakdown in exercise		Leucine metabolite. 2002 review was positive.
bioflavonoids (Chemicals based on flavone structure. Include rutin and some compounds from citrus fruits)	Antioxidants. Treatment or prevention of herpes, cancer, diabetic cataracts, abnormal bleeding, allergies, other.	One study suggests that maternal intake may contribute to infant leukemia.	Pharmacologic use in strengthening capillaries in hypertension? Shown not to help resistance to colds and flu. One study suggests that dietary flavonoids protect against lung cancer.

Name	Claimed benefits	Toxicity	Notes
blue-green algae (Spirulina)	Source of vitamins A and B ₁₂ , protein, minerals, chlorophyll, neuropeptides, and DNA. Mental and physical stimulant. Treatment of headache, Alzheimer's, allergies, cancer, others. Aid in weight loss. Stimulate immune system	Some algae have toxins causing gastrointestinal disturbances and other symptoms. May be contaminated with insect parts.	Nutrients can easily be obtained from other foods. Chlorophyll - see below. Neuropeptides would be digested. Even if not, would not cross blood-brain barrier. Claims for DNA are preposterous.
chlorophyll	Treatment for ulcers, hypertension, allergies, infections, other.		No role in human metabolism. Is digested, not absorbed intact.
colloidal minerals	More efficiently absorbed.		Promoted by Joel Wallach, who has made dubious statements about nutrition and disease. Claims of superior absorption are unfounded.
conjugated linoleic acid (CLA) (a group of linoleic acid isomers)	Weight loss, bodybuilding. Prevention of heart disease, diabetes, cancer	Animal studies showed enlarged livers and insulin resistance. Human studies have shown adverse effects on blood lipids and C-reactive protein.	Found in milk and meat of some ruminant animals. Some benefits found in animal studies but not yet with humans.
digestive enzymes (various proteases, barley diatase, bile extract)	Improve digestion, prevent inflammation, enhance immunity, other. Pancreatic enzymes promoted as cancer cure (see cancer handout, N. Gonzalez).		Not needed in intestine (except for deficiency of pancreatic enzymes). Would be digested and not contribute to metabolism elsewhere.
dolomite	Source of calcium and magnesium	May have toxic levels of lead, mercury, arsenic	Poorly absorbable form of these nutrients
fibers, water-soluble (e.g., psyllium)	"Aid intestinal cleansing by pulling heavy metals and toxins out of the body." Aid dieting, due to feeling of fullness.		Soluble fibers may lower cholesterol. One study found they may <i>increase</i> recurrence of colorectal cancer.
flaxseed oil (with the ω -3 fatty acid ALA)	Lower cholesterol; reduce inflammation; prevent cancer; reduce PMS	Diarrhea, interference with vitamin absorption.	Evidence for cholesterol and cancer benefits is promising but preliminary.

Name	Claimed benefits	Toxicity	Notes
gamma-hydroxybutyrate (GHB)	Bodybuilding. Recreational drug	Vomiting, dizziness, tremors, seizures. Severe withdrawal symptoms.	Caused several deaths. Banned by FDA, but illegal use continues. Similar problems with gamma-butyrolactone (GBL) and butanediol (BD).
gamma-linolenic acid (GLA) (from black currant seed, evening primrose, and other oils)	Precursor of prostaglandin E ₁ , giving various benefits.		Alleged benefits (and claimed deficiency of gamma-linolenic acid are not substantiated. 2003 trial found ineffective for eczema. 2005 trial found ineffective for breast pain. 2000 Cochrane review suggested potential for use with rheumatoid arthritis.
Gerovital (GH3)	Anti-aging remedy; prevention of many diseases	Low blood pressure, breathing problems, convulsions	Major component is procaine. No benefit in controlled trial.
"glandulars" (material from animal organs)	Alleged to treat the corresponding organ (e.g., adrenals)	Bacterial contamination. Potential spread of prion diseases.	Would be digested like other foods, not targeted to any particular organ.
5-hydroxy-L-tryptophan (5HTP)	Treatment of insomnia, depression, obesity, attention deficit disorder	Possibly dangerous impurities detected	
methylsulfonyl-methane (MSM)	Source of dietary sulfur; "joint support"		Not a source of dietary sulfur (possibly a product of sulfur amino acid metabolism)
Noni juice (Tahitian Noni) (fruit of <i>Morinda citrifolia</i>)	Contains proxeronine, precursor of xeronine, which allegedly enhances nutrient uptake and cell function. Claimed to enhance immune system and help many illnesses.	Liver problems reported in three users in 2005.	Two animal studies support antitumor effects.

Name	Claimed benefits	Toxicity	Notes
probiotics (bacteria meant to survive in intestine and provide benefits) ("prebiotics" are nutrients given to help the growth of beneficial bacteria)	Provide healthy balance of intestinal microbes; treatment of diarrhea and other intestinal problems; reduce allergies; boost immune system; other claimed benefits.		Some evidence in support of treatment or prevention of diarrhea and respiratory infections, in treating food allergies, and in enhancing immune system, but much data is preliminary and/or may not apply to healthy individuals. Difficult to alter the resident population - may need to be given repeatedly. Many products contain bacteria that do not survive digestive process.
propolis ("bee glue" - a waxy plant material collected by bees and used as cement)	Antibiotic properties - used in creams and lozenges	Skin inflammation; mouth ulcers	
Pycnogenol®	Antioxidant; improve circulation		Pine bark extract. FDA: no evidence of effectiveness against disease.
raw (unpasteurized) milk	More nutrients, since not destroyed in heating.	Illnesses and deaths have been caused by <i>Salmonella</i> and other bacteria.	Vitamin C and thiamine levels are 10% lower with pasteurization, but milk is not an important source of these.
RNA and DNA	"Rejuvenate" cells, improve memory, prevent wrinkling of skin. Provide nucleotides for T cells.	Increased uric acid	No nutritional requirement - can be synthesized <i>de novo</i> . Would be digested. Even if not, unlikely to function in cells.
royal jelly (secretion of bees, given to future queens)	Prevention or treatment of chronic fatigue syndrome, asthma, insomnia, emotional disturbances, others. Increase stamina, enhance immune system, slow aging.	Anaphylaxis has caused at least one death.	Secreted bee hormones unlikely to have any effect on human metabolism (if not digested first)
sea salt, seawater	Supplies needed minerals. Helps prevent cancer, heart disease, others.		

Name	Claimed benefits	Toxicity	Notes
"smart" drinks (contain phenyl-alanine, cysteine, choline, taurine, etc.) (are also "smart" drugs)	Enhance mental performance	Irritability or insomnia from Phe; gastroenteritis and pancreatitis from choline; Cys could harm fetus	
superoxide dismutase (SOD), catalase	Protect from oxidative damage, thus preventing aging and degenerative diseases.		Will mostly be digested rather than being absorbed intact. Even if absorbed, unlikely to reach a useful site of action.
tissue salts (cell salts)	Treatment of various disorders	Nontoxic - extremely small amounts of ordinary chemicals.	Similar to homeopathic remedies. Tiny doses of common mineral salts sold as solutions or lactose pills, labeled with Latin names.
vanadium (vanadyl sulfate)	Insulin-like effects; provide extra energy during exercise	High doses produce gastrointestinal disturbances and green tongue.	Vanadium compounds inhibit tyrosine phosphatases. Research supports insulin-like actions in animals; human benefits not yet documented.
wheat germ oil (octacosanol)	Increased vigor and endurance		

Diets and Weight Loss

Overview

Many Americans are greatly concerned with being overweight, for reasons of health and/or appearance. Dieting and weight loss are major areas for "alternative" products and advice. A new best-selling diet book appears nearly every year. Diet formulations, as well as nutritional supplements, herbal preparations, and devices are marketed.

Some general points:

1. Should consider whether the diet provides adequate nutrition (protein, vitamins, minerals, calories), and whether there is an appropriate balance of carbohydrate, protein, and fat. Potential beneficial antioxidants, phytochemicals, and ω -3 fatty acids should also be considered.
2. Rapid weight loss is often seen in the early stages of a diet, but this may be mostly water.
3. Most people who lose weight on a diet later regain it.

Some components of diet products (other than macronutrients)

Vitamins and minerals

Carnitine - to enhance burning of fat (but not needed in diet)

Ephedra (ma huang) - alleged appetite suppressant and/or metabolic stimulant. See herb handout for risks. With increasing concern over the safety of ephedra, leading manufacturers are now replacing it with bitter orange (*Citrus aurantium*). (This contains the active ingredient synephrine, which could produce adverse cardiovascular effects. No convincing evidence of effectiveness in weight loss.)

Other "thermogenic" herbs

Other herbs - to eliminate excess water. Some may also have laxative effect. Some "dieter's teas" contain "senna, aloe, buckthorn, and other plant-derived laxatives that, when consumed in excessive amounts, can cause diarrhea, vomiting, nausea, stomach cramps, chronic constipation, fainting, and perhaps death." (Kurtzweil, *FDA Consumer*, July-Aug. 1997, 6-11).

Arginine and lysine - supposedly to "protect muscle tissue"

Plant fibers (e.g., glucomannan), or other bulk producers (e.g., methylcellulose), to create sensation of fullness in stomach. Same effect could be obtained from whole grains, fruits, etc. Such products have not been demonstrated to be effective in weight loss - fullness of stomach has little to do with appetite.

Caffeine - some products contain hundreds of milligrams per dose. *Kola nuts* and *guarana* are sometimes used as caffeine sources.

Recent regulatory actions

In recent years, the FDA and FTC have taken action against numerous companies for their promotion of weight loss products.

In 2003 the FTC issued a major report on deceptive weight-loss claims. Among the points made are:

- Products that would cause malabsorption of calories would appear to have effects limited to about 1/3 lb. per week.
- Thermogenic effects have not been well characterized but are clearly limited. Claims of extended weight loss of 2 lbs. per week without exercising or reducing caloric intake (which would necessarily be due to thermogenic effects plus malabsorption) are unreasonable.
- Unsupervised weight losses of 3 lbs. per week or more over extended time entail significant health risks.

SOME POPULAR PRODUCTS FOR WEIGHT LOSS

Calorad - major ingredient is hydrolyzed collagen. Weight loss could arise by eliminating evening snacks in order to take as directed.

Cellasene - mixture of herbs and other ingredients claimed to reduce cellulite. Claims seem dubious, and no published research in support. In July 2000 the FTC filed charges against the distributors for making unsupported claims.

Chitosan - chitin is a polymer of N-acetylglucosamine, found in some animal shells; allegedly binds fat and carries it through the digestive system. *Chitosan* is deacetylated form. Some evidence for reduction of cholesterol, but several controlled studies found no benefit in weight loss. Possible risks include allergic reactions, heavy metal contamination, and loss of fat-soluble vitamins. FTC took action against unsupported claims in 2005.

CortiSlim and similar products to control cortisol - while there is an association between cortisol and obesity, this is not the reason most people are overweight. Moreover, no evidence that the ingredients in the product reduce cortisol. Also contains ingredients that are alleged to be thermogenic and to control blood glucose.

Chromium picolinate - see above, p. 12. Claimed that it "boosts catabolism and energy levels," reducing craving for sugar. Pittler and Ernst (*Am. J. Clin. Nutr.* 79, 529-536 (2004)) concluded that "the observed effect with chromium picolinate is, although statistically significant, not clinically meaningful."

Green tea extract - used for its thermogenic effects. Very limited human results suggest that there may be a thermogenic effect, but no controlled study has shown usefulness in weight loss.

Hoodia gordonii - southern African plant, said to suppress appetite. No published studies in support.

Hydroxycitrate - from *Garcinia cambogia*; used in Citrin, CitriMax, Hydroxycut. Inhibitor of an enzyme (ATP citrate lyase) needed for formation of malonyl CoA. Since malonyl CoA inhibits fatty acid oxidation, hydroxycitrate could therefore increase fatty acid oxidation. How this would lead to reduced appetite is unclear. Controlled trials have given conflicting results.

Pyruvate - see above, p. 14.

Starch blockers - amylase inhibitors. Products marketed decades ago were ineffective. Now, more potent extracts are being used, but effectiveness has not been documented.

Usnic acid - acts as an uncoupler of oxidative phosphorylation. Liver damage has been reported.

Zantrex-3 - contains caffeine, green tea, and several herbs that act as stimulants.

Some devices

Electrical muscle stimulation (EMS) - has legitimate medical use (physical therapy, prevention of muscle atrophy, etc.), but no evidence that it can help weight loss. FTC took action against some marketers in 2005.

Wraps, sweatsuits, etc. - cause temporary weight loss through sweat.

Diet patches containing homeopathic medicines

Currently popular diets

"Eat Right for Your Type" - popularized by Peter D'Adamo (a naturopath). Proposes that ABO blood types reflect different genetic heritages which should lead to different optimum diets, avoiding reactions of lectins with blood cells. Biochemical and evolutionary premises are absurd.

Food Combining - popularized by Harvey and Marilyn Diamond (*Fit for Life*). Based on invalid concepts that certain food combinations lead to incomplete digestion, loss of nutrients, and buildup of toxic waste.

Low carbohydrate - premises include the idea that carbohydrates cause insulin secretion, leading to storage as fat rather than use for energy; that the rapid increase in insulin causes a drop in blood glucose, leading to hunger and more eating; and that insulin causes production of "bad" eicosanoids, which lead to heart disease, cancer, diabetes, and other problems. Weight loss could arise from restricted calories and ketosis-induced appetite suppression. There is also a rapid initial weight loss due to reduction in glycogen (and its associated water). Possible problems include inadequate nutrient intake, constipation, ketosis, kidney problems, and increased cholesterol (with risk of heart disease). Variations: Atkins Diet; Zone Diet (Barry Sears); 40-30-30 Diet. (Note: ketogenic diets are under investigation for reduction of seizures in epileptic children.)

A review of insulin and fat metabolism (Schwartz (2000) *Science* 289, 2066-7) noted:

The pervasive notion that insulin causes obesity...has hindered acceptance of insulin as a signal to the brain that limits weight gain. Although the concept that insulin triggers weight gain has little scientific merit, it remains a key selling point for advocates of diets that are low in carbohydrate and high in protein and fat. It is true that obesity is strongly associated with increased circulating insulin levels (hyperinsulinemia), but this relation is most likely due to obesity-induced insulin resistance, rather than

to obesity-promoting effects of insulin, because increased insulin secretion actually protects against subsequent weight gain in obese humans. If hyperinsulinemia has adverse consequences, obesity does not appear to be among them.

The American Heart Association Nutritional Committee issued an advisory (*Circulation* 104, 1869-1874 (2001)) that high protein diets are not supported by evidence of effectiveness, and pose health risks. Reddy et al. (*Am. J. Kidney Dis.* 40, 265-274 (2002)) reported that a low carbohydrate, high protein diet for 6 weeks “delivers a marked acid load to the kidney, increases the risk for stone formation, decreases estimated calcium balance, and may increase the risk for bone loss.”

Low carbohydrate diets attracted more attention beginning in 2002, with publication of a favorable article in the *New York Times Magazine*, and a meeting report of positive outcomes in a small, short-term trial of the Atkins diet. In 2003, three studies supportive of the Atkins or other low carbohydrate diet were reported:

- Samaha et al., *New Engl. J. Med.* 348, 2074-2081: in a 6 month trial, subjects on a low carbohydrate diet lost more weight than those on a low fat diet. They also had greater decreases in triglycerides, larger increases in insulin sensitivity, and no adverse effects on lipid profiles.
- Foster et al., *New Engl. J. Med.* 348, 2082-2090: subjects on a low carbohydrate diet lost more weight at 6 months, but not at 12 months. They also had greater decreases in triglycerides and increases in HDL. (Both of these studies had high dropout rates.)
- Brehm et al., *J. Clin. Endocrinol. Metab.* 88, 1617-1623: compared a very low carbohydrate diet (*ad lib.*) to a calorie-restricted low fat diet for six months. The former resulted in greater weight loss, and lipids improved similarly in both groups.

In early 2004, the Atkins organization reduced the recommended percentage of fat in the diet to 60% of calories and the amount of saturated fat to 20%. (Some feel that this was in response to the increasingly popular *South Beach Diet*, which has some similarities to Atkins in the initial two weeks, but then adds back more healthy carbohydrates.)

In a 2004 review, Astrup et al. (*Lancet* 364, 897-899) wrote, “The success of the low-carbohydrate diet might be due to the restriction of the variety of food choices - the monotony and simplicity of the diet could inhibit appetite and food intake. Also, protein induces a stronger satiating effect than fat and carbohydrate, which would decrease ad-libitum food intake and bodyweight.” However, since the long-term safety has not been demonstrated, they concluded that “low-carbohydrate diets cannot be recommended.”

In a critical commentary on the Atkins diet, Ornish (*J. Am. Diet. Assoc.* 104, 537-542 (2004)) noted that “an Atkins diet is high in disease-promoting substances and low in protective ones,” and “The goal is to lose weight in ways that enhance health rather than in ways that may harm it.”

Two studies reported in 2004:

- Yancy et al. (*Arch. Intern. Med.* 140, 769-777): a 6 month trial comparing low carbohydrate and low fat diets. Weight loss was twice as great with the former, and adherence and lipid profiles were better.
- Stern et al. (*Arch. Intern. Med.* 140, 778-785): a one-year followup to the earlier study of Samaha et al. (see above). The difference in weight loss was no longer significant, but lipid profiles were still better with the low carbohydrate diet.

By late 2004, it appeared that the low carbohydrate diet craze had passed its peak. Atkins Nutritionals filed for bankruptcy in mid-2005.

Dansinger et al. (*JAMA* 293, 43-53 (2005)) compared Atkins, Ornish, Weight Watchers, and Zone diets in a one-year study. Each diet produced modest weight loss and improvement in cardiac risk factors. However, only 25% of the subjects were able to adhere to the diets for a year.