Dietary Supplement Use in the Elderly
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Overview

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Dietary supplements, as sold in the United States, encompass a wide range of products, which include vitamins, minerals, amino acids, herbs, botanicals, and other substances. The frequency of use of dietary supplements among the elderly is high compared with the general population. According to results from the Third National Health and Nutrition Examination Survey conducted between 1988 and 1994, 56% of middle age and older adults consumed at least one supplement on a daily basis as compared with 40% in the general population. In 2001, the Nutrition Business Journal estimated the total sales of dietary supplements at $17.8 billion dollars.

The amount of scientific evidence supporting the safety and benefits of dietary supplements among the elderly varies according to the nature and form of the supplement. For certain supplements, e.g., vitamins and minerals, recommended levels of use in the elderly have been established by the Institute of Medicine. All supplements are not safe, and the inappropriate use of some supplements can result in adverse health consequences. Inconsistencies arise as a result of a lack of product standards and the level of scientific evidence required to demonstrate safety and benefits of dietary supplements. Concerns exist regarding supplement use in the elderly population. One concern, relates to the use of prescription drugs and their interactions with dietary supplements. Additional concerns are the potential adverse effects due to perisurgical complications, interactions with over-the-counter medications, contamination of preparations, and mislabeling.

The need for this conference was prompted due to the high prevalence of use of dietary supplements combined with inadequate scientific knowledge regarding supplements and the elderly. The goal of the conference was to develop a research program that will focus on dietary supplements and the elderly. Critical issues examined:

- The interaction between physiologic changes that result from aging and dietary supplement use.
- Data on dietary supplement use: Which segments of the elderly population are using which supplements? Under what circumstances are the supplements being used and what are the attitudes and beliefs influencing supplement use behaviors?
- Age-related changes in physiology and their effect on the bioavailability of nutrients and other bioactive substances.
- Identifying data gaps related to dietary supplement use in the elderly in relation to safety, efficacy, and various types of interactions (e.g., with prescription drugs, over-the-counter medications, surgical procedures, disease states, etc.).
- Evaluation of current justifications for use, including:

- The roles diet and/or dietary supplements have in meeting the national health goals for the elderly.
- The need for supplements in the maintenance of health and wellness, and/or decreasing the risks of disease.
- Effects of dietary supplement use in the elderly on risk factors for chronic disease(s).

The conference was divided into three plenary sessions, each session encompassing a series of discussions related to the general topic and ending with a discussion by a panel of experts who addressed a predetermined set of questions highlighting current research needs.

Plenary Session I: Overview of Dietary Supplements

Dr. Elizabeth Yetley, Food and Drug Administration (FDA), Rockville, Maryland, discussed the FDA's regulation of dietary supplements and evaluated the needs of the agency to improve this process. In 1994, when the Dietary Supplement Health and Education Act (DSHEA) (www.cfsan.fda.gov/~dms/dietsupp.html) was passed, dietary supplements were categorized as food rather than drugs, based on the premise that they had a history of safe use and were therefore safe for use in the general population, unless proven otherwise. As with all foods, FDA's role is to evaluate the safety of supplements, independent of their benefits. While drugs are intended to treat or cure a disease, supplements are intended to reduce the risk of illness in a healthy population or to otherwise support health. For drugs the burden of proof of pre-market safety falls on the manufacturer, while the burden of proof of a product's post-market safety falls on the FDA for drugs and supplements alike. Little premarket safety or efficacy data are available for supplements because many manufacturers rely on a presumed history of safe and effective use of these products. Dr. Yetley stated the importance of having data to assist the FDA in:

- evaluating individual sensitivities,
- characterizing food and drug interactions,
- understanding the effects of varying patterns of use on toxicity and efficacy,
- developing analytical methods,
- validating biological markers for use in national surveys.

Dr. Katherine L. Tucker, Tufts University in Boston, Massachusetts, characterized supplement use in the elderly by race, gender, and socioeconomic status. Additionally she demonstrated trends in increased use over recent years and defined which supplements were most commonly used. Dr. Tucker found that non-Hispanic white females from a higher socioeconomic status are more likely to use dietary supplements. NHANES III data further supported this by demonstrating low levels of use in both African American and Hispanic populations. Data from the Framingham Heart and Offspring Studies 1988-1989 reported that in the original cohort of individuals aged 67-96, 26% of men and 33% of women used dietary supplements. In the Offspring Cohort from 1991-1995, focusing

on individuals aged 60y +, 33% of men and 45 % of women used supplements, while in 1995-1999 43% of men and 59% of women used dietary supplements. This shows a clear trend in increased supplement use over the last 15 years and emphasizes the need for further research in the various areas of supplement use in the elderly population. This trend was further supported by data from the Veteran's Administrative Normative Aging Study. Multivitamin/mineral preparations were reported as the most frequently used, with vitamins C, E, and calcium as the next most prevalently consumed. While there is presently limited data on herbal and other supplement use, a recent nationwide telephone survey reported that 11% of men and 14% of women used ginkgo, garlic, glucosamine, saw palmetto, and ginseng most commonly. Dr. Tucker cited the need for more specific information in areas such as dosage, duration of use, confounding effects, and prevalence and pattern of dietary supplement use in the elderly population.

Dr. Suzanne P. Murphy, Cancer Research Center of Hawaii, University of Hawaii, Honolulu, reiterated findings similar to those of Dr. Tucker and further characterized elderly vitamin/mineral supplement users. Dr. Murphy found that vitamin/mineral supplement use was more common among Caucasians, women, and individuals with a higher household income and a higher education level. In terms of ethnicity, Asians also have a high prevalence of vitamin and mineral supplement use. Age seems to affect vitamin/mineral supplement use, with use increasing up to age 50, but remaining fairly constant after that. Dr. Murphy indicated that individuals with healthy lifestyles appear to be more frequent vitamin/mineral supplement users. Several different studies support this conclusion. Individuals who frequently drink alcohol and who smoke are less likely to take supplements than their non-drinking, non-smoking counterparts. While the level of physical activity is positively associated with taking vitamin/mineral supplements, BMI appears to have an inverse association with their use. Diet choices also appear to relate to supplement intake. Older adults who take supplements tend to eat healthier diets and individuals taking supplements tend to have diets higher in fiber, fruits and vegetables, and lower in percent energy from fat. While these data are for vitamin/mineral supplement use, the information on non-vitamin/mineral supplement use is limited. It should be noted that non-vitamin/ mineral supplement users were similar to vitamin/mineral supplement users in most lifestyle characteristics with the exception that they tended to be obese and have high alcohol intakes. Overall there is a need for increased information on both vitamin/mineral and non-vitamin/mineral supplement use, including more recent data on use, the effects of time and chronic diseases on changes in supplement use, and the reporting of age-specific factors that affect use.

Dr. Pamela S. Haines, Department of Nutrition, School of Public Health, University of North Carolina at Chapel Hill, characterized reasons for dietary supplement use in the elderly. Individuals appear to be motivated to take supplements by a number of different factors, which include health maintenance, a reaction to changes in eating habits or health status that arise from acute or chronic conditions, as a way to prevent aging, and as a way

to have more control over personal health concerns. In addition, social factors, such as higher rates of education, a demand for more information about a wider variety of products, and environmental factors, such as increases in television and internet advertising and increases in available transportation, have altered individuals' choices about supplement use. Supplement users also appear to fall into categories: individuals who are unsatisfied with current medical care, people who prefer to follow the growing movement for health promotion and the use of complementary and alternative medicine, individuals treating both real and perceived symptoms of aging, and those who are dealing with chronic conditions. Overall, older adults appear to take supplements due to beliefs that they will incur some benefit, gain some element of control, or improve their overall quality of life. Changes in the social norm and increased sources of advertising have also increased these individuals access to supplement information.

Dr. Virginia A. Stallings, Children's Hospital of Philadelphia, University of Pennsylvania School of Medicine, Philadelphia, reviewed scientific evidence from two reports released by the Food and Nutrition Board, Institute of Medicine, National Academy of Sciences, Washington, D.C. One report evaluated the medicare coverage of nutrition conditions while the second report was the 1997 Dietary Reference Intakes (DRIs). The medicare report determined that overall the elderly have a poor nutritional status, which is significant since most chronic diseases have nutritional components. Since the current Medicare system focuses on treatment rather than prevention of disease, the question arose as to the efficacy of nutrition treatment for disease. Research supported the use of nutrition treatment in dyslipidemia, hypertension, heart failure, diabetes, pre-dialysis kidney failure, osteoporosis, and undernutrition. Further research demonstrated that 45 % of elderly in a community setting have an inadequate dietary intake, most of who had existing chronic diseases such as diabetes, hypertension, and dylipidemia. Overall, the findings demonstrated a paucity of evidence, high quality or otherwise, in individuals over 65, with a particular lack of clinical trials. Dr. Stallings also discussed the evolution of, and the foundation for, the current DRIs. They were derived from the recommended dietary allowances that were originally devised as essential nutrient intakes for all healthy people. In 1997 the DRI's evolved and encompassed new divisions by gender and age, dividing the oldest age category into 50-70 and 70+. These changes reflected the concept that there are metabolic and nutritional changes associated with age and gender. In particular, aging has been found to alter individuals' needs for vitamins D and B12 while folate intake has been found to decrease risk of cardiovascular disease. However, these changes again brought to light that there is an overall lack of evidence on the nutritional needs of the elderly. Dr. Stallings determined that a strong need exists for additional research in relation to age and gender, with a focus on research utilizing clinical trials. She also highlighted the importance in a shift of the medicare model from treatment of disease to prevention.
(DRI Reference: http://www.iom.edu/iom/iomhome.nsf/pages/Fnb+Dri?OpenDocument)

Plenary Session II: Special Issues of the Aging Population

Dr. Tamara B. Harris, Laboratory of Epidemiology, Demography, and Biometry, National Institute on Aging, National Institutes of Health, Bethesda, Maryland, discussed the physiological changes that occur with aging and their possible effects on dietary supplement use. Dr. Harris noted that, as individual's age, they experience a variety of physiological changes, many of which alter a person's ability to absorb and utilize different drugs. Older persons often experience increases in body fat, changes in the physiology of the gut, and decreases in liver and renal functions. In drug metabolism this results in an increased half-life for fat-soluble drugs, changes in drug absorption, and in alterations in drug excretion. Additionally, diseases that result from aging may also affect drug metabolism. While dietary supplements are not regulated the same way as prescription medications, it was noted that they might be absorbed and metabolized in a similar manner. Although all older persons are often grouped into one category, realistically the aging population is a heterogeneous group that falls on a continuum from healthy to frail. While physiological changes from aging may affect dietary supplement metabolism, attitudes about communication and perceptions of the elderly may actually be an area of greater concern.

Dr. Marc Blackman, National Center for Complementary and Alternative Medicine, National Institutes of Health, Bethesda, Maryland, evaluated the roles of growth hormone, DHEA, and melatonin in aging. Presently, there are numerous claims regarding the benefits of hormone supplementation in the elderly; however, the evidence to support these claims is sparse. Both growth hormone and insulin-mediated growth hormone factor (IGF-the agent controlling the actions of growth hormone) have been shown to decrease with age. Similarly, testosterone has been shown to decrease in aging men. A double-blind randomized placebo-controlled intervention study by Dr. Blackman examined the role of growth hormone and either testosterone or estrogen-progestin (gender dependent) supplementation on a group of healthy older individuals. The study demonstrated that growth hormone, given with or without sex hormones, leads to a significant increase in lean body mass and decrease in body fat in both men and women. However, these increases did not result in strength or aerobic capacity increases for women or men taking only a single hormone. Men taking both hormones did have a significant increase in aerobic capacity. Hormone treatment, singularly or paired, significantly decreased LDL values in both men and women, while not affecting HDL levels, resulting in a more beneficial lipid profile overall. On a less positive note, the growth hormone treatment (alone or with testosterone) resulted in the development of a prediabetic state or diabetic blood glucose levels in 50% of men, salt and water retentive symptoms in both men and women, and withdrawal bleeding and breast tenderness in women on the estrogen-progestin combination without growth hormone. Side effects were reversed by a reduction or cessation of treatment. DHEA is most often used by athletes. Animal data has shown that DHEA will ameliorate many of the negative effects of aging in old rodents. However, these data included pharmacological doses in rodents, not humans. Evidence supporting DHEA use is sparse, and one study demonstrated that

while individuals said DHEA improved their overall well being, physiologically it increased IGF-1 levels in women resulting in a decrease in HDL cholesterol. Melatonin also has little data supporting many of its uses. While it may be useful in relieving sleep disorders in elderly individuals, its use in mood disorders, sexual and reproductive function, cancer prevention, immune function, and aging are unclear. Overall it appears that there is relatively little evidence regarding the roles these hormones play in aging. Dr. Blackman called for the need for more hard data in this area, and cautioned against believing the overstated claims that are often made.

Dr. Barry Forman, Beckman Research Institute, Duarte, California, presented the effects of dietary supplements on the genetic regulation of the Pregnane X Receptor (PXR). In order to remain healthy and prevent toxicities from chemicals in food, drugs, the environment, and even by-products from our own physiological reactions, individuals must be able to inactivate toxic chemicals and clear them from the body. PXR is a nuclear receptor, which regulates the cytochrome P450 genes, and P-glycoprotein genes found in the liver and intestine, respectively. These genes are actively involved in the clearance of drugs from the body. While this pathway appears to have developed as a protective mechanism, a number of drug-drug interactions occur through PXR that limit the therapeutic activity of the drugs involved. In terms of dietary supplements, it has been found that approximately 50 percent of herbal agents, taken from the shelves of a health food store and tested by Dr. Forman, effectively activate this receptor. This activation may lead to problems with drug resistance in the elderly. Dr. Forman called for the need to determine which dietary supplements activate the PXR receptor and to understand the effects this would have on drug metabolism.

Dr. Robert M. Russell, Tufts University, Boston, Massachusetts, discussed the effects of high-dose beta-carotene supplements on lung cancer. Several epidemiologic studies have demonstrated a decreased risk of cancer, particularly lung cancer, in individuals who consume a diet rich in carotenoid-containing fruits and vegetables and who have higher blood levels of beta-carotene. Conversely, the Alpha-Tocopherol Beta-Carotene Cancer Prevention Study (ATBC Study) and The Carotene and Retinol Efficacy Trial (CARET trial) tested doses of 20-30 mg beta-carotene in smokers and workers exposed to asbestos and found an 18% and 25% increase in lung cancer, respectively. The Physicians Health Study found that a 50 mg dose of beta-carotene had no effect on lung cancer risk; however, only 11 % of this group were smokers. From these epidemiological and clinical studies, a clear relationship between beta-carotene and cancer could not be identified. Dr. Russell's group used the ferret as an animal model to determine whether high dose beta-carotene supplements cause a predisposition to lung cancer and, if so, what the mechanism of action would be. It was found that animals exposed to cigarette smoke and a high dose beta-carotene supplement had the highest levels of lung cell proliferation and squamal metaplasia. These animals also had significantly decreased concentrations of retinoic acid and expression of the retinoic acid receptor beta gene in the lungs.

Additionally, ferrets in this group had increased amounts of C-jun and C-fos genes (biomarkers for carcinogenesis). A second study was then undertaken in which ferrets were given either a high (pharmacologic) or low (physiologic) dose of beta-carotene. Animals in the high-dose smoke-exposed group demonstrated the same effects seen previously, while animals in the low-dose group did not have these physiological changes. From these studies Dr. Russell demonstrated that while beta-carotene appears to have a role in the development of lung carcinomas, dosage is an important factor to consider. He also proposed a number of mechanisms through which beta-carotene may lead to lung cancer, all of which are initiated by oxidized beta-carotene metabolites.

Dr. Mark Messina, Nutrition Matters, Inc., Port Townsend, Washington, reviewed the role of soy isoflavones in cancer and their potential positive and negative relationship with the cancer drug tamoxifen. Soybean isoflavones are thought to play a preventative role in cancer. Particular interest has been paid to their role in decreasing breast cancer risk. Although this role is still unclear, one hypothesis has been that consumption of soy products in childhood leads to a decreased breast cancer risk in adulthood. Isoflavones, an active component of soy, are phytoestrogens and may exert hormonal estrogenic and anti-estrogenic effects. Additionally, isoflavones have non-hormonal properties, such as, signal transduction, antioxidant effects, and antiangiogenesis, through which they may also mediate their physiologic and anti-cancer effects. Despite the seemingly positive influences isoflavones have on cancer risk, concerns have arisen that they may negatively affect the efficacy of tamoxifen due to their estrogen like hormonal properties. The data supporting this hypothesis has proven to be somewhat inconsistent. Overall it appears that while there is some basis for avoiding soy products while on the drug tamoxifen, the evidence regarding the interaction of isoflavones and tamoxifen is both positive and negative. Dr. Messina concluded that some of the data does point towards a beneficial effect of isoflavones and that it is imperative that human studies be undertaken in the near future.

Dr. Michael Holick, Boston University School of Medicine, Boston, Massachusetts, gave an overview of vitamin D and discussed the importance of maintaining an adequate vitamin D status. He also reviewed the effects of an inadequate status on a number of different disease states. Vitamin D is known to be important to the maintenance of bone health, as well as playing a role in the prevention of cancers, hypertension, and a number of other diseases common to the elderly. Vitamin D deficiency is very common in US adults, and approximately 50% of the free living and institutionalized elderly are vitamin D deficient. Vitamin D is important in enhancing the absorption of calcium, inhibiting cellular growth, and activating both T and B-lymphocytes function, and is believed to downregulate the rennin/angiotension system. A vitamin D deficiency may lead to osteoporosis, osteomalacia, and cancer of the colon, prostate, breast, and ovaries. In animal models this vitamin aids in the prevention of a disease similar to multiple sclerosis. Moderate hypertension may also be effectively treated through exposure to

light in the ultraviolet B range. Despite its importance, vitamin D only occurs naturally in oily fish (such as salmon and mackerel) and cod liver oil. Several foods such as milk, bread, and cereals are fortified with vitamin D. The best way to maintain an adequate vitamin D status is through exposure to sunlight; however, increases in skin pigmentation, sunscreen, higher latitudes, the greater Zenith angle of the sun during certain seasons, and aging all alter the amount of Vitamin D the body can produce. The National Academy of Sciences has suggested that the recommendation for vitamin D intake by the elderly be increased to 600 IU/day; however, without sunlight exposure this may not be enough. Currently 1000 IU/day appears to be a more adequate vitamin D intake. Overall, Dr. Holick highlighted the significant role vitamin D has in health maintenance and disease prevention. He also made it clear that many US adults and particularly the elderly are not meeting their requirements for this vitamin.

Dr. Bruce N. Ames, University of California at Berkeley/CHORI, Berkley, discussed the role that micronutrients and metabolites play in the prevention of DNA damage, in reversing certain diseases resulting from an inability of enzymes and coenzymes to bind, and in alleviating the breakdown of mitochondria that occurs from oxidation (attack by free-radicals). Vitamins B6 and B12, folic acid, iron, and zinc all appear to affect the body's ability to prevent or repair DNA damage. A deficiency of vitamins B6, B12, and/or folic acid can lead to increased incorporation of uracil into DNA resulting in chromosomal breaks, similar to those seen from radiation. Iron deficiency, the most prevalent deficiency worldwide, can lead to a leakage of oxidants out of mitochondria, and consequently to mitochondria and mitochondrial DNA (mtDNA) damage. Zinc deficiency causes oxidation and DNA damage, in addition to hindering certain zinc-containing repair mechanisms that repair DNA damage. The administration of high doses of vitamins has been found to remedy or alleviate approximately 50 genetic diseases caused by a low binding affinity between various enzymes and co-enzymes. Mitochondrial oxidative decay is though to have a significant role in aging and may be affected by intake of metabolites. Metabolites acetyl carnitine (ALCAR) and lipoic acid (LA) have been shown to reduce several of the symptoms of aging seen in old rats. Dr. Ames demonstrated the significant role micronutrients and metabolites have at the genetic level in the prevention and alleviation of diseases and symptoms associated with aging.

Dr. Herbert S. Rosenkranz, Florida Atlantic University, Boca Raton, proposed the use of computational methods such as structure-activity relationships (SAR), data mining, and bioinformatics, to determine the safety and efficacy of dietary supplements. Structure-activity relationships are already in use with dietary supplements to examine cancer chemoprevention, inhibition of key enzymes, and antioxidants. In order to develop an SAR model there must first be valid efficacy data and information on chemical structures. In the case of chemopreventative agents and antioxidants, data are available on 100-400 chemicals. However, for a number of agents there are inadequate data on efficacy

markers, and SAR models cannot be developed. In addition to determining efficacy, SAR models can also be used to determine possible toxicities of different dietary supplements. There are already several SAR models of toxicological phenomena, which can be helpful in determining possible hazards and mechanistic information, and to predict drug-drug interactions. When combined with data mining, SAR modeling becomes an effective tool in producing computer-generated biological or toxicological profiles. These profiles may help in the identification of agents that are different structurally, but are mechanistically similar and, therefore, may act as chemopreventative agents. In order to use these computational methods as effective tools, it is necessary to identify further chemopreventative targets and obtain experimental data on how substances influence these targets. Data from DNA microarrays (a relatively new technology that allows researchers to examine multiple DNA samples simultaneously) also appears to be an effective way to generate substrates for SAR analyses. In the future, computational methods may be a way to examine the safety and efficacy of dietary supplements before utilizing animal and human models.

Plenary Session III: Evidence-Based Studies

Dr. Barnett S. Kramer, Office of Disease Prevention, National Institutes of Health, Bethesda, Maryland, discussed the methodology and potential problems associated with the application of scientific evidence to decision making. When drawing conclusions based on scientific evidence it is necessary to consider the source of the evidence (the type of study and the limitations of the study) and to whom the recommendations apply (to an individual or a large population). The gold standard of scientific studies is the double blind randomized placebo controlled trial that is designed to eliminate all possible bias. However, problems may arise when ethical issues prevent this type of trial from being possible. In this case data from other types of studies may be all that is available for drawing conclusions and making recommendations. On a large scale, evidence-based reviews may be used to make recommendations. These reviews involve a systematic review of all available evidence and are designed to avoid biases occurring from preferred notions or misleading experiences. However, these studies require significant resources and are not always practical. In addition to considering the type of study, a consideration of shortcomings within studies is also necessary. In many cases, studies test an intermediate outcome that may or may not lead to the final outcome of interest. Self-selection bias may occur when individuals self select themselves for a study. It is also important to take into account the recipient of the decision. Decision-making falls on a continuum from decisions for oneself to across-the-board recommendations for an entire population. The implications of a wrong decision are magnified as one moves across the spectrum and severe damage can result if incorrect recommendations are implemented in a population. Dr. Kramer provided significant insight into the many considerations and complications of using scientific evidence to draw conclusions and make recommendations. He highlighted the necessity of using accurate evidence, with proper endpoints, and applying those to recommendations to a specific population. Dr.

Kramer stressed the need to make sure that correct recommendations go out to the public, so that their faith in the scientific, academic, and medical communities is not undermined.

Dr. Susan T. Mayne, Yale University, New Haven, Connecticut, reviewed the evidence pertaining to the role antioxidant nutrients play in primary and secondary cancer prevention. She noted that findings from the studies were mixed, ranging from those that supported the use of antioxidant nutrients to those that found the additional use of certain nutrients to be harmful. Antioxidant nutrients were originally believed to be beneficial by neutralizing the free radicals formed from oxidative stress, thus preventing oxidative damage. However, data do not consistently support this theory. Observational epidemiological studies have supported the use of vitamin C in cancer prevention, yet the Linxian trial found no benefit from additional vitamin C. Beta-carotene supplementation has had no proven benefits in preventing carcinogenesis and has been found in certain studies to actually lead to increases in cancer, as was reported in Dr. Russell's presentation. Vitamin E has been shown to decrease incidence of prostate cancer in the ATBC trial, and selenium has shown some promise in cancer prevention, but the data are from trials with small numbers. Overall, the data are not consistent enough to support the recommended use of antioxidant nutrients for primary or secondary cancer prevention. Evidence has supported the development of second-generation antioxidant trials, one of which is the Selenium and Vitamin E Chemoprevention Trial (SELECT trial) trial (www.clinicaltrials.gov). The SELECT trial will look at the effect of vitamin E and selenium (as selenomethionine), singularly and in combination, on prostate, lung, colon, and other cancers, deaths, and cardiovascular disease events.

Dr. Gail B. Mahady, Center for Botanical Dietary Supplement Research on Women's Health, College of Pharmacy, University of Illinois, Chicago, summarized the research on the use of black cohosh and red clover in the treatment of menopausal symptoms. According to the findings from face-to-face interviews of over 500 women at the University of Illinois Botanical Center, nearly 80% of women age 40-65 use one or more botanical dietary supplement. Many women use dietary supplements to treat the symptoms of menopause, which can include depression, moodiness, sleep disorders, vaginal dryness, hot flashes, and joint paint. Black cohosh (*Actaea racemosa*) has traditionally been associated with the treatment of menopausal symptoms, such as hot flashes and vaginal dryness. Research has suggested that while black cohosh may be as effective as low-dose conjugated equine estrogens in alleviating menopausal symptoms in healthy women, the supplement does not relieve hot flashes in breast cancer patients on tamoxifen. Red clover (*Trifolium repens*) is also traditionally used to treat menopausal symptoms. However, the clinical data are scant and inconclusive as to its efficacy in this regard. Presently, there is some concern about the safety of red clover, which contains the phytoestrogen isoflavone, whose constituents may act in a manner similar to steroidal estrogens. Overall there is limited evidence supporting the safety and efficacy of both

black cohosh and red clover. Black cohosh appears to be safe and effective in certain groups of individuals, while the safety and efficacy of red clover is still controversial.

Dr. Carl W. Cotman, Institute of Brain Aging and Dementia, University of California, Irvine, examined the effects of diet and dietary supplements on maintenance and improvement of cognitive function. As individuals age, the high rate of oxygen metabolism in the brain leads to a buildup of oxidative damage. This damage is thought to adversely affect cognitive function. Dr. Cotman discussed the effects of antioxidants, *Ginkgo biloba*, folate and homocysteine, and fatty acids, cholesterol, and statins, on cognition. Antioxidants appear to improve cognitive maintenance, but the levels of improvement are small, and the trials examining this were not clinical trials and had variable outcomes. A rigorous study on the effects of vitamin E on Alzheimer's disease showed that while vitamin E slowed the rate of decline, it did not result in improved cognitive function. Evidence on *Ginkgo biloba* appears to be inconclusive, with one study showing no effect on dementia patients, while another reported only minimal improvements. In terms of homocysteine and folate, high levels of homocysteine in the blood, as well as low intakes of folate and B12 are associated with increased risks for Alzheimer's disease. Clinical trials have demonstrated that fatty acids may improve cognitive function; however, further studies of omega-3 fatty acids, among others, are needed. High serum cholesterol is a risk factor for Alzheimer's disease. The statins, drugs taken to lower cholesterol, have been shown to decrease beta-amyloid deposits in animals, delay the onset of dementia in humans, and decrease the risk for Alzheimer's disease. Dr. Cotman concluded that antioxidants, folate, B vitamins, and cholesterol-lowering strategies might provide a beneficial improvement in cognitive function, while the effects of ginkgo are unclear.

Dr. Emily Chew, National Eye Institute, National Institutes of Health, Bethesda, Maryland, reported on the preventative effects of antioxidants on cataracts and age-related macular degeneration (AMD). Epidemiologic evidence has supported the role of antioxidants as protectors against cataracts and AMD; however, studies have not been consistent in their findings. The Age-Related Eye Disease Study (AREDS) was a randomized, controlled clinical trial with 4,757 participants who had different degrees of AMD. The study looked at the effects of the antioxidants vitamin C, E, and beta-carotene, and zinc on AMD and cataracts. Participants were enrolled in the study based on the number of drusen (deposits occurring underneath the retina of the eye) found in the eye and were divided into either the AMD or cataract group. Supplementation with antioxidants and zinc reduced the progression from intermediate to advanced AMD by 25%. Patients in the intermediate AMD group also benefited. While the affects of antioxidants and zinc on AMD appear very positive, this same treatment had no effect on the progression of or surgery for cataracts. Dr. Chew reported that these antioxidant and zinc treatments are now recommended for the participants with at least an intermediate risk of progressing to the advanced stages of AMD. Additionally, antioxidant and zinc

treatments should be considered for patients with moderate to large drusen and/or AMD in one eye.

Dr. Howard N. Hodis, University of Southern California Atherosclerosis Research Unit, Los Angeles, discussed the role that plasma homocysteine, the B-vitamins, and the antioxidant vitamins C, E, and beta-carotene play in cardiovascular disease. A large body of information demonstrates that lowering LDL cholesterol decreases the risk for cardiovascular disease (CVD), yet even with this reduction many patients still develop CVD. A number of observational studies have shown that increases in vitamins E and C and carotenoid intakes decrease the risk for CVD. Conversely, data from randomized controlled trials, with the exception of two short-term trials, have found that antioxidants were not effective in preventing primary or secondary CVD outcomes. Although these trials focused on individuals with pre-existing disease or who were at very high risk for CVD, the Vitamin E Atherosclerosis Prevention Study (VEAPS) looked at healthy, low risk individuals and found results similar to those of the clinical trials. While the VEAPS trial focused on individuals with adequate levels of antioxidant vitamins, it is hypothesized that individuals with low levels of serum and tissue antioxidants may receive cardiovascular benefits from antioxidant supplementation. Plasma homocysteine (an amino acid normally found in the blood) is now considered an independent risk factor for atherosclerotic vascular disease. Elevated concentrations of homocysteine lead to a 90% increase in cerebrovascular disease in both men and women. This is a particular concern for the elderly, who have a 25% rise in homocysteine levels after age 50 and a continuous rise in homocysteine levels after age 60. This rise in homocysteine appears to occur simultaneously with the drop in levels of folate, vitamin B6, and vitamin B12. Decreased B-vitamin intake may be due in part to malabsorption, but insufficient dietary intake is also a key factor. More than 40 epidemiological studies demonstrating an association between elevated plasma homocysteine and CVD show that the elderly population may be at increased risk of CVD associated with low dietary intake of B-vitamins. In conclusion, while these findings do not support the use of antioxidants in the prevention of CVD in vitamin-replete individuals, further studies need to examine their effects in deficient populations. While there does appear to be a causal relationship between levels of plasma homocysteine and CVD, further randomized trials need to be undertaken before recommendations can be made regarding B-vitamins and the prevention of CVD.

Dr. Bess Dawson-Hughes, Tufts University, Boston, Massachusetts, discussed the need for supplement use in the prevention of osteoporosis. There are many lifestyle factors that provide additional risks for osteoporosis; however, protein, vitamin K, calcium, and vitamin D are the key nutrients involved in bone health. High protein intakes were originally thought to increase the urinary excretion of calcium. Recent studies have shown that protein stimulates the production of a bone growth factor, IGF-1, which may offset increased urinary calcium losses. Vitamin K is needed for the formation of

osteocalcin, the most prevalent noncollagenous protein found in bone. Data from the ongoing Framingham study 1988-1995 have shown that as vitamin K intakes increase, the risk for hip fracture decreases. Low intakes of calcium and vitamin D are known risk factors for the development of osteoporosis. Inadequate levels of vitamin D, also discussed in Dr. Holick's lecture, result in decreases in calcium absorption, increases in bone loss, and an overall increase in fracture risk. There is mixed evidence as to whether vitamin D supplementation alone will decrease hip fractures, yet in conjunction with calcium supplementation there appears to be an overall decrease in fracture rates. Overall, protein and vitamin K may play a role in the development of osteoporosis, and further clarification of their roles in this process is needed. The amount of each nutrient key to the maintenance of bone health needs to be determined. Calcium and vitamin D appear to work in conjunction to decrease fracture rates in the elderly. However, the elderly have low dietary intakes of both these nutrients and may require supplements to meet their needs.

Dr. Gabriel Fernandes, University of Texas Health Science Center at San Antonio, reviewed the role of *Echinacea*, vitamin E, zinc, and n-3 fatty acids in immune function. As individuals age, factors in both the environment and in genetic makeup result in a decline of the immune system. Many of the elderly have turned to supplements as a way to remedy these age-related changes in immune function. *Echinacea* is thought to have anti-inflammatory and antiviral activities, help alleviate the symptoms of cold and flu, function as an immunostimulatory agent, and treat and/or prevent upper respiratory infections. After reviewing 16 randomized trials, Dr. Fernandes concluded that the evidence supporting *Echinacea's* efficacy is not convincing and further evaluations of "good quality" *Echinacea* products need to undertaken. In the elderly, high levels of vitamin E are believed to stimulate immune function. One study looking at respiratory infections indicated that vitamin E's efficacy was dependent on an individual's health and the vitamin was only effective in immune-impaired patients. Zinc deficiency can occur in the elderly for a variety of reasons and may lead to increases in immune dysfunction, skin and respiratory infection, susceptibility to infection, chromosome breakage, increases in esophageal cancer, and impaired wound healing. Zinc supplementation restores an individual's ability to fight infection and heal wounds; yet large doses of zinc actually seem to be toxic to immune cells. N-3 fatty acids may alter the inflammatory disease process. Diets with a high n-6/n-3 fatty acid ratio (n-6 fatty acids are found in vegetable oils, plant sources, and seeds while n-3 fatty acids are found in fish, fish oils, and enriched oils) are believed to be related to a number of inflammatory disorders and autoimmune diseases. Future research needs to further examine the role of *Echinacea*, vitamin E, zinc, and n-3 and n-6 fatty acid supplementation in immune function of both the healthy and the chronically ill elderly.

Panel Discussion I

Panel Questions

1. How can we design studies that will best determine dietary supplement usage in the elderly (e.g., large national surveys, small local samples, specific groups)?
2. What types of study designs would facilitate more effective interventions to modify dietary supplement use to be more aligned with science?
3. What behavioral characteristics and attitudes determine why the elderly use dietary supplements and what type of dietary supplements are used?

Discussants on Panel I included Ronni Chernoff, VA GRECC; Annette Dickinson, Council for Responsible Nutrition; Jeanne Goldberg, Tufts University; and Jean Lloyd, Administration on Aging. The panel reviewed the various research needs in regards to dietary supplement use in the elderly. They concluded that there needs to be a determination of the target population, more information on the dose and duration of supplement use, a better understanding of why individuals do or do not use dietary supplements and how to change use behaviors, development of optimal interventions for populations with a high supplement need and a low use and vice versa. In terms of study design several factors need to be considered: language differences, ethnicity, whether to include free living and/or institutionalized elders, whether to use urban or rural individuals, how to collect data, and where supplements are purchased. In addition, several behavioral characteristics and attitudes towards supplement use need to be considered: benefit as a reason for use, the difference between regular and occasional users, the longevity of regular use, supplements as a means to maintain quality of life or functionality, the settings in which the elderly live, considerations of individuals with optimal vs. sub optimal status, and ways to account for the diversity among the elderly and their beliefs. The need for good qualitative research that would give a better understanding of the target population was cited as a way to design more effective interventions. The use of the Internet was suggested as a possible tool to effectively communicate information and gather data about supplement use in the elderly. This panel discussion helped to highlight the many considerations needed to design effective studies and interventions that will further our knowledge regarding the use of dietary supplements in the elderly.

Panel Discussion II

Panel Questions

1. Should there be special consideration when formulating dietary supplements to meet changing physiological needs of the elderly?
2. What types of new methodologies can be applied to determining safety and effectiveness of dietary supplements (e.g., modeling), and how can they take into account special characteristics of the elderly?
3. How are individual differences, which are particularly evident in research on the elderly, taken into account in explaining interactions of dietary supplements with

disease states, prescription medications, genetic factors, and environmental exposures?

Discussants for Panel II included Joseph T. Hanlon, University of Minnesota; David Kroll, National Products Laboratory Research Triangle Institute; Leila G. Saldanha, Consumer Healthcare Products Association; and Gary Williams, New York Medical College. The panel reiterated concerns about a lack of communication between the elderly and their physicians regarding supplement use. This can result in adverse events related to supplement use going unreported and may hinder the ability to detect drug-supplement interactions in the elderly. A collection and follow up of case reports was suggested as a way to account for adverse events occurring from supplement use in the elderly. Despite concerns, there are actually a relatively low number of drug-supplement interactions, and adverse events occurring from these interactions may not be a severe problem. Certain supplements, when combined with anticoagulants such as the drug Coumadin, may be dangerous in elderly patients since they increase the possibility of bleeding hemorrhages. Age-related changes in physiology may cause unwanted effects of supplements to be amplified in the elderly population; gastrointestinal symptoms were used as an example. Gene polymorphisms (naturally occurring variations of a gene) were discussed as a means of developing products specific to the needs of the elderly. Additionally, the changing needs of the elderly are taken into account with the new DRI's, which is helpful in defining levels of consumption in the elderly. Several suggestions were made for further research including new surrogate markers in animals for toxicity, the need to measure alterations in metabolic properties of the body (which occur from treatment), and the need for studies looking at polypharmacy. Another research concern was the need for a paradigm for supplement research where pre-clinical studies were followed by human trials. The rush for many herbals to large-scale clinical trials (Phase III trials) prematurely was cited as a research shortcoming. The discussion from this panel emphasized several concerns specific to the elderly population and emphasized the need for research that would take those concerns into consideration.

Panel Discussion III

Panel Questions

1. What types of clinical studies (small, large) are still needed to answer questions about the efficacy of supplements?

2. Can the populations in existing epidemiological studies be utilized to answer questions about who, where, what, and why of dietary supplement use in the elderly?

3. What evidence is required from studies on experimental animals, in cells systems, and at the molecular and genetic levels to provide insight into the mechanism of action of dietary supplements in the elderly?

Discussants for Panel III included Flint Beal, Cornell University Medical College; Steven Dentali, American Herbal Products Association; Julie Mares-Perlman, University of Wisconsin; and Mark Mattson, NIA Intramural Program. The panel discussed the needs for different types of studies and the contribution these studies have made to understanding supplement use in the elderly. The panelists concluded that further research is needed to accurately assess exposure to multivitamins, to examine the mechanisms of botanicals and supplements, to develop in vitro and in vivo assays for biochemical processes common to age-related diseases, to develop surrogate biomarkers in plasma, and to measure blood concentrations of supplements and develop a dose response curve from those measurements. The need for strong preclinical data was emphasized (as in the Panel II discussion). For example, one suggested preclinical process would include the development of biochemical and cellular assays for initial screening of supplements, followed by testing of the extracts in drosophila models, and proceeding to testing of the extracts in transgenic mouse models. In the case of botanicals, reproducible extracts need to be used in research. Research in the basic sciences is needed to focus on a number of factors: the acquisition of data to determine if supplements affect the general mechanisms of aging, screening of complex herbal extracts, and the development of plasma markers to determine efficacy. Epidemiological studies are important to supplement research. They can be used to obtain data that cannot be tested ethically in clinical trials, to help generalize clinical findings to a larger population, to project long-term impacts of findings, to obtain an understanding of a larger variety of health behaviors, and to look at population subgroups. Possible problems occurring from the use of epidemiologic studies include inconsistencies in categorizing populations, the need to better categorize the history and behaviors of supplement use, and the need to develop standards for the assessment of supplement information. In general the panel found that there is a strong need for the development of preclinical evidence to support clinical studies, and that basic science, epidemiological studies, and clinical research are all vital to understanding the use of dietary supplements in the elderly.

Final Summary

The goal of this conference was to examine existing research on dietary supplement use in the elderly and determine the path of future research. The population of supplement users was more clearly defined, and the reasons for use in those populations were considered. Physiological changes in the elderly occur due to the aging process as well as from chronic disease. These changes were examined and their impact on supplement use was evaluated. Evidence-based studies looking at cancer, menopause, cognitive function, cataracts, macular degeneration, cardiovascular disease, osteoporosis, and immune function were presented and evaluated for the roles that supplements play in these various conditions. Lecturers discussed the importance of evidence-based reviews and the link between science and recommendations, the regulation of dietary supplements, and gave an overview of the IOM reports. From this varied expanse of information, workshop participants identified six thematic areas:

Behaviors of Use

- Further data are needed to characterize the behaviors associated with supplement use in the elderly. In terms of behavior characterization there is a need for a better understanding of the prevalence of use, a better description of use patterns in various cultural groups worldwide, an increased understanding of events which trigger dietary supplement use, and the characterization of acute and chronic patterns of use.

Education and Dissemination

- Improvements need to be made regarding ways that supplement information is communicated and disseminated. In order to improve communication regarding dietary supplements, cost effective methods to distribute information need to be developed, and communication between physicians and patients needs to be improved.

Methodology

- Methodologies including standardization of formulations, development of biomarkers and animal models (such as those looking at absorption, metabolism, and human pathology) representative of the aging population, improved methods to assess exposure, and the establishment of models assessing drug-supplement interactions need to be created and implemented. There is a need for more effective means of survey methodology, the development and validation of biomarkers for oxidative stress, and the development of indexes that more appropriately characterize menopausal symptoms. Pre-clinical data is needed in a number of areas: tests of herbal supplements for PXR activation, metabolic studies that examine the breakdown of the main dietary carotenoids, and the need for pharmacological kinetic studies.

Clinical Studies

- Preclinical and clinical trials evaluating supplement safety and efficacy are needed, as well as the development of a strong preclinical foundation before proceeding to clinical trials. Clinical studies are needed examining soy intake in Asian women and its relation to cancer, the efficacy of red clover in the treatment of menopausal symptoms, and the need for data examining the long term effects of dietary supplement use on AMD.

Informational Databases

- Supplement databases on a number of different topics such as ethnicity, gender, lifestyle, age, and health status are needed to help make information more available to the public and the scientific community. Databases are needed to help define patterns of use, to characterize exposure, and to capture the various types of products available.

The conference resulted in a large number of specific recommendations that fell under each of these thematic areas. While this list is not all-inclusive, it does demonstrate some of the more specific needs in the various thematic areas.

In summary, this conference evaluated existing evidence on dietary supplement use in the elderly. While the information presented was extensive, the data available on this topic is only a fraction of what is necessary to fully understand and responsibly recommend the role of supplements in elderly nutrition. The use of supplements in the elderly population is continually increasing and creates an immediate need for research to fill the knowledge gaps.
