



OSU Oregon State University

The Linus Pauling Institute

R E S E A R C H N E W S L E T T E R



From the Director

*Balz Frei, Ph.D.
LPI Director and Endowed Chair
OSU Distinguished Professor of
Biochemistry and Biophysics*

To say we had a busy summer and fall at the Linus Pauling Institute would be a vast understatement! In the first week of September, the Institute moved into our new home, the Linus Pauling Science Center. It is a dream come true, 15 years after the Institute arrived on the campus of Oregon State University. The new building, designed by the world-renowned architect firm Zimmer Gunsul Frasca, headquartered in Portland, Oregon, is simply magnificent. The Linus Pauling Institute's top two floors of the Center are connected by a two-story, "cathedralesque" atrium, which provides an independent identity for the Institute. The continuous, open laboratory space, housing the Institute's 15 laboratories and three research programs—Cancer Chemoprotection, Healthy Aging, and Cardiovascular and Metabolic Diseases—provides flexibility and facilitates collaborations in state-of-the-art facilities. The building maximizes functionality and efficiency and is, at the same time, aesthetically very pleasing with its modern design, ample natural light, straight lines, extensive use of glass and natural



Photo by Eckert & Eckert

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LPI Diet and Optimum Health Conference

*Stephen Lawson
LPI Administrative Officer*

The sixth LPI Diet and Optimum Health Conference, co-sponsored by the Oxygen Club of California, convened on the OSU campus in Corvallis from September 13 to 16. The conference featured 21 speakers from around the world and was organized into five sessions:

- Vitamin E: Biological Functions and Controversies
- Micronutrients, Diet, and Immune Function
- Diet and Cardiovascular Disease
- Gut Microbes and Probiotics: Role in Health and Disease
- Caloric Restriction Mimetics, Diet, and Healthy Aging

Forty-six posters depicting experimental projects were displayed beginning Wednesday afternoon. An additional eight posters were selected for oral presentations on Thursday afternoon.

The conference concluded on Thursday with the presentation of the Linus Pauling Institute Prize for Health Research to Dr. Connie Weaver of Purdue University, followed by her lecture on calcium and bone health. For more details, please see the article on page six.

Vitamin E: Biological Functions and Controversies

Chaired by **Maret Traber** (LPI)

- **Danny Manor** (Case Western Reserve University) discussed the role of the alpha-tocopherol transfer protein (TTP) in the regulation of vitamin E in the body. TTP is synthesized in the liver and distributes only the natural or *d*-alpha-tocopherol form of vitamin E to the blood. Mutations in TTP, therefore, affect vitamin E status. Appropriate neuronal responses to stimuli are lacking in

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Continued from cover — From the Director

wood, and some amazing art work. This, together with the many formal and informal meeting places, provides a first-rate working space that fosters cutting-edge scientific research and development of new ideas and research projects, and greatly enhances the intellectual environment of the Institute. We are truly privileged—and very happy—to be in such fabulous facilities!

In September, we also held our sixth Diet and Optimum Health conference on the OSU campus in Corvallis, which allowed us to showcase the new Center. The conference attracted 220 registrants and was very successful, thanks to all the excellent talks and poster presentations. The sixth Linus Pauling Institute Prize for Health Research was awarded to Dr. Connie Weaver, Distinguished Professor and Head of the Department of Foods and Nutrition at Purdue University and an OSU alumna. Dr. Weaver was honored for her groundbreaking work in human calcium metabolism and bone health, which revolutionized our understanding of the importance of building peak bone mass during adolescence, the factors that contribute to bone loss in postmenopausal women, and dietary and lifestyle factors that help prevent osteoporosis. Summaries of Dr. Weaver's research and all the talks of the conference are provided in this issue of the Newsletter.



Dr. Viviana Perez

We also recently filled a new faculty position in the Institute's Healthy Aging Program with an outstanding candidate, Dr. Viviana Perez, from the Institute for Longevity and Aging Studies at the University of Texas Health Sciences Center at San Antonio. In addition to being a Principal Investigator in the

Institute, Dr. Perez holds an Assistant Professor position in OSU's Department of Biochemistry and Biophysics. Her research focuses on the roles of oxidative stress and protein homeostasis in the aging process and how dietary restriction and rapamycin extend life span, a topic which she addressed in her talk at the Diet and Optimum Health conference (see inside). Dr. Perez brings with her a prestigious New Scholar Award in Aging from the Ellison Medical Foundation. She received her Ph.D. degree in Biomedical Sciences from the University of Chile, Santiago.

In addition, we hired a new Research Associate to help maintain and expand the Institute's Micronutrient Information Center (MIC;

<http://lpi.oregonstate.edu/infocenter>). Dr. Giana Angelo joined us from the Fred Hutchinson Cancer Research Center in Seattle, WA. She holds a Ph.D. degree in Cellular and Molecular Nutrition from Tufts University in Boston, MA, where she did research on vitamin D. Dr. Angelo will be working with Dr. Victoria Drake, MIC Manager, to



Dr. Giana Angelo

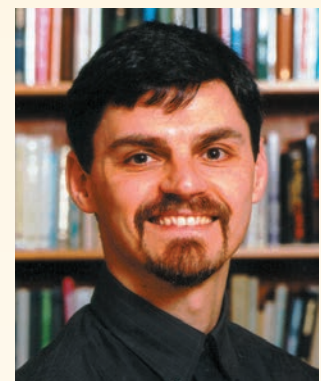
critically review and synthesize basic, clinical, and epidemiologic research literature in order to update existing articles and write new ones for the MIC. She will also respond to questions from donors, health and nutrition professionals, and the media concerning topics represented in the MIC.



Dr. Maret Traber

Finally, thanks to a large bequest LPI recently received, we have been able to establish two new endowed Professorships in the Institute. Dr. Maret Traber was selected as the inaugural recipient of the "Helen P. Rumbel

Professorship in Micronutrient Research," and Dr. Rod Dashwood for the "Helen P. Rumbel Professorship in Cancer Prevention." A celebration and public announcement took place at the grand opening of the Linus Pauling Science Center on October 14, where Dr. Dashwood presented his work on genetic and epigenetic aspects of cancer development and the protective role of dietary factors, and Dr. Traber talked about the biological functions and value of vitamin E in protecting against oxidative stress. On behalf of everybody in the Institute, I welcome Drs. Perez and Angelo and congratulate Drs. Traber and Dashwood for their well-deserved recognition! **LPI**



Dr. Rod Dashwood

mice that have the gene for TTP deleted, illustrating that vitamin E is important in normal brain function.

- **Qing Jiang** (Purdue University) showed that metabolites of gamma-tocopherol, a form of vitamin E found in soybean and corn oils and the most commonly consumed form of vitamin E in the American diet, possess anti-inflammatory activities greater than either alpha- or gamma-tocopherol.
- People born now have a 33% risk for diabetes, and cardiovascular disease is the cause of death in 80% of diabetics. **Andrew Levy** (Technion-Israel Institute of Technology) focused on the influence of vitamin E on cardiovascular disease risk in people with variations in the haptoglobin gene. Haptoglobin binds to hemoglobin released from red blood cells and prevents oxidative damage. Diabetics with the haptoglobin 2-2 gene (Hp 2-2) have an increased risk for cardiovascular disease, which is attenuated by supplemental vitamin E. Conversely, vitamin E may be harmful in diabetics with the Hp 2-1 gene, so genotype screening may be valuable.
- **Etsuo Nikki** (National Institute of Advanced Industrial Science and Technology, Japan) addressed difficulties in assessing the antioxidant role of vitamin E *in vivo*. He stated that vitamin E reduces the risk for free radical-mediated chronic diseases “if given to right subjects at right timing.” Vitamin E may be more effective if given early in disease development. Antibodies raised against oxidatively damaged biomolecules may be good markers for evaluating antioxidant interventions.

Micronutrients, Diet, and Immune Function

Chaired by **Adrian Gombart** (LPI) and **Emily Ho** (LPI)

- **George Liu** (UCLA) reported on the effect of nicotinamide, a derivative of nicotinic acid (collectively known as niacin or vitamin B₃), on enhancing immune function. Nicotinamide amplifies the amount of a transcription factor, C/EBP ϵ , needed for the mature function of immune system cells called neutrophils and macrophages. Mice were infected with *Staphylococcus aureus* (MRSA), the most common cause of soft tissue infections in people. Treatment with nicotinamide dramatically killed the pathogen in the blood by enhancing the production of antimicrobial compounds in neutrophils.
- **Carlos Camargo** (Harvard) noted that supplementary vitamin D in people with low vitamin D levels decreased the risk for acute respiratory infections. In a Boston study, vitamin D supplementation in pregnant women reduced the incidence of wheezing in their children. In a New Zealand study, vitamin D insufficiency in pregnant women increased the risk of respiratory infections in their children. In Afghanistan, vitamin D treatment prevented subsequent pneumonia in children. An analysis of the totality of evidence suggests that vitamin D may be more effective in preventing rather than treating respiratory infections.
- **Elizabeth Gardner** (Michigan State University) discussed the role of nutrition in influenza infection.

Although antibody response doesn't seem to be affected by nutritional status, the response of T cells needed to fight infection is influenced by nutrition. Specifically, caloric restriction, a strategy observed to extend life span in many animals, increases the susceptibility to influenza infection in mice by adversely affecting the activity of natural killer cells, which are important in the early stage of infection. These data suggest that caloric restriction can extend life span only in a germ-free environment.

- Sepsis is caused by overwhelming bacterial infection and often results in death due to the collateral effects of immune activity. **Daren Knoell** (The Ohio State University) noted that zinc levels are low in septic and critically ill patients. In mice, zinc deficiency decreases survival from sepsis, and zinc restoration three days before sepsis improves survival. After sepsis in mice, intraperitoneal injection of zinc—but not oral zinc—improves survival.
- **Peter Hoffmann** (University of Hawaii) explained the relationship between selenium and immune response. He found that high levels of selenoprotein K are present in immune cells and that mice without selenoprotein K are more susceptible to viral infection. Selenoprotein K is important in the proper function of T cells, neutrophils, and macrophages. Strategies using nanotechnology may be developed to target selenium to immune cells.
- **Robert Chapkin** (Texas A&M University) studies the role of polyunsaturated fatty acids in immune function, especially as it relates to inflammatory bowel disease. Omega-3 fatty acids (n-3 fatty acids) like eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) found in fish oil suppress T-cell activation through effects on lipid “rafts” in cell membranes. Therefore, supplementation may be beneficial in people with hyperactive immune systems but immunosuppressive in healthy people.

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Katie Lebold, Caitlin Crimp, and Sherry Farley



Maret and Biff Traber

Diet and Cardiovascular Disease

Chaired by Balz Frei (LPI)

- Cooking food results in pleasant flavors and palatability. However, **Veronika Somoza** (University of Vienna, Austria) noted that high-temperature cooking of processed food in the Western diet produces both beneficial and harmful compounds, including carcinogens like heterocyclic amines (“cooked-meat mutagens”), as well as advanced glycation end products (AGE) and lipid hydroperoxides associated with heart disease and diabetes. Mild cooking, replacement of high-fructose corn syrup with sucrose, and increasing the intake of substances like vitamin C that counteract some of the harmful compounds are strategies to lower disease risk.
- **Teresa Fung** (Simmons College, Boston) discussed the epidemiological associations between diet and cardiovascular disease. Connections between diet and disease risk can be assessed in several ways: correlations between actual food intake and disease or adherence to prudent dietary recommendations. Many studies have found that prudent patterns (i.e., plant-based, minimally processed foods, Mediterranean diet) are associated with decreased risk for heart disease, while the Western diet (refined grains and meat) increased the risk for heart disease.
- **Ramon Estruch** (Barcelona University, Spain) focused on the healthful effects of the Mediterranean diet, which is rich in fruit, whole grains, vegetables, legumes, nuts,

olive oil, fish, and seafood but has little chicken, milk, or red meat. The diet also includes moderate intakes of alcohol, usually as red wine. Dr. Estruch and colleagues are conducting a clinical trial to evaluate the effects of a Mediterranean diet on the risk of death from heart disease, incidence of cardiovascular events like strokes and heart attacks, incidence of cancer and diabetes, and mortality from all causes. To date, compliance to the diet has resulted in decreased oxidative stress and inflammation, lower BMI, decreased waist circumference, and decreased risk for metabolic syndrome.

Gut Microbes and Probiotics: Role in Health and Disease

Chaired by Sharon Krueger (LPI)

- **Cindy Davis** (U.S. National Cancer Institute) discussed the microbiome—the bacteria (“probiotics”) that populate the gastrointestinal tract. Such organisms affect health, including cancer risk and, possibly, obesity. “Prebiotics” include dietary factors like soy, fiber, and ellagitannins in berries that are metabolized by gut bacteria to compounds like equol, butyrate, and ellagic acid, respectively, each of which protects against cancer. Microbiotica also influence energy balance; lean people typically have populations of gut bacteria different from those in obese people. • **Bruce German** (University of California-Davis) talked



Christine Merrill, Alan Taylor, Neil Mann, and Gary Merrill

about the evolutionary relationship between breast milk and *Bifidobacterium infantis*, a bacterial strain that colonizes the infant’s gastrointestinal tract until weaning. Complex oligosaccharides in breast milk are indigestible in the infant’s gut but can be metabolized only by *B. infantis*, releasing compounds that regulate metabolism, protect against pathogens, and educate the immune system. • The role of probiotics in disease prevention and treatment is gaining acceptance. **Robert Martindale** (Oregon Health & Science University) discussed a study showing that probiotics routinely delivered via coated drinking straws halved the number of sick days taken by workers in a car factory. In other studies, probiotic use decreased the incidence of ear infections in healthy nursery school children, decreased gestational diabetes, and decreased mortality and pneumonia by 50% in patients on ventilators. Vancomycin-resistant *enterococci*



Olga Vlasenko, Maret Traber, Lester Packer, and LeeCole Legette

(VRE), a common cause of hospital infections, can be cleared by probiotics, further demonstrating their clinical utility.

Caloric Restriction Mimetics, Diet, and Healthy Aging

Chaired by **Tory Hagen** (LPI) and **Viviana Perez** (LPI)

- **Richard Miller** (University of Michigan) discussed several strategies that increase life span in mice, including rapamycin (an immunosuppressant drug derived from bacteria); deletion of the gene for migration inhibition factor, which is a pro-inflammatory cytokine; a low-methionine diet, which may provide resistance to stress and toxins; and food restriction early in life. In contrast, resveratrol, simvastatin, curcumin, and green tea extract did not affect life span in mice. Additionally, calorically restricted mice are more susceptible to infections.
- Resveratrol is a compound produced in grapes in response to stress. According to **Julie Mattison** (U.S. National Institute on Aging), its effects are species-specific, although supplementation to mice and monkeys fed high-fat or diabetes-inducing diets has resulted in health improvements. For example, monkeys kept on such diets and given very high doses of resveratrol exhibited less arterial stiffening and inflammation and improved glucose control compared to control animals. The mechanism responsible for those effects is unknown.
- **Jamie Barger** (LifeGen Technologies, Madison, WI) presented information on the identification of genes that serve as biomarkers of caloric restriction. Such biomarkers may be useful in determining the utility of compounds like resveratrol or quercetin—a flavonoid—on increasing life span. Of nearly 21,000 genes surveyed in mice, 11 served as markers of caloric restriction. Low doses of resveratrol or quercetin slightly mimicked caloric restriction, but the combination was synergistic.
- **Gordon Lithgow** (The Buck Institute for Age Research, California) discussed the importance of protein homeostasis—dysfunctional proteins replaced with normal proteins—in longevity. Using small worms (*C. elegans*), he has shown that curcumin, lithium, and Thioflavin T, a dye that binds to aggregated and misfolded proteins, extend life span in worms. Chelating metals in worms to maintain “metallostasis” also increased life span.
- **Viviana Perez** (LPI) showed that rapamycin and dietary restriction increased life span in mice, but only dietary restriction decreased fat mass, resulting in improved glucose control and insulin tolerance. Dietary restriction also delayed the onset of

Alzheimer’s and amyotrophic lateral sclerosis (ALS) in mouse models. Since there are differential effects of dietary restriction and rapamycin on disease and because



Front row: Kate Shay, Dove Keith, Drupadi Dillon, and Judy Butler; Standing: Nick Thomas, Liam Finlay, and Luis Gomez

they work through different mechanisms, rapamycin does not act as a dietary restriction mimetic.

Oral Abstracts

Eight abstracts on a variety of topics were selected for oral presentations:

Mark Levine (U.S. National Institute of Diabetes and Digestive and Kidney Diseases) discussed the cytotoxicity of high concentrations of vitamin C achieved by intravenous infusion against cancer cells. Physician surveys show that high-dose IV vitamin C has minimal side effects. Cell culture, mouse studies, and some preliminary studies with cancer patients suggest that IV vitamin C combined with standard drug therapy (gemcitabine) may be especially effective against pancreatic cancer.

Margreet Vissers (University of Otago, New Zealand) noted that consuming kiwi fruit raises blood levels of vitamin C more than vitamin C added to drinking water. Vitamin C inhibits hypoxia-inducible factor 1 (HIF-1), a transcription factor induced by the low-oxygen environment in tumors. HIF-1 promotes the survival of cancer cells and enhances angiogenesis (blood vessel formation), which is needed by rapidly growing tumors to supply nutrients and remove waste.

Silvia Maggini (Bayer Consumer Care, Switzerland) presented **David Kennedy’s** (Northumbria University, UK) abstract on the effect of multivitamins/minerals on cognitive performance and mood. In several studies

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The Linus Pauling Institute Prize for Health Research



Dr. Connie Weaver of Purdue University was presented with the 2011 Linus Pauling Institute Prize for Health Research, consisting of a medal and \$25,000, for her outstanding work on calcium and bone health. She pioneered the use of stable isotopes in elucidating calcium metabolism and has been a very effective advocate for science in the public realm.

Dr. Weaver received her B.S. from Oregon State University and a Ph.D. from Florida State University, where she held her first faculty appointment. She has been a Professor of Foods and Nutrition at Purdue since 1988, Department Head since 1991, and Distinguished Professor since 2000. Dr. Weaver has served as an advisor to many organizations and in 1996 served on the National Academy of Sciences' Food and Nutrition Board Dietary Reference Intakes Panel for Calcium and Related Nutrients. She was elected to the Institute of Medicine of the National Academies in 2010 and the Food and Nutrition Board of the Institute of Medicine in 2011. She has written over 160 peer-reviewed research articles.

Dr. Weaver's lecture focused on the critical need for adequate calcium intake during skeletal development and during the "fracture zone" period after 50 years of age. About 50% of women over 50 have fractures, and there is a linear relationship between bone mineral density and the risk for fracture. Failure to reach optimal bone mineral density in adolescence predicts osteoporosis later in life. About 99% of the body's calcium is in bone, and over 30% of bone is calcium. Calcium is critical for the structural strength of bones and to reduce bone resorption by maintaining a positive calcium balance. While environment and genes play a role in bone development and health, dietary calcium intake is exceedingly important early in life. For example, bone accrual is most rapid during ages 12 to 15 for girls and boys, and peak bone mass is reached at age 20. A daily calcium intake of 1,300 mg results in maximal retention for bones, and boys more efficiently retain calcium than

girls. There are also racial differences: African-American girls absorb more calcium and deposit more calcium in bones than Caucasian girls, and Chinese-American adolescents require less calcium intake for maximal retention in bones. Transient low bone mineral density for body size may explain the increased risk for fracture in teens, especially in the distal radius and among obese children. Dr. Weaver noted that without calcium supplementation, many Americans would be deficient in calcium status.

Many recommendations for calcium intake have emerged from research conducted at Purdue's "Camp Calcium," a summer camp where scientists study calcium metabolism in children, especially as affected by gender and ethnicity. Camp Calcium was started by Dr. Weaver 20 years ago to gather more information on calcium metabolism and bone health in a controlled environment.

Nomination letters cited Dr. Weaver's "strong commitment to being actively engaged in public health policy" and her work on calcium metabolism as "an elegant example of translational research, using unique and innovative technologies, that has had tremendous impact on programs that aim to maximize peak bone mass and improve bone health." **LPI**



Drs. Balz Frei and Connie Weaver

conducted in labs or by mobile phone, subjects taking multivitamin/minerals had improvements in stress, mental health, mental vigor, and analytical performance.

Gene Bowman (Oregon Health & Science University) noted that randomized controlled trials of the effect of single nutrients in Alzheimer's disease have been disappointing. Studies that rely on food-frequency questionnaires in these patients may be inaccurate because even mild memory deficits attenuate their validity. Higher blood levels of *trans* fat were associated with increased brain atrophy and poor memory and attention, whereas omega-3 fatty acids were associated with better executive function. Blood levels of B vitamins and vitamins C, D, and E were associated with increased brain volume.

Tetsuya Konishi (Niigata University of Pharmacy and Applied Life Sciences, Japan) discussed the biochemical effects of Schisandrin B, a lignan from the Chinese vine *Fructus schisandrae*. Schisandrin B lowers oxidative stress and brain damage in mice induced by drugs like scopolamine and cisplatin, as well as protecting against neurotoxicity, DNA damage, and cognitive impairment.

Katie Meyer (University of Minnesota) described a long-term, observational diet study of about 5,000 adults in four U.S. cities. Based on food-frequency questionnaires, the subjects' diets were ranked according to quality. Periodic measurements of F₂-isoprostanes, which are makers of oxidative stress, revealed that the highest diet quality correlated with the lowest oxidative stress. Diet quality was based on intake of 46 food groups scored as beneficial, neutral, or adverse for health according to current science. The highest quality diet consisted of whole grains, fruit, vegetables, fish, nuts and seeds, and was low in red meat.

Neil Mann (Royal Melbourne Institute of Technology University, Australia) addressed dietary changes during recent human evolution and the effect of a high-protein diet similar to that consumed in the Paleolithic era on body weight and glycemic control in type 2 diabetics. Conventional recommendations for diabetics to consume low-fat, high-carbohydrate diets result in elevated blood glucose and triglycerides, whereas high-protein diets are associated with weight loss, better glycemic control, lower systolic blood pressure, and lowered dose of medication like metformin.

Kate Shay (LPI) reported on newly characterized pathways involved in lipoic acid activity. A transcription factor called Nrf2 controls about 200 genes involved in oxidative/toxicological stress response. Nrf2 accumulates in the nucleus of cells treated with lipoic acid, which also attenuates the degradation of Nrf2. These effects improve cellular response to various stressors.



LPI's Galen Miller and Dr. John Maguire of the Oxygen Club of California

Young Investigator Awards

Young Investigator Awards were presented to three graduate students or post-doctoral fellows. Their abstracts were selected as the most outstanding of the submissions.

The Linus Pauling Institute Young Investigator Awards were given to Dr. **Vijayasree V. Giridharan** of the Department of Functional and Analytical Food Sciences, Niigata University of Pharmacy and Applied Life Sciences, in Niigata City, Japan (“Schisandrin B, a component of medicinal herb *Schisandra chinensis*, attenuates β -amyloid-induced cognitive dysfunction and neuro-inflammation by modulating NF- κ B signaling”); and Dr. **LeeCole Legette** of the Linus Pauling Institute (“Pharmacokinetics of xanthohumol, a prenylflavonoid derived from hops”).

The Oxygen Club of California Young Investigator Award was given to **Galen W. Miller**, a graduate student in the Linus Pauling Institute and OSU's Molecular and Cellular Biology Program (“Normal brain development requires alpha-tocopherol delivery via the alpha-tocopherol transfer protein during zebrafish embryogenesis”).

LPI



Drs. Vijayasree V. Giridharan, LeeCole Legette, John Maguire, and LPI's Adrian Gombart

A dream come true — September 2011

The Linus Pauling Science Center



Photo by Eckert & Eckert



Photo by Karl Maasdam



Photo by Barbara McVicar

Oregon's "Percent for Art" program coordinated the selection of art for the Linus Pauling Science Center



Photo by Karl Maasdam

William Shumway's *Resonance*, a gift of Janet and Henry Nielsen

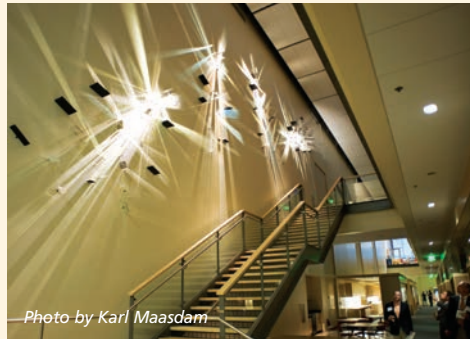


Photo by Karl Maasdam

Stephen Knapp's lightpainting *Structure, Space and Time* (also below right)



Photo by Karl Maasdam

Chris Dean's *Gold Will Stay and Opposite and Equal* (far right)



Photo by Barbara McVicar



Photo by Stephen Knapp



Photo by Barbara McVicar

Linus Pauling Institute lobby and atrium
Krysten Cunningham's *Oloid* sculpture, a gift from the Oxygen Club of California, is at left



Photo by Eckert & Eckert



Multivitamin/mineral Supplements

Victoria J. Drake, Ph.D.
Manager, LPI Micronutrient
Information Center

Although there is no standardized definition, a multivitamin/mineral (MVM) supplement is generally described as a dietary supplement that contains around 100% of the Daily Value (DV) of most vitamins and nutritionally essential minerals. MVM supplements, however, do not contain the DV for some of the essential minerals (e.g., calcium and magnesium) because the resulting pill would be too bulky to swallow. Notably, DVs listed on the supplement label are largely based on outdated recommendations made in 1968 and therefore do not reflect current dietary intake recommendations by the U.S. government—the Recommended Dietary Allowance (RDA) or Adequate Intake (AI) for micronutrients. For a comparison between the DVs and the current recommendations, see the table at right. Although not typically the case, manufacturers may choose to include micronutrients at levels equivalent to current recommendations in their products. Additionally, many companies market gender- and age-specific formulations of MVM supplements.

An estimated one-third of Americans aged one year and older take MVMs—the most popular type of dietary supplement in the United States. Studies have found that MVM supplement use is more prevalent in certain subgroups, including females, non-Hispanic whites, older adults, and individuals with higher education. Some other studies have associated MVM use with people who have generally healthier diets or rate their health as good or excellent. Daily use of a MVM supplement can help fill nutritional gaps and improve micronutrient status. Many Americans are apparently eating sufficient (or excessive) calories while, at the same time, not meeting daily intake recommendations for vitamins and essential minerals. Indeed, select micronutrient inadequacies are quite common in the United States: a national survey (NHANES 2003-2006) found that 60% of the U.S. population do not meet intake recommendations from diet and supplement use for vitamin E, 45% for magnesium, 38% for calcium, 34% for vitamin A, 25% for vitamin C, 8% for vitamin B₆, and 8% for zinc. Vitamin D insufficiency is also very common among Americans.

Moreover, micronutrient inadequacies have been documented in other industrialized countries, and multiple micronutrient deficiencies, especially of vitamin A, iodine, iron, and zinc, are widespread in the underdeveloped world. Micronutrient deficiencies have been estimated to affect almost two billion people worldwide. Such nutritional deficiencies can increase susceptibility to infectious diseases

but may also increase risk for chronic, age-related diseases, such as cardiovascular disease, osteoporosis, and cancer. Micronutrient deficiencies have further been linked to cognitive dysfunction. Given the fact that many people are not meeting micronutrient intake recommendations, a daily multivitamin/mineral supplement would offer insurance that most micronutrient needs are met.

However, it is not known whether taking a MVM supplement will decrease the risk of chronic disease. A number of observational studies as well as randomized

Comparison between the Daily Values (DV) and the Dietary Reference Intakes (RDA or AI) for Adults

Micronutrient	DV	RDA or AI for Adult Males (amount/day)	RDA or AI for Adult Females (amount/day)
Biotin	300 mcg	30 mcg	30 mcg
Folate	400 mcg	400 mcg ^a	400 mcg ^a
Niacin	20 mg	16 mg ^b	14 mg ^b
Pantothenic Acid	10 mg	5 mg	5 mg
Riboflavin	1.7 mg	1.3 mg	1.1 mg
Thiamin	1.5 mg	1.2 mg	1.1 mg
Vitamin A	5,000 IU	3,000 IU ^c	2,333 IU ^c
Vitamin B ₆	2 mg	1.3-1.7 mg	1.3-1.5 mg
Vitamin B ₁₂	6 mcg	2.4 mcg ^d	2.4 mcg ^d
Vitamin C	60 mg	90 mg	75 mg
Vitamin D	400 IU	600-800 IU	600-800 IU
Vitamin E	30 IU	22.5-33 IU ^e	22.5-33 IU ^e
Vitamin K	80 mcg	120 mcg	90 mcg
Calcium	1,000 mg	1,000-1,200 mg	1,000-1,200 mg
Chloride	3,400 mg	1,800-2,300 mg	1,800-2,300 mg
Chromium	120 mcg	30-35 mcg	20-25 mcg
Copper	2 mg	900 mcg	900 mcg
Iodine	150 mcg	150 mcg	150 mcg
Iron	18 mg	8 mg	8-18 mg
Magnesium	400 mg	400-420 mg	310-320 mg
Manganese	2 mg	2.3 mg	1.8 mg
Molybdenum	75 mcg	45 mcg	45 mcg
Phosphorus	1,000 mg	700 mg	700 mg
Potassium	3,500 mg	4,700 mg	4,700 mg
Selenium	70 mcg	55 mcg	55 mcg
Zinc	15 mg	11 mg	8 mg
Choline ^f	None established	550 mg	425 mg

^aDietary Folate Equivalents

^bNE, niacin equivalent: 1 mg NE = 60 mg tryptophan = 1 mg niacin

^cRetinol Activity Equivalents

^dIntake for adults >50 years should be from supplements or fortified foods due to the age-related increase in food-bound malabsorption

^e22.5 IU of natural-source alpha-tocopherol (*d*-alpha-tocopherol); 33 IU of synthetic alpha-tocopherol (*d*l-alpha-tocopherol)

^fConsidered an essential nutrient, although not strictly a micronutrient

controlled trials (RCTs) have examined the effect of MVMs on reducing the risk of various cancers, cardiovascular conditions, and other diseases, but results are largely conflicting. Inconsistent findings among studies may be partially attributed to variations in MVM supplement composition, as well as dose and duration of use. Additionally, both observational studies (studies in which a group is simply observed over time with no experimental intervention) and RCTs have inherent limitations that make it difficult to determine whether MVM use might help prevent chronic disease. For example, people who volunteer to be part of such studies are commonly healthier than the average person, and some studies have found that those who take MVM supplements have an overall healthier diet and lifestyle than those who do not take MVMs.

Observational studies may be subject to residual confounding if all of the potential confounding variables are not accounted for in the statistical model. Such studies can only detect associations between MVM use and health endpoints rather than establish cause-and-effect relationships. While RCTs are able to establish cause-and-effect associations, they are ill-suited to study the effects of micronutrients. In particular, the placebo group in RCTs of micronutrients is not a true placebo or non-exposed group because a micronutrient-free state does not exist in the body without deficiency disease, and it is obviously not ethical to deprive the control group of essential micronutrients. Additionally, RCTs of MVM supplements are conducted in generally healthy people (as opposed to those with some disease) and thus would likely take years or decades to observe a measurable effect; compliance during such a long-term study is highly problematic. Short-term RCTs that assess DNA damage, inflammation, insulin sensitivity, lipid profile, blood pressure, immune function, or other biomarkers of disease are more practical and may be useful in determining whether MVMs help prevent chronic disease.

While the health effects of MVM supplements are difficult to determine, MVM supplement use is generally considered safe for healthy people. U.S. government regulations, called current good manufacturing practices (CGMPs), ensure that dietary supplements meet quality standards for identity, purity, strength, and composition, as long as supplement manufacturers comply. Although excessive intakes of select micronutrients can be unsafe, the amounts of micronutrients in MVM products approximate the DVs. For most micronutrients, the DV is considerably lower than the tolerable upper intake level (UL)—the highest level of daily intake of a specific nutrient likely to pose no risk of adverse health effects in almost all individuals of a specified age. The Food and Nutrition Board of the Institute of Medicine recommends that the total daily intake of micronutrients—from foods, fortified foods, and supplements—should not exceed the UL. The DV for vitamin A (5,000 IU) is considerably higher than the current RDA (2,333 IU/day for women and 3,000 IU/day for men), and excessive retinol



(preformed vitamin A) intakes have been linked with bone fractures in older adults. For these reasons, the Linus Pauling Institute (LPI) recommends that adults take a MVM supplement providing no more than 2,500 IU (750 mcg) of preformed vitamin A, usually labeled as vitamin A acetate or vitamin A palmitate, and no more than 2,500 IU of additional vitamin A as beta-carotene.

Additionally, because men and postmenopausal women are not at risk for iron deficiency and excess iron can have detrimental health effects, LPI recommends that men and postmenopausal women take a MVM supplement without iron. MVM supplements formulated for men or older adults generally do not contain iron, but one must examine the supplement label. Although MVMs are safe for most people, certain drug-nutrient interactions are possible; thus, the use of all nutritional supplements should be discussed with a competent healthcare provider.

According to national surveys, many Americans have inadequate dietary intake of key micronutrients, possibly increasing their risk for age-related diseases, such as osteoporosis, cardiovascular disease, and some forms of cancer. Micronutrient inadequacies may also be associated with impaired immune responses and untoward effects on cognition. Many Americans are apparently consuming an energy-dense diet that is lacking in essential micronutrients. Given the facts that dietary habits are difficult to change and that many people often cannot afford micronutrient-rich fruits and vegetables, the Linus Pauling Institute recommends a daily MVM supplement as nutritional insurance. For information on healthy eating, see the LPI “Rx for Health”: <http://lpi.oregonstate.edu/lpirx2.html>. Although the specific consequences of chronic micronutrient inadequacies are difficult to document, it is sensible to ensure adequacy for health by taking a daily MVM supplement at low cost and low risk. **LPI**

Multivitamin/mineral Supplements and Mortality

A recently published paper from the Iowa Women's Health Study (*Arch. Intern. Med.* 171:1625-1633, 2011) concluded that "In older women, several commonly used dietary vitamin and mineral supplements may be associated with increased total mortality risk; this



association is strongest with supplemental iron." For many, this report is alarming, especially since approximately half of the U.S. population takes at least one dietary supplement. However, we found insufficient evidence to support the claims of the authors that dietary supplement use is associated with increased risk of mortality in older women.

Pros and Cons of Observational Studies

First, it is important to note that the Iowa Women's Health Study is an observational study. In observational studies, scientists examine associations between dietary and lifestyle factors and the incidence of disease in the study population, which is referred to as a "cohort." Although observational studies provide valuable ways to generate hypotheses that can be further tested in randomized, placebo-controlled trials, they cannot establish cause and effect. Observational studies instead establish associations between a given trait and disease outcome, but they do this only after mathematically adjusting for multiple confounders—characteristics that might confound or confuse the association—such as age, gender, exercise habits, and body weight. Further, despite the statisticians' best efforts to take all of these confounding factors into consideration, there are numerous additional factors that haven't been discovered yet or were not measured in the study. This phenomenon is called "residual confounding" and is a major reason why observational studies can only generate hypotheses.

In the Iowa Women's Health Study, 38,772 postmenopausal women were asked to report their supplement use at only three time points many years apart (1986 at baseline, 1997, and 2004), and their self-reported information was then related to the occurrence of death during the corresponding interval. The authors of the study emphasize that the most consistent findings were a dose-dependent increase in mortality risk with supplemental iron and a dose-dependent decrease in mortality risk with supplemental calcium.

Study Limitations

After closer examination of the data, we note several important limitations:

1. *Healthy person or survivor bias*

The supplement users were healthier and lived longer overall. As a result, a higher percentage of them stayed in the study, while many non-users were lost to follow-up and their mortality data could not be assessed. The authors report that supplement users were, in fact, "healthier" compared to non-users at baseline, characterized as having a lower prevalence of diabetes mellitus, high blood pressure, and smoking status; having a lower body mass index (BMI) and waist-to-hip ratio; being more physically active; and being more likely to have healthful dietary patterns. This differential retention during the study period biases the results, contributing to a spurious association between supplement use and mortality.

2. *Reverse causality*

People may begin taking supplements as they age or when they are diagnosed with disease. As a result, death is likely due to old age or disease, not dietary supplement use. In fact, the data reveal that self-reported supplement use increased substantially at each study interval: 62.7% in 1986, 75.1% in 1997, and 85.1% in 2004. As the study cohort aged, more women began taking dietary supplements. Furthermore, subjects with cardiovascular disease, diabetes mellitus, or cancer were excluded from the analysis at baseline but not afterwards. Considering that the follow-up period spanned 19 years and the mean age at baseline was 60.1 years, it is likely that disease emerged during the study period. The authors do not state the cause of death; therefore, it is misleading to blame the supplement—rather than a serious chronic disease—for mortality.

3. *Recall bias*

Self-reported use of dietary supplements is prone to recall error, and such data tend to be selective and inaccurate. Importantly, there is no information on

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Vitamin E and Prostate Cancer in Healthy Men

A paper published recently from the Selenium and Vitamin E Cancer Prevention Trial (SELECT) in the *Journal of the American Medical Association (JAMA 306:1549-1556, 2011)* concluded that “dietary supplementation with vitamin E significantly increased the risk of prostate cancer among healthy men.” This alarming news spread fast, and many men are now wondering if it is prudent to take vitamin E supplements in light of this new information.

To date, two large randomized, placebo-controlled trials (RCTs) have been conducted in healthy men to investigate the effect of vitamin E supplementation on prostate cancer: The Physicians’ Health Study (PHS) II and SELECT. PHS II (*JAMA 301:52-62, 2009*) followed 14,641 healthy men, aged 50 years and older, given 400 International Units (IU) of synthetic vitamin E every other day for eight years. In SELECT, 35,533 healthy men, aged 50 and older, received 400 IU of synthetic vitamin E every day for seven years. In both trials, there was no benefit of taking vitamin E supplements on prostate cancer risk. After a median time of 5.5 years in SELECT, vitamin E supplementation was discontinued, yet follow-up of the study participants continued for 1.5 years in order to document additional events. Unexpectedly, the SELECT updated analysis published recently in *JAMA* found a 17% increased risk of being diagnosed with prostate cancer in men who had taken the vitamin E supplement compared to those who had received placebo. No biological mechanism was proposed to explain the increased incidence of prostate cancer.

Why Did They Look at Vitamin E in the First Place?

Vitamin E functions as a powerful, fat-soluble antioxidant in our cells and tissues. Antioxidants neutralize the effects of free radicals, highly reactive species that oxidize DNA, proteins, and lipids inside our cells, potentially causing damage and contributing to disease. In particular, oxidative DNA damage may cause mutations and, hence, increase the risk of certain cancers, including prostate cancer. Free-radical exposure is an unavoidable aspect of our lives, as these radicals are produced as a natural by-product of many biological processes, such as cellular respiration and inflammation, in addition to coming from our environment, particularly cigarette smoke. Antioxidants produced in the body and ingested in the diet are essential to reduce oxidative stress and counteract the potentially harmful effects of free radicals.

Some studies support a beneficial role for vitamin E in cancer and cardiovascular disease prevention. For example, the Women’s Health Study (*JAMA 294:56-65, 2005*) followed 39,876 women who took 600 IU natural vitamin E every other day for ten years. The investigators found that supplemental vitamin E decreased cardiovascular-related deaths by 24% but had no effect on cardiovascular

events, overall cancer incidence, or cancer-related deaths. In general, studies have reported mixed results, and the impact of vitamin E supplementation on chronic disease risk remains controversial.

Why Are the Results Different?

The Women’s Health Study (WHS), PHS II, and SELECT are RCTs, also referred to as clinical trials or intervention studies. In RCTs, individuals are randomly assigned to either treatment (vitamin E in this case) or placebo, and the impact of the intervention on disease incidence is evaluated after several years.

The important issues that emerge from these RCTs are vitamin E dose (200-400 IU/day), vitamin E form (natural *vs.* synthetic), and population studied. Synthetic vitamin E (*all-rac*-alpha-tocopherol or *dl*-alpha-tocopherol) has half the bioactivity of naturally occurring vitamin E (*RRR*-alpha-tocopherol or *d*-alpha-tocopherol)—hence, the “effective dose” in PHS II and SELECT was only 100 and 200 IU/day, respectively, and 300 IU/day in WHS. Higher doses may be needed to effectively reduce oxidative stress. In one dose-response study, significant reductions in plasma F₂-isoprostanes (a marker of oxidative stress) occurred only at daily doses of at least 1,600 IU of natural-source vitamin E. Notably, this dose is above the tolerable upper intake level (UL) of 1,500 IU/day set by the Food and Nutrition Board of the Institute of Medicine.

The fact that the vitamin E doses used in the RCTs appear insufficient to lower oxidative stress may explain the lack of benefit with respect to cancer risk. It remains unknown whether oxidative stress plays a causal role in prostate cancer. Furthermore, it remains unexplained

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supplement dose (with the exception of calcium and iron), formulation, or frequency provided for the analysis. Daily supplement habits can vary considerably over time, and multivitamin/mineral supplements are not uniformly formulated. Many contain amounts of reactive metals like iron that are not needed as supplements by postmenopausal women (or men).

4. Generalizability issues

The cohort consisted of only white, postmenopausal women with higher than average rates of supplement use. This is not a representative population and the applicability of the findings to premenopausal women, men, other ethnic groups, and the general population is not appropriate.

LPI's Recommendation

According to data from the National Health and Nutrition Examination Survey (NHANES), many Americans are not meeting current intake recommendations for several micronutrients. Even when considering micronutrient intake from fortified foods and dietary supplements, an estimated 70% of the U.S. population aged 2 years and older do not meet the estimated average requirement (EAR) for vitamin D, 60% for vitamin E, 45% for magnesium, 38% for calcium, 34% for vitamin A, and 25% for vitamin C. Multivitamin/mineral supplements are a simple, inexpensive, and safe way to help fill these nutritional gaps and improve micronutrient status.

As part of its “Rx for Health” (<http://lpi.oregonstate.edu/lpirx2.html>), LPI recommends a daily multivitamin/mineral supplement as nutritional insurance to meet micronutrient needs. Some multivitamin/minerals may provide excessive iron or vitamin A, which can have untoward health effects. Therefore, LPI recommends that men and postmenopausal women take a multivitamin/mineral without iron and containing no more than 2,500 International Units (IU), or 750 mcg, of preformed vitamin A (usually labeled vitamin A acetate or vitamin A palmitate) and no more than 2,500 IU of additional vitamin A in the form of beta-carotene. For more information on multivitamin/mineral supplements, see the article on page 10 of this Newsletter.

In summary, it would not be prudent to discourage the use of all vitamin and mineral supplements based on a single, flawed study. Each micronutrient fulfills one or several specific biological functions in normal metabolism and good health. It is not sensible to discourage the use of micronutrient supplements when so many people in the U.S. and around the world have insufficient dietary intakes of many vitamins and minerals. **LPI**

why vitamin E supplementation in SELECT was associated with a 17% increased risk of prostate cancer, whereas vitamin E supplementation in PHS II and WHS was not associated with increased risk of any type of cancer in men and women, respectively.

Finally, the population studied in SELECT was healthy males consuming a well-balanced diet, most of whom likely were not vitamin E deficient or under increased oxidative stress. Unfortunately, neither baseline vitamin E levels in the study participants' blood nor their oxidative stress status was assessed. In situations of stress, disease, or deficiency, meeting an increased demand with vitamin E supplementation may be warranted. However, in healthy people, vitamin E supplementation shows no added benefit on disease risk, as confirmed by the RCTs discussed here. For example, a study on the effect of supplemental vitamin E on cancer risk in 29,000 Finnish male smokers (the Alpha-Tocopherol Beta-Carotene [ATBC] trial) reported in 1998 that daily supplements of 75 IU/day of synthetic vitamin E for five to eight years were associated with a 32% and 41% reduction in prostate cancer diagnosis and mortality, respectively, compared to unsupplemented smokers. However, among other limitations, the ATBC study was not designed to assess prostate cancer incidence as a primary endpoint. Since oxidative stress was not measured in the study subjects, the mechanism for the possible protective effect of low-dose vitamin E remains obscure. Factors other than oxidative stress play an important role in the etiology of prostate cancer, such as endogenous hormones, race, age, and dietary fat intake.

Based on the lack of conclusive evidence for a benefit of vitamin E supplementation in cancer and cardiovascular disease prevention in generally healthy adults and the potential for harm in certain subpopulations, the Linus Pauling Institute has revised its “Rx for Health” (<http://lpi.oregonstate.edu/lpirx2.html>) and no longer includes a recommendation for supplementation with 200 IU/day of natural-source vitamin E.

What to Do?

Vitamin E is an important micronutrient, and meeting daily recommendations is critical for optimum health. The Recommended Dietary Allowance (RDA) of vitamin E for adult men and women is 22.5 IU per day. Notably, more than 90% of individuals aged 2 years and older in the U.S. do not meet the daily requirement for vitamin E from food sources alone. Major sources of vitamin E in the American diet are vegetable oils, nuts, whole grains, and green leafy vegetables.

Taking all the issues discussed above into consideration, LPI recommends that generally healthy adults take a daily multivitamin/mineral supplement, which usually contains 30 IU of synthetic vitamin E, or 90% of the RDA. **LPI**



Developments

Michele Erickson
LPI Director of Development

DON'T MISS this last chance opportunity to make a tax-free gift to the Linus Pauling Institute from your IRA!

Donors who are 70½ or older can donate up to \$100,000 per year from their IRA directly to a charity without paying income tax on the money. This is a significant incentive that removes the tax penalty for some donors who want to use their IRAs to fund a charitable gift. The IRA Charitable Rollover Legislation is only valid through December 2011.

- Gifts can only be made from an IRA. Pension, 401k, profit sharing and other forms of retirement funds do not fall under this legislation. However, donors can roll over non-qualifying accounts (e.g., 401k) into the qualifying IRA account in order to make a gift.
- Gifts can be made to multiple charities in any combination that does not exceed the \$100,000 per year per person limit.

- Gifts from your IRA can fulfill your annual required minimum distribution in part or in full.
- Gifts can only be made directly to public charities to be eligible for tax benefits. A gift cannot be made to a charitable remainder trust or charitable gift annuity.

The Next Step

Contact both your IRA administrator and your tax professional if you are considering a gift under this law. Feel free to call the OSU Foundation Gift Planning Office at 1-800-336-8217 or OSUFGiving@oregonstate.edu with any questions.

LPI

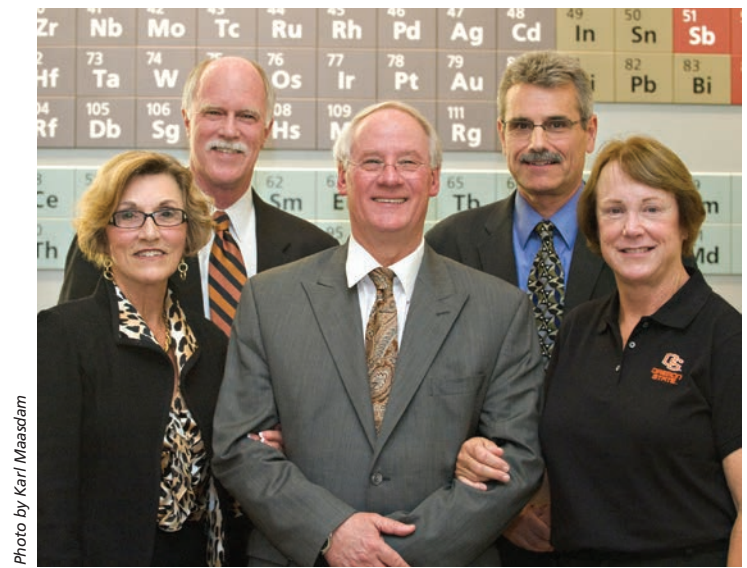


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- Arnold E. Molzon
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**Micronutrient
Research for
Optimum Health**



Photo by Karl Maasdam

The Linus Pauling Science Center

LPI and Chemistry moved into our new 105,000-square-foot building in September.

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