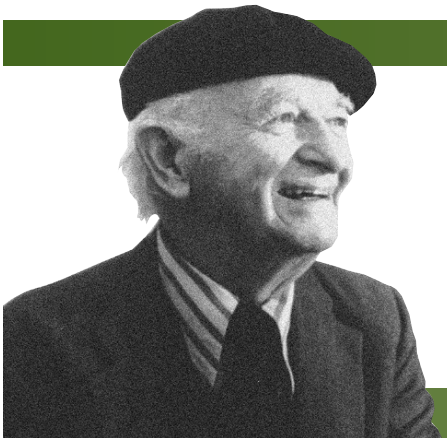
SPRING/SUMMER 2011



OSU Oregon State University

The Linus Pauling Institute

RESEARCH NEWSLETTER

From the Director

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

For three reasons, 2011 is a banner year for the Linus Pauling Institute. First, the new Linus Pauling Science Center is nearing completion and will open its doors in August. The architects, general contractor, and project manager have done an outstanding job keeping construction of the new building near-flawless, on schedule, and on budget. The $62.5 million, 105,000-square-foot science center is the most expensive academic building project in the history of Oregon State University and will be a working memorial to our founder and OSU alumnus, Dr. Linus Pauling. The top two floors of the four-story building will be dedicated to the Institute and provide state-of-the-art laboratory space for our faculty, students, and research staff in the Institute's three major research programs: the Cancer Chemoprotection Program, the Healthy Aging Program, and the Cardiovascular and Metabolic Diseases Program. The new building will represent a leap forward for the Institute, bringing together our scientists, students, and administrative staff under a single roof for the first time, promoting increased interactions and new collaborations, and generating scientific discoveries in disease prevention and health promotion through research in nutrition, micronutrients, and dietary supplements.

Second, the new building will also provide laboratory and office space for two new Principal Investigators in the Healthy Aging Program. This program, directed by long-time LPI faculty member and Jamieson Endowed Chair in Healthspan Research, Dr. Tory Hagen, has two principal goals: to better understand the cellular and molecular processes underlying the biology of aging, such as declining energy metabolism and immune function and increased chronic inflammation and oxidative stress; and to identify dietary and lifestyle regimens, including

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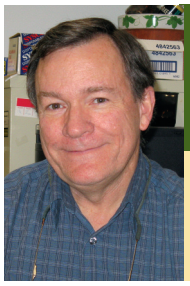

Not All Fats Are Created Equal

An Interview with Donald B. Jump, Ph.D.
Professor of Nutrition
LPI Principal Investigator

Q. You're from the East Coast, but you spent a few years at Oregon State University in the 1970s. What were you doing here then?

A. I was working with George Beaudreau in the Department of Agricultural Chemistry. I had completed my master's degree at Rutgers and wanted a change. I grew up in Delaware, where the highest point is 400 feet above sea level, and I had seen pictures of the West and thought that would be a great place to go. While doing my master's work, I worked for the Institute of Cancer Research and learned how to culture cells, mainly mammary cancer cells. I worked with George for about three years on cell culture and retroviruses and decided to go back to graduate school for a doctorate in biochemistry from Georgetown University.

Q. You rose through the ranks to become a professor at Michigan State University and then joined the Linus Pauling Institute in 2007. What attracted you to LPI?

A. LPI is an internationally recognized center for nutrition research with a strong focus in the area of micronutrients, antioxidants, and supplements. My area of research is omega-3 fatty acids as regulators of lipid metabolism. Omega-3 fatty acids, also called n-3 fatty acids, are often taken as supplements. N-3 fatty acids are generally beneficial to human health. I was attracted to the LPI because of its capacity to carry out sophisticated analyses of lipids using chromatographic and mass spectrometric methods.

Q. What do you like to do in your free time?

A. My wife and I work on our old house and property. The property was neglected when we purchased it in

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— DESIGNATED BY THE NATIONAL INSTITUTES OF HEALTH AS A —
Center of Excellence for Research on Complementary and Alternative Medicine

Continued from cover — From the Director

dietary supplements, to postpone age-related diseases and deficits of daily living, thereby extending healthspan. We are currently conducting a national search for a faculty position in "Biochemistry of Aging" and have identified an outstanding candidate with expertise in the role of protein stability and oxidative stress in healthy aging. I am looking forward to introducing our new faculty member to you in the next Research Newsletter. The final position in the Healthy Aging Program, which we hope to fill in the next two years, will focus on the causation and prevention of age-related neurodegenerative diseases, such as Alzheimer's or Parkinson's disease.

Third, in 2011, we will hold our Diet and Optimum Health conference in Corvallis for the first time, which allows us to showcase the beautiful campus of OSU and the new Linus Pauling Science Center. This will be our sixth Diet and Optimum Health conference, and it will feature some of the most prominent scientists in the fields of nutrition, aging research, and preventive and orthomolecular medicine. The program includes sessions on the role of diet and micronutrients in immune function, cardiovascular diseases, and healthy aging, as well as two sessions focusing on vitamin E and probiotics. The detailed program with all the speakers and topics appears on pages 8-9. In addition, we will award the sixth Linus Pauling Institute Prize for Health Research, which recognizes innovation and excellence in research relating to the roles of micronutrients, phytochemicals, and dietary antioxidant and anti-inflammatory factors in promoting health and preventing disease. The awardee will join our illustrious list of previous winners, Drs. Bruce N. Ames from the University of California, Berkeley, and Children's Hospital Oakland Research Institute; Walter Willett from Harvard; Paul Talalay from Johns Hopkins; Mark Levine from the National Institutes of Health; and Michael Holick from Boston University School of Medicine. The fall edition of the Newsletter will provide a summary of the conference and a detailed profile of this year's LPI Prize winner, along with a glimpse of the new Linus Pauling Science Center. LPI

LPI is grateful for the bequests we have received from the following friends this past year:

Dorothy B. Alcocer
Audrey M. Carlan *(pledged intent)*
Frances Reilly Cunningham
Arthur Kahn
Sidney Licht
Victoria J. Mastrobuono
Janet P. Roberts
Francis B. Rosevear
Earl Winston Schulz
Christen J. Wegener
George B. Whatley

Continued from cover — Interview with Dr. Donald Jump

2007; we have renovated some parts of the house and made some improvements to the property. We also have a boat and like to sail off South Beach near Newport. We really like the coast. I grew up on the East Coast, and my wife is from Oregon, so we both have an affinity for the ocean.

Q. In the early 1980s, you studied the effect of thyroid hormones on liver function. What did you find?

A. Thyroid hormones are hydrophobic hormones that regulate nuclear receptors; these receptors regulate gene expression. When I was a post-doctoral fellow at the University of Minnesota with Jack Oppenheimer, we established that thyroid hormone receptors are found in or bound to active regions on DNA (chromatin). I learned a lot about endocrinology during my time at the University of Minnesota; that knowledge had a significant influence on my first academic position at Michigan State University (MSU).

Q. Are there interactions between thyroid hormones and dietary factors that affect liver function?

A. There is significant interaction between carbohydrates and thyroid hormone—a synergy in the control of genes involved in lipid metabolism. Glucose, insulin, and thyroid hormones were found to regulate multiple genes involved in liver fat metabolism. At MSU, we had established mechanisms to measure gene expression in the liver; we carried out time-course studies to examine the effects of thyroid hormone action and sucrose (a simple carbohydrate) on liver gene expression. We applied this same approach to examine the effect of dietary fat and carbohydrate on liver gene expression. Rats were fed high-sucrose diets or diets supplemented with n-3 and n-6 fatty acids to examine their effects on liver gene transcription. Sucrose stimulated the expression of genes that make fat, while polyunsaturated fatty acids attenuated the expression of these genes. This discovery was the first to document effects of dietary fatty acids on gene expression, and it set the stage for much of our future research.

Q. Your cell culture studies with fat cells showed that a form of vitamin A called retinoic acid regulates certain genes involved in lipid metabolism. What impact does that have on health?

A. That's an interesting question. It turns out that the thyroid hormone receptor interacts with a form of the retinoic acid receptor in cells. Both receptors function to control lipid metabolism.

Q. Would that explain why some people with hypo- or hyperthyroid activity are thin or fat?

A. Perhaps. We first used cells that had the capacity to differentiate from fibroblasts—cells in connective tissue—to adipocytes or fat cells. We found that none of the cells responded to thyroid hormone, which prompted us to look at retinoic acid regulation of adipocyte function. That's when we found a retinoic acid regulatory scheme. While interesting, the implications of this finding to human health remain unclear.

Q. ***Could deficiencies in vitamin A in certain areas of the world affect lipid metabolism?***

A. Possibly.

Q. ***You've published a long series of papers on how dietary fats affect liver genes that regulate endogenous fatty acid synthesis and oxidation. Which dietary fats are important in these effects?***

A. All types of dietary fats affect liver metabolism and gene expression. Saturated fats promote fatty acid synthesis, while polyunsaturated fats inhibit fatty acid synthesis and promote fatty acid oxidation. Human diets typically contain more saturated and monounsaturated fats than polyunsaturated fats.

Q. ***What are the differences between saturated, monounsaturated, and polyunsaturated fats?***

A. The term saturation refers to the absence of chemical double bonds between carbon atoms in the fatty acid chain. The fatty acid is "saturated" with hydrogen atoms. Saturated fatty acids tend to have a more rigid structure. Unsaturated fatty acids have at least one double bond. The flexibility of that fatty acid increases as the number of double bonds increases. Monounsaturated fatty acids have one double bond; polyunsaturated fatty acids have two or more double bonds. The bulk of fatty acids are found in cell membranes and storage lipids, like triglycerides. Fatty acids in membranes affect the structure and function of the membrane. A bulky lipid—an unsaturated fat—or a non-bulky lipid like a saturated fat will influence the structure of the membrane and the function of proteins imbedded in membranes differently. There are many receptors in plasma membranes that communicate environmental signals to the inside of the cell. As the nature of the lipids in membranes changes, the function of these receptors and the control of cell function also change.

Q. ***That suggests that there is an optimum concentration of the various types of fats in the body to maintain proper membrane fluidity and function.***

A. Yes, but that optimum concentration is likely to be influenced by gender, age, genetic background, and health status.

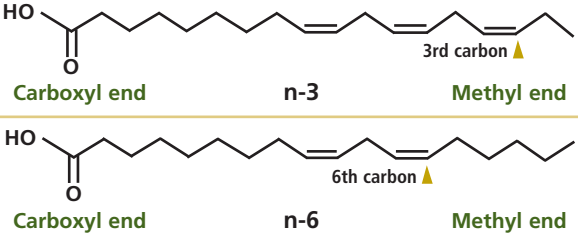
Q. ***What about* trans *fat?***

A. *Trans* fat is unsaturated fat, but the double bond is in a different configuration. There are two fundamental configurations for double bonds, either *trans* or *cis*. Natural double bonds in corn oil are in the *cis* configuration, whereas the hydrogenation of corn oil produces fatty acids with the *trans* configuration. Unsaturated fats with the *trans* configuration behave more like saturated fats.

Q. ***Do* trans *fats occur naturally in our diet or do they come mostly from processed products?***

A. Ruminants generate *trans* fats during the process of food digestion. Ingesting dairy products or meat from ruminants will increase the dietary intake of *trans* fats. Processed foods containing "hydrogenated vegetable oil" or "partially hydrogenated vegetable oil" are another source of dietary *trans* fats.

OMEGA-3 (n-3) AND OMEGA-6 (n-6) FATTY ACIDS



A vertex between two lines indicates a carbon atom, which can make four bonds. Carbon atoms bind each other and oxygen or hydrogen *(not shown)* atoms in this diagram. Double bonds are indicated by parallel lines.

Q. ***What is the difference between n-3, n-6, and n-9 fatty acids?***

A. The number refers to the location of the double bond in the molecule. Fatty acids have a carboxyl end and a methyl end—the alpha and the omega, respectively. In n-3 fatty acids, the double bond is three carbons from the methyl end. An n-6 fatty acid has the double bond six carbons away, and in an n-9 fatty acid, the double bond is nine carbons away from the methyl end.

Q. ***What foods contain n-3, n-6, and n-9 fatty acids?***

A. All of the plants in our diet have varying amounts of the saturated and unsaturated fatty acids of the various classes that we just discussed. The predominant n-3 fatty acid in plants is alpha-linolenic acid. It's found in soybean oil, canola oil, and walnuts. Olive oil contains n-9 fatty acids like oleic acid. Linolenic and alpha-linolenic acids are essential fatty acids that we have to get from our diet in order to make longer chain polyunsaturated fatty acids that are very important in biological functions—the long chain, highly unsaturated n-3 fatty acids are found in salmon, other cold water fish, and in fish oil supplements (anchovy oil). These are known to be cardioprotective and control blood lipids.

Q. ***The brain contains a lot of n-3 fatty acids, which also affect cognition, mood, and learning. Since the fats found in most dietary plants are not efficiently converted to n-3 forms in our bodies, does this suggest that early humans consumed lots of fish?***

A. This is an interesting question. There is some evidence suggesting that humans in the plains of Africa migrated to the coast. Once there, they would have had more access to fish that are enriched in very long chain n-3 fatty acids. Dietary conversion of alpha-linolenic acid to n-3 fatty acids like eicosapentaenoic (EPA) and docosahexaenoic (DHA) fatty acids is slow but effective. Vegetarians who consume plants with n-3 fatty acids don't have unusual health problems. Also, certain tissues maintain their lipids despite significant variation in diet.

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Continued from page 3 — Interview with Dr. Donald Jump

Q. Are sufficient amounts maintained because of the slow turnover and slow loss in the brain and nervous tissue?

A. That is one interpretation, but more study is required to assess mechanisms controlling tissue-specific synthesis and turnover of polyunsaturated fatty acids, for example, in the central nervous system.

Q. Polyunsaturated fats, or PUFAs, are important in energy metabolism, for cell structure, and as regulators of gene expression, especially those that control n-9 fatty acid synthesis. What do n-9 fatty acids do in the body?

A. N-9 fatty acids are monounsaturated fats found in olive oil, for example, and also synthesized in the body from glucose. They are very important for making storage lipids like triglycerides. An early step in making triglycerides is adding oleic acid to glycerol-phosphate. Triglycerides are the main storage form for lipids in adipose tissue in our bodies. Elevated triglycerides in the blood are an independent risk factor for cardiovascular disease.

Q. Why do elevated triglyceride levels contribute to heart disease?

A. Good question! High blood triglyceride levels may be a marker for abnormal or ectopic storage of lipids in tissues. Accumulating triglycerides in muscle, liver, and other tissues induces inflammation and insulin resistance, resulting in type-2 diabetes. Type-2 diabetes is a risk factor for cardiovascular disease.

Q. How do n-3 fatty acids suppress triglycerides?

A. N-3 fatty acids like the ones in fish oil inhibit the synthesis of triglycerides by lowering the cellular level of substrates for triglyceride synthesis. This is achieved by inhibiting fatty acid synthesis and enhancing fatty acid oxidation.

Q. Do n-6 fatty acids promote insulin resistance?

A. The short answer is no. In general, the n-3 and n-6 polyunsaturated fatty acids are beneficial in the prevention of chronic disease. However, too much, or an imbalance of n-6 versus n-3 fatty acids may cause health problems. Our modern diets provide too much n-6 and not enough n-3 fatty acids. The n-6 fatty acids are precursors to inflammatory lipids. And inflammatory lipids play an important protective role in many biological functions that are very important. When n-6 fatty acids are in excess, they tip the balance to a point of enhanced inflammation within the tissue.

Q. Is that mediated by prostaglandins?

A. Yes, mainly eicosanoids. Prostaglandins, leukotrienes, and thromboxanes are all made from these fats and have a wide variety of functions. For example, prostaglandins are synthesized in almost all cells. These eicosanoids control platelet aggregation, calcium flux, hormone regulation, cell growth, metabolism, vasodilation, bronchodilation, and other functions. Isoprostanes are eicosanoids made from the free-radical mediated peroxidation of the n-6 fatty acid, arachidonic acid, and have been used as biomarkers of oxidative stress.

Q. Which fatty acids are anti-inflammatory?

A. N-3 fatty acids—the fish oils.

Q. How do dietary fats affect the retinopathy that can accompany diabetes?

A. Diabetic retinopathy is a problem with the vascular system of the retina; it is similar to atherosclerosis. Diabetic retinopathy involves enhanced storage of lipids and a loss of vascularity within the retina.

Q. Do dietary fats influence tumorigenesis and, if so, how?

A. The impact of dietary fat on tumorigenesis is controversial. There are studies in animals suggesting that n-6 fatty acids promote the progression of colon cancer, while n-3 fatty acids attenuate the development of colon cancer.

Q. Is there any evidence that dietary fats affect tumor growth in people?

A. At this time, the evidence is not compelling. There are nearly 90 clinical trials investigating the impact of dietary fat on cancer. In contrast, excess body fat is a risk factor for numerous cancers.

Q. Is there much evidence that fish oil supplementation is beneficial?

A. There are over 470 clinical trials—ongoing or completed—investigating the impact of n-3 fatty acids on human health. There is certainly a lot of interest in these fats and their impact on health and disease. Many scientists are trying to find out if studies carried out in cell culture and animals are applicable to humans. N-3 fatty acids are clearly beneficial in the control of blood triglyceride levels and in cardioprotection. These clinical trials may reveal beneficial effects of n-3 fatty acids on other processes, like inflammation and cognitive function.

Q. Are the doses used in these animal studies greater than what people would consume in a diet that includes fish?

A. Typically, yes. And in some cases they are biased toward a particular kind of n-3 fatty acid. In our studies on fatty liver disease, we look at the effect of EPA, DHA, and a combination of EPA and DHA. Most fish oil capsules contain a combination of EPA and DHA, and the ratio of these two is highly variable depending on the source.

Q. Do you recommend supplementation with fish oil?

A. Yes. Before taking fish oil, consult with your physician to be sure that there is not some underlying problem, such as increased bleeding time. Aspirin, vitamin E, and a drug called Plavix inhibit platelet aggregation, which is a key event in blood coagulation. If you take these compounds and use fish oil, you may significantly increase the time it takes to stop bleeding. If someone is taking an anticoagulant or planning surgery, they should discontinue use of fish oil supplements.

Q. The ratio of the intake of n-6 to n-3 fatty acids has changed dramatically over the past few generations as our diets have changed. Do we know anything about the optimal ratio?

A. In general, a high n-6 to n-3 ratio is considered pro-inflammatory. More studies are required to define the optimal ratio.

Q. Do you think that consuming fatty fish a couple times a week is equivalent to taking a fish oil supplement or is it better to take a fish oil supplement regularly?

A. I think a supplement is probably better for health because it's more uniform and continuous.

Q. If one chooses to take a fish oil supplement, what criteria are important in making the selection?

A. Look at the composition of the fatty acids on the bottle and make sure that it has a level of DHA and EPA that is consistent with cardiovascular protection—about 500 mg of combined DHA and EPA per day—as an absolute minimum.

Q. How does EPA or DHA influence the risk for strokes and heart attacks?

A. That is complicated and related, in part, to the control of blood lipid levels. Generally, fish oils lower triglycerides but may elevate cholesterol in some individuals. Consumption of fish oil changes the characteristics of the polyunsaturated fatty acids within the arterial wall so that they may be less prone to cause inflammation. Membrane lipids contain both n-6 and n-3 fatty acids. If those are predominately n-6 fatty acids, which are substrates for making eicosanoids, then membrane phospholipid metabolism by phospholipases generates n-6 fatty acids that enter the prostaglandin synthesis pathway and produce inflammatory eicosanoids. Membrane-associated n-3 fatty acids are less likely to be cleaved out of membrane phospholipids. Moreover, n-3 fatty acids are poor substrates for enzymes that generate prostaglandins. So fish oil has the potential to reduce inflammation by lowering the production of inflammatory eicosanoids.

Q. How does alpha-linolenic acid from walnuts, for example, benefit cardiovascular health?

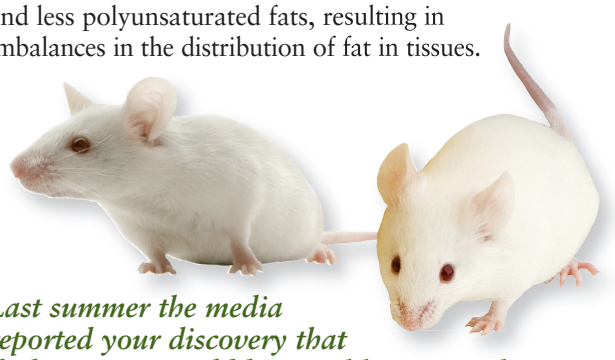
A. The benefit gained from alpha-linolenic acid is that it is a precursor to DHA and EPA. However, alpha-linolenic acid is not as efficacious in cardioprotection as DHA and EPA. Thus, supplementing the diet with DHA and EPA provides better cardioprotection.

Q. Some large-scale epidemiological studies found that walnut consumption, which is rich in alpha-linolenic acid, was associated with decreased risk for atrial and ventricular fibrillation (cardiac arrhythmia).

A. Again, that probably relates to the conversion of alpha-linolenic acid to EPA and DHA, which are anti-arrhythmic.

Q. There is a lot of interest in the obesity epidemic among children and adults in America. How would you gauge the contribution of dietary fats or carbohydrates to this?

A. Simple carbohydrates like sugar and calorically dense, high-fat foods contribute to the problem, as well as a lack of exercise. There's ongoing debate about the relative importance of simple carbohydrates and dietary fats in obesity. For a long time, we thought that carbohydrates like simple sugar (glucose, fructose, and sucrose) were not well converted to fat in humans. We now know that's not true. There is a reasonable amount of scientific evidence that elevated carbohydrate intake will contribute to increased fat deposition. The body has only so much capacity to store carbohydrates, and it does so in the form of glycogen. If you fill up the glycogen pool, the rest becomes fat. Dietary fat, on the other hand, is also very important because of the nature of the fat that we eat, which tends to be more biased toward saturated and monounsaturated fats and less polyunsaturated fats, resulting in imbalances in the distribution of fat in tissues.



Q. Last summer the media reported your discovery that diabetic mice could be cured by manipulating a gene that makes a fat-metabolizing enzyme. How does that work? Is there any way to increase that enzymatic activity in humans?

A. First of all, the term "cure" was media hype. Our work may have promise for an alternative method to treat some diabetic complications. Humans with metabolic syndrome and obese mice that have characteristics of metabolic syndrome have a polyunsaturated fat profile in blood that is different from normal, healthy humans or mice. A large number of enzymes in the liver participate in the production of polyunsaturated fatty acids. We examined the effect of obesity and diabetes on these enzymes and found that one enzyme, called elongase-5, had decreased levels of activity in livers of fat mice. We then restored fatty acid elongase to normal levels in livers of obese, diabetic mice; this treatment corrected the hyperglycemia and fatty liver, but did not correct the obesity. In other words, the mice were obese, but no longer diabetic.

Q. How did you raise the enzyme levels in the livers of the mice?

A. We used an adenovirus-mediated gene therapy approach to elevate expression of the enzyme. We engineered an adenovirus to contain the gene expressing fatty acid elongase-5. Infection of mice with the adenovirus leads to the expression of the enzyme in the liver and no other tissue. The liver starts making more of the enzyme within 24 hours after infection.

Q. Are there compounds that raise the enzyme level in the liver?

A. Our studies in mice have shown that fibrates increase the expression of this enzyme. Fibrates are used to

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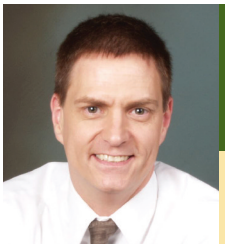


MicroRNAs Play Critical Roles in Development Responses to Dietary Constituents

Robert Tanguay, Ph.D., OSU Distinguished Professor of Molecular Toxicology
Department of Environmental and Molecular Toxicology

Summary: *MicroRNAs—non-coding RNAs that affect gene regulation—have emerged in recent years as important regulators of many cellular and physiological processes. In zebrafish, microRNAs prevent excess vitamin A from causing spine defects during development. Exposure to alcohol during early development in zebrafish interferes with microRNA activity, resulting in abnormalities in the development of the nervous system.*

It is well established that dietary constituents can either positively or adversely affect fetal development, but we don't have a good understanding of the relevant mechanisms. As you may remember from biology class, there are several forms of RNA. During a process called transcription, enzymes produce complementary RNA from DNA. Messenger RNA transfers information from DNA to the cell's ribosome, where proteins are made. Over the past ten years, another kind of RNA—non-coding RNA (ncRNA)—has emerged as a pivotal player in fundamental physiological and cellular processes and has been increasingly implicated in cancer, immune disorders, and cardiovascular, neurodegenerative, and metabolic diseases. MicroRNAs (miRNAs) are a class of ncRNA molecules that are predicted to post-transcriptionally regulate the expression of 30-60% of all human protein-coding genes, and as such, microRNAs play key roles in cellular and developmental processes. MicroRNAs have emerged as targets of developmental, hepatic, neurological, and carcinogenic toxicological agents and have increasingly been identified as regulators of xenobiotic-metabolizing enzymes. The goal of our pilot study funded by LPI was to determine whether misregulation of miRNA expression during development constitutes a specific mechanism by which developmental toxicants exert their effects.

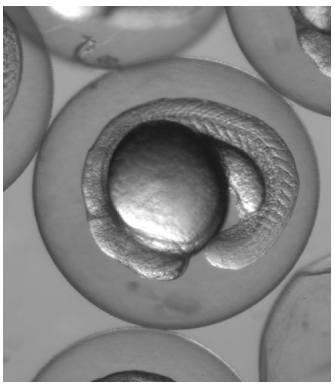
Jill Franzosa

Vitamin A is necessary for normal vertebrate growth and development. Jill Franzosa, a graduate student in my laboratory, investigated the developmental role of miRNAs using an active form of vitamin A, all-*trans* retinoic acid (RA). We know that excesses or deficiencies of RA adversely affect development. In this study, we demonstrated that treating zebrafish in early developmental stages with RA results in a distinct curved body axis similar to the axis and spine defects observed in other vertebrates, including humans. To determine whether specific miRNAs are misexpressed after RA exposure, gene analyses were conducted at several critical developmental stages. Strikingly, the expression of three miRNA family members was significantly repressed by RA treatment during the early stages of somitogenesis (development of skin and skeletal muscle and bones). Based on a prediction that miRNAs target the key RA-inactivating enzyme, cyp26a1, we then confirmed, for the first time, that cyp26a1 is a *bona fide* target of the specific miRNA family. We also showed that repression of the implicated miRNA by genetic alterations resulted in similar embryonic defects. When specific miRNA mimics were injected into embryos, axis defects induced by developmental exposure to RA were prevented. Together, these results indicate that the axis defects elicited by exposure to RA during development result partly from repression of specific miRNAs and subsequent misregulation of cyp26a1. This study sheds light on the role of miRNAs in mediating the teratogenic effects of retinoic acid and provides a more in-depth view of the genetic regulatory mechanisms that control the action of vitamin A during normal development.

Dr. Tamara Tal

In other studies, postdoctoral fellow Tamara Tal used alcohol as a neurotoxicant in zebrafish to examine the role of miRNAs in the development of a functional nervous system. While miRNAs are critical to nervous system development, the neurobehavioral function of miRNAs is unknown. Prenatal alcohol exposure produces a range of conditions in offspring, collectively referred to as fetal alcohol syndrome disorder (FASD). Epidemiological studies suggest that the majority of children with FASD have deficits in neurobehavioral function, even in the absence of clinically discernable physical abnormalities. We assessed larval zebrafish neurobehavior by measuring the distance moved during alternating periods of light and dark. Transient exposure to alcohol during early neural development resulted in increased physical activity. These alterations in behavior persisted in juveniles that had been developmentally exposed to alcohol.

At developmental stages in zebrafish coincident with alcohol-induced neurobehavioral abnormalities, expressions of multiple miRNAs in the central nervous system were significantly altered. Subsequent computational analyses revealed that alcohol disrupts expression of miRNAs that direct neurogenesis.



Zebrafish embryo

We then used genetically altered zebrafish to examine the functional role of alcohol-sensitive miRNAs. Decreasing the activity of miRNAs in the central nervous system produced behavioral hyperactivity in larval and juvenile fish similar to that observed with alcohol. These data indicate that ethanol exposure causes errors in the expression of miRNAs that may collectively choreograph nervous system development and function and support the concept that miRNA signaling pathways are targets of developmental neurotoxicants like alcohol.

Zebrafish

Our research resulted in numerous awards and recognitions. Jill Franzosa's research was honored with the Elsevier best platform presentation award in toxicogenomics at the 2010 Society of Environmental Toxicology and Chemistry annual meeting, first place poster award at the 2010 Pacific Northwest Association of Toxicologists Conference, poster award winner at the 2010 Aquatic Animal Model for Human Disease Annual Meeting, first place in the Molecular Biology graduate student award at the 2010 Society of Toxicology annual meeting, and a first place platform presentation award at the 2009 Pacific Northwest Association of Toxicologist Conference.

Dr. Tamara Tal's research in alcohol-sensitive microRNAs was recognized at the 2010 Pacific Northwest Association of Toxicologists Regional Conference, won a first-place poster award at the 2010 International Neurotoxicology Conference, won a first-place postdoctoral research award from the Molecular Biology specialty session, and won a second-place poster award from the Neurotoxicology specialty section at the 2010 Society of Toxicology annual meeting. Both Dr. Tal and Jill Franzosa recently presented their research in the symposium session titled "Uncovering the role of microRNAs in toxicology" at the 2011 Society of Toxicology annual meeting.

Based upon the success of this project, Jill was also awarded a prestigious predoctoral National Institutes of Health Ruth L. Kirschstein NRSA Fellowship to investigate the role of microRNAs in aging. Together, these findings will generate new fundamental knowledge about the role of microRNAs in mediating basic biological responses to chemical or dietary toxicological insult. LPI

Continued from page 5 — Interview with Dr. Donald Jump

manage dyslipidemia in humans; fibrates lower blood levels of cholesterol and triglycerides.

Q. Do you have any dietary recommendations for the prevention or treatment of diabetes with respect to fatty acids?

A. The American Diabetes Association (www.diabetes.org) has an excellent Web site for this information. If your body mass index (BMI) exceeds 30, you may develop diabetes and metabolic syndrome as you grow older. I think dietary supplements of n-3 fatty acids are prudent for just about everybody as long as they are not on an anticoagulant therapy.

Q. What are your plans for future research?

A. We have two major projects under way in the lab. In one, we are investigating the use of n-3 fatty acids as a way to prevent the development of fatty liver associated with diet-induced obesity. The second line of investigation is a continuation of the "gene therapy approach" described above. We are defining the mechanism used by polyunsaturated fatty acids to control diabetic complications. LPI

Bill Town's Story of Inspiration

As a dedicated high school science teacher, Bill Town was creative in his efforts to inspire his students. He decided the class needed a scientific hero who worked in a lab. Bill's choice was Linus Pauling, a two-time Nobel Prize-winner and charismatic chemist. So, for Dr. Pauling's birthday on February 28th, Bill bought a birthday card, had all his students sign it, and mailed it to Dr. Pauling. It was a wonderful surprise for everyone when the class received a thank-you note from Dr. Pauling himself! The following year, when Bill pulled out a birthday card, the students organized a birthday party for Dr. Pauling. It became a February tradition that lasted for most of Bill's teaching career.

When it was time to plan his will, Bill knew that he wanted his estate to support science education and science teaching. Since Linus Pauling was an inspiration for him and his students, Bill felt remembering the Linus Pauling Institute in his will was a fitting way of thanking Dr. Pauling for showing students the fun of chemistry and the love of science.

All of us at the Linus Pauling Institute deeply appreciate Bill's act of inspiration in remembering LPI in his estate. As part of the LPI Legacy Endowment Fund, Bill's gift will continue the legacy of a truly great scientist and humanitarian, while generating new discoveries that create a better future for everyone.

Have you remembered LPI in your estate plans? We'd be honored to recognize you as a member of the Linus Pauling Institute Legacy Circle. Contact Michele Erickson at 541-737-3744 or Michele.Erickson@oregonstate.edu.

6TH INTERNATIONAL CONFERENCE ON

DIET AND OPTIMUM HEALTH

Organized and sponsored by the Linus Pauling Institute • Co-sponsored by the Oxygen Club of California

SEPTEMBER 13-16, 2011 • CORVALLIS, OREGON • USA

Tuesday, September 13, 2011

2:00pm Registration begins

3:00 Welcome and Opening Remarks
Balz Frei, Linus Pauling Institute, Oregon State University, Corvallis, OR

SESSION 1 - 3:15 TO 5:15 PM

VITAMIN E: BIOLOGICAL FUNCTIONS AND CONTROVERSIES

Chair: Maret Traber, Linus Pauling Institute, Oregon State University, Corvallis, OR

3:15 The α-tocopherol transfer protein: Biochemical mechanisms and health implications
Danny Manor
Case Western Reserve University, Cleveland, OH

3:45 Anti-inflammatory effects of vitamin E forms and their metabolites
Qing Jiang
Purdue University, West Lafayette, IN

4:15 The effect of vitamin E supplementation on cardiovascular risk in diabetic individuals with different haptoglobin phenotypes
Andrew P. Levy
Technion Faculty of Medicine, Technion-Israel Institute of Technology, Haifa, Israel

4:45 Does vitamin E decrease chronic disease risk by protecting against free radicals?
Etsuo Niki
National Institute of Advanced Industrial Science and Technology, Osaka, Japan

6:30 Welcome Reception and Tour of the Linus Pauling Science Center

Wednesday, September 14, 2011

6:00am Organized Walk/Run

7:30 Breakfast provided

SESSION 2 – 8:30 AM to Noon

MICRONUTRIENTS, DIET, AND IMMUNE FUNCTION

Chairs: Adrian Gombart and Emily Ho, Linus Pauling Institute, Oregon State University, Corvallis, OR

8:30 Nicotinamide (vitamin B_3) and innate immune response to microbial infection
George Liu
Cedars-Sinai Medical Center and UCLA School of Medicine, Los Angeles, CA

9:00 Vitamin D and infectious diseases
Carlos A. Camargo, Jr.
Harvard Medical School, Boston, MA

9:30 The impact of nutrition on the immune response against influenza
Elizabeth M. Gardner
Michigan State University, East Lansing, MI

10:00 Coffee/Tea Break

10:30 Zinc, inflammation, and susceptibility to sepsis
Daren Knoell
The Ohio State University, Columbus, OH

11:00 Inflammation, neutrophil function, and trace element status in the morbidly obese
Pam J. Fraker
Michigan State University, East Lansing, MI

11:30 Polyunsaturated fatty acids and their impact on the immune system
Robert S. Chapkin
Texas A&M University, College Station, TX

12:00 Lunch provided




SESSION 3 – 1:30 to 3:00 PM

DIET AND CARDIOVASCULAR DISEASE

Chair: Balz Frei, Linus Pauling Institute, Oregon State University, Corvallis, OR

1:30 A diet based on high-heat-treated foods promotes risk factors for diabetes mellitus and cardiovascular diseases
Veronika Somoza
University of Vienna, Vienna, Austria

2:00 Dietary patterns and risk of mortality from cardiovascular disease
Teresa Fung
Simmons College and Harvard School of Public Health, Boston, MA

2:30 New evidence on the effects of a Mediterranean-style diet on cardiovascular disease
Roman Estruch
Hospital Clinic, University of Barcelona, Barcelona, Spain

3:00 Coffee/Tea Break

SESSION 4 – 3:30 to 5:00 PM

GUT MICROBES AND PROBIOTICS – ROLE IN HEALTH AND DISEASE

Chair: Sharon Krueger, Linus Pauling Institute, Oregon State University, Corvallis, OR

3:30 The human microbiome and cancer
Cindy Davis
Division of Cancer Prevention, National Cancer Institute, Bethesda, MD

4:00 Evolutionary glycomics: Breast milk oligosaccharides and *bifidobacteria infantis*
J. Bruce German
University of California, Davis, CA

4:30 Pre and probiotics: Food fad or bacterial therapy?
Robert G. Martindale
Oregon Health & Science University, Portland, OR

5:00 - 7:00pm
Poster Session, hors d'oeuvres and drinks provided

Thursday, September 15, 2011

6:00am Organized Walk/Run

7:30 Breakfast provided

SESSION 5 – 8:30 AM to Noon

CALORIC RESTRICTION MIMETICS, DIET, AND HEALTHY AGING

Chairs: Tory Hagen, Linus Pauling Institute, Oregon State University, Corvallis, OR and Viviana Perez, University of Texas Health Science Center at San Antonio, San Antonio, TX

8:30 Protective effect of resveratrol in mice and monkeys
Julie Mattison
Aging, Metabolism, and Nutrition Unit, National Institute on Aging, Baltimore, MD

9:00 How to help your mouse live longer: Diets, drugs, MIF-KO, and sibs
Richard Miller
University of Michigan, East Lansing, MI

9:30 Lipoic acid and healthspan: Mechanisms of action
Tory Hagen
Linus Pauling Institute, Oregon State University, Corvallis, OR

10:00 Coffee/Tea Break

10:30 Protein and metabolic homeostasis in aging and longevity
Gordon J. Lithgow
The Buck Institute for Research on Aging, Novato, CA

11:00 Mitochondrial decay in human aging: A translational approach
Chrisitaan Leeuwenburgh
University of Florida, Gainesville, FL

11:30 Rapamycin and dietary restriction: Do they share a common mechanism in lifespan extension?
Viviana Perez
University of Texas Health Science Center at San Antonio, San Antonio, TX

12:00 Lunch provided

SESSION 6 – 1:20 to 4:00 PM

ORAL ABSTRACTS AND YOUNG INVESTIGATOR AWARD FINALISTS

Eight 20-minute talks; TBA

4:00 Coffee/Tea Break

SESSION 7 – 4:15 to 5:30 PM

LPI PRIZE CEREMONY AND PLENARY LECTURE BY AWARDEE

Chair: Balz Frei, Linus Pauling Institute, Oregon State University, Corvallis, OR

6:30 Reception

7:00 Banquet Dinner

Friday, September 16, 2011

Travel Day

For more information about the Conference, please visit the LPI Web site at http://lpi.oregonstate.edu/conf2011 or phone the Institute at 541-737-5075.

The New Dietary Reference Intakes for Vitamin D

Adrian Gombart, Ph.D., Associate Professor of Biochemistry and Biophysics
LPI Principal Investigator

The Institute of Medicine (IOM) released new dietary reference intakes (DRIs) for calcium and vitamin D on November 30, 2010. The IOM concluded that vitamin D plays a key role in bone health and that current evidence does not support other health benefits from vitamin D supplementation, although the IOM called for additional research targeted at other health outcomes to continue. The changes in the recommended dietary allowance (RDA) for vitamin D were based solely on bone health. The IOM raised the RDA in children (1-18 years) and adults (19-70 years) from 200 IU to 600 IU per day and raised the tolerable upper intake level (UL) for adults from 2,000 IU to 4,000 IU per day. For the elderly (>70 years), the RDA was increased to 800 IU per day. The majority of vitamin D experts were disappointed by these conservative increases, but they should be considered steps in the right direction.

The IOM also made another very important change. After reviewing the published literature, they concluded that the serum level of vitamin D sufficient for bone health is above 20 ng/ml rather than 30-32 ng/ml, a value that has been used extensively by physicians. During the press conference, they said that it was warranted by the available scientific evidence even though it had not been one of their tasks. By lowering the sufficient level, they, in effect, reduced the number of people that would be considered to have inadequate serum levels of vitamin D. This change will likely cause significant confusion for both physicians and their patients, but it should be noted that it is only relevant to bone health and may not be optimal for other health benefits that have been attributed to vitamin D.

While the new RDA may bring many people into the new sufficient range, a cut-off of 20 ng/ml is controversial in the vitamin D research community because it does not consider other areas of health that the IOM has concluded are not supported by the currently published data.

The IOM is very conservative and based their decisions on a lack of randomized controlled trials (RCTs) that demonstrate a clear benefit from taking vitamin D supplements beyond bone health, but there is overwhelming evidence that supports biological plausibility for a role of vitamin D in numerous other health outcomes. For example, most non-bone cells have receptors for vitamin D, and we know that the function of immune cells is affected by vitamin D. The IOM narrowly focused on RCTs as the "gold standard"—an almost impossible hurdle to clear when applied to micronutrients. For example, subjects in the placebo group in an RCT will still have some of the micronutrient under evaluation in their bodies—unlike an RCT testing drugs; otherwise, they would get deficiency diseases. While anecdotal reports or single studies seem to be good enough for the IOM to determine the UL, multiple RCTs demonstrating similar outcomes are required for the RDA. Clearly, this is a double standard. DRIs need to take into account the totality of evidence, not just RCTs.

LPI continues to recommend a daily intake of 2,000 IU of vitamin D. This is well below the UL of 4,000 IU set by the IOM and should ensure that individuals, particularly in areas of the world where sun exposure is limited for extended periods of the year, get enough vitamin D. Also, to adjust for individual differences and ensure adequate body vitamin D status, LPI recommends aiming for a serum 25-hydroxyvitamin D level of at least 80 nmol/l (32 ng/ml). You can find this information and the recommendations for infants and children in the LPI Micronutrient Information Center section on vitamin D (http://lpi.oregonstate.edu/infocenter/vitamins/vitaminD).

LPI

Powered by Oranges!

All of us at the Linus Pauling Institute believe that an active lifestyle and regular exercise are critical for achieving a healthy body weight and optimum health. But, talking the talk isn't enough—we also need to walk the walk! That's why I'm taking LPI's message about a healthy lifestyle to the streets. I am training hard to participate in the August 5-6 Cascade Lakes Relay race together with several LPI graduate students, my family, and our team captain, Scott Leonard, a senior research assistant in the Institute. Our 12-member team, aptly named "Linus Pauling Institute—Powered by Oranges," will have to cover 216 miles in the beautiful Oregon Cascade Mountains, running day and night. I'm sure it will be a very exciting—and exhausting—event! Follow the team, read tips on staying healthy, and join us with your support by going to http://lpi.oregonstate.edu and clicking on "Powered by Oranges."

Balz Frei, Director, Linus Pauling Institute

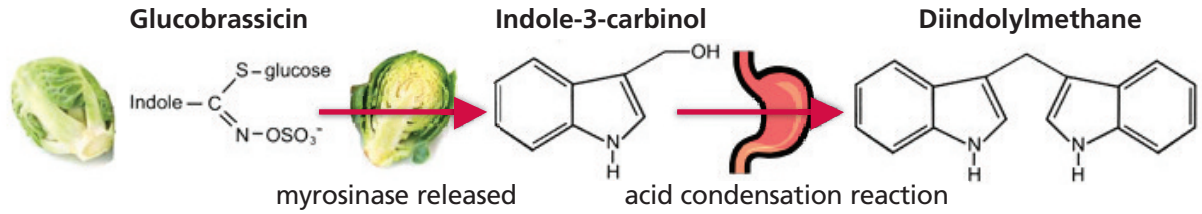
Protecting the Fetus from Carcinogens

Lyndsey Shorey
LPI Graduate Fellow

Summary: *Feeding indole-3-carbinol (I3C), a phytochemical found in cruciferous vegetables, to pregnant mice can protect against cancer in the offspring from* in utero *exposure to chemical carcinogens. In the body, I3C reacts to form another compound, diindolylmethane (DIM). Human leukemia cells in culture treated with DIM exhibited depressed growth and increased apoptosis (programmed cell death), which is beneficial for cancer protection.*

In 1997 a panel of scientists from the World Cancer Research Fund and the American Institute for Cancer Research estimated that 30-40% of all cancers could be prevented by modifying lifestyle factors like diet and exercise. Ten years later, the panel reported only a "probable" protective effect of fruits and vegetables on cancer risk. While vegetables are generally known to be healthful, as they are high in fiber, vitamins, and minerals, and low in fat and cholesterol, it has been difficult to demonstrate a direct association between overall vegetable consumption and cancer prevention in humans due to the heterogeneity of exposures, genetics, and, ultimately, the diseases collectively referred to as cancer. However, certain types of vegetables produce phytochemicals that are not essential nutrients but may have beneficial health properties.

Broccoli, Brussels sprouts, mustard, kale, cabbage, horseradish, and arugula are in the *Cruciferae* plant family and are a rich source of a class of phytochemicals known as glucosinolates. Glucosinolates are sulfur-containing compounds that contribute to the sometimes bitter or pungent aroma and flavor of these vegetables. In order for glucosinolates to become biologically active, they must be metabolized by myrosinase—a plant enzyme released from the plant tissue when it's chopped or chewed—into two classes of chemicals known as indoles and isothiocyanates, which are widely accepted as responsible for the beneficial health properties of crucifers. Over 100 different glucosinolates have been identified, and when acted upon by myrosinase, they yield unique products. Some glucosinolates are found in all cruciferous vegetables, and others may be especially enriched in particular vegetables. For example, indole-3-carbinol (I3C) is derived from the glucosinolate glucobrassicin, abundant in broccoli, Brussels sprouts, kale, and cabbage. Interest in isothiocyanates as anticancer agents has been growing since the 1960s, and sulforaphane (SFN), derived from another glucosinolate (glucoraphanin), abundant in broccoli and broccoli sprouts, has become the most studied isothiocyanate.



Conversion of glucobrassicin in food to diindolylmethane in the stomach.

Previously, our lab utilized a transplacental mouse model to look specifically at the ability of maternal diet to alter cancer risk in offspring exposed to chemicals *in utero* and/or through lactation. Women are unavoidably exposed to environmental pollutants during pregnancy, and the fetus is especially sensitive to these chemicals. One class of chemicals known as polycyclic aromatic hydrocarbons (PAHs) are produced from the combustion of fossil fuels and released into the air we breathe and the soil in which our food grows. If pregnant mice are exposed only once to the PAH dibenzo[*def,p*]chrysene (DBC), their offspring succumb to T-cell lymphoblastic lymphomas during early adulthood and lung tumors later in life. We have used this model to demonstrate significant protection against DBC-induced lung tumors and T-cell lymphomas in offspring when the maternal diet is supplemented with 2,000 parts per million (ppm) I3C.

Multiple mechanisms exist for the anti-carcinogenic actions of indoles and isothiocyanates. These mechanisms are broadly classified as either blocking or suppressive, based on the respective phases, known as initiation and progression, of cancer development during which these mechanisms are effective. Before the anticancer effects of these phytochemicals were known, their ability to modulate metabolism and detoxication of foreign substances in the body had been identified. Indoles and isothiocyanates are considered blocking agents, as they are capable of altering the rate and extent to which a person, tissue, or cell can eliminate certain carcinogens. Furthermore, these compounds can be effective in reducing the progression of cancer cells by targeting what are known as cancer survival pathways. Normal cells have intrinsic sensors that are encoded by our DNA and prevent them from dividing when an error in the replication machinery occurs. When a cell is exposed to certain carcinogens, resultant mutations in its DNA may change the code so that these sensors are damaged or deleted, resulting in uncontrolled regulation of cell growth and activation of the survival pathways, leading to cancer.

My work has primarily focused on the suppressive mechanisms of I3C on human cancer cells from a patient with T-cell leukemia. I3C is highly unstable; when it enters an acidic environment, such as the stomach, two or more I3C molecules readily link together to form what is known as an acid condensation product. The primary product of this reaction is the dimer diindolylmethane (DIM). In rodents and humans consuming I3C, very little I3C is measurable in plasma or urine. Therefore, DIM, which is detectable in plasma, is thought to contribute greatly to some of the effects attributed to I3C.

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We treated leukemia cells with I3C or DIM and found that many of the same molecular targets were altered by either of the treatments, but DIM was 8-9 times more potent than I3C. Our studies are the first to use DIM in leukemia cells, and our results are consistent with reports in other cancer cells that DIM and/or I3C block the division and proliferation of cancer cells and induce programmed cell death by modulating specific cellular proteins that regulate these processes. Dietary supplementation with DIM also reduced the growth of these human leukemia cells transplanted into mice. Therefore, our data support the current theory that DIM may mediate the physiological effects of I3C.

Food Source	Serving size (vol)	Serving size (g)	Glucosinolates (mg/serving)	To achieve 2,000 ppm I3C	
				Grams	Servings
Brussels sprouts	1/2 cup	44	104	20.5	0.5
Garden cress	1/2 cup	25	98	12.4	0.5
Mustard greens	1/2 cup	28	79	17.2	0.6
Horseradish	1 tbsp	15	24	30.3	2.0
Kale	1 cup	67	67	48.6	0.7
Watercress	1 cup	34	32	51.6	1.5
Turnip	1/2 cup	65	60	52.6	0.8
Cabbage (savoy)	1/2 cup	45	35	62.4	1.4
Cabbage (red)	1/2 cup	45	29	75.3	1.7
Broccoli	1/2 cup	44	27	79.1	1.8
Cauliflower	1/2 cup	50	22	110.3	2.2
Bok choi (pak choi)	1/2 cup	35	19	89.4	2.6
Kohlrabi	1/2 cup	67	31	104.9	1.6

Cruciferous vegetables have great potential to reduce the risk of certain cancers. Epidemiological studies have suggested an inverse relationship between cruciferous vegetable consumption and gastric, endometrial, and colorectal cancer and cancers of the lung, prostate, breast, and bladder. One explanation as to why these studies have been more suggestive than definitive may be genetic differences in how individuals metabolize these compounds —some of us need to consume more cruciferous vegetables in order to receive the same level of protection. Cooking and storage processes, such as chopping, pickling, freezing, stir-frying, or microwave cooking, also variably influence the amount of glucosinolates in the edible portion of these vegetables. Therefore, it is often difficult to demonstrate the potential health benefits of a particular food when looking at highly heterogeneous human data compared to controlled laboratory studies.

The concept that the fetal and early postnatal environment may program the developing individual to have altered susceptibility to disease in adulthood is an exciting and growing field of research termed "fetal origins." Currently, we are using the trans-placental model to study whether the whole foods from which I3C, DIM, and SFN are derived can also reduce the cancer risk of offspring exposed to carcinogens *in utero*. We are supplementing the diet of pregnant mice with broccoli sprouts, Brussels sprouts, I3C, SFN, or the combination of I3C and SFN, and we will monitor the offspring for up to 10 months of age (middle age in a mouse). This study will assess the molecular changes that occur during the development of the lymphomas and lung tumors and the amelioration of these changes by either the active phytochemicals or the whole foods. We will specifically explore epigenetic mechanisms—processes that result in heritable changes in regulation of genes not involving modification of the DNA sequence—as they relate to the fetal origins of cancer. LPI

Micronutrients and Cognitive Function

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

Summary: *Deficiencies of vitamins (B vitamins, vitamins C, D, and E) or minerals (calcium, iodine, iron, magnesium, selenium, and zinc) impair cognitive function. More research, including clinical trials, is necessary to determine if micronutrient supplementation improves cognitive abilities in healthy people, attenuates age-related cognitive decline, or improves mental function in patients with Alzheimer's disease.*

Good nutritional status is imperative for normal cognition. Several micronutrients (vitamins and nutritionally essential minerals) have important biochemical roles in the brain and are needed for proper cognitive function. This article summarizes the basic needs of the brain for cognition, the cognitive effects of select micronutrient deficiencies, and the present knowledge regarding the cognitive effects of micronutrient supplementation.

Basic Needs for Cognitive Performance

Micronutrients are directly or indirectly involved in a number of cognitive processes that are dependent on energy metabolism in brain cells, blood supply to the brain, synthesis of neurotransmitters (chemicals that are released from a nerve cell and result in the transmission of an impulse to other cells), neurotransmitter binding to its receptors, nerve impulse propagation, and homocysteine metabolism.

The brain is a highly metabolically active tissue that needs a constant supply of glucose (sugar) to meet energy needs. Glucose metabolism in the brain requires several vitamins, including thiamin, riboflavin, niacin, and pantothenic acid, that function as enzyme cofactors in the oxidation of glucose to carbon dioxide and water. Certain minerals, such as magnesium, iron, and manganese, are also needed to complete the metabolism of glucose.

Proper blood supply to the brain is necessary to deliver oxygen, glucose, and macronutrients, as well as micronutrients, for normal cognitive function. Good nutrition can help maintain optimal blood supply to the brain and lower the risk of stroke—a pathological condition that results from impaired blood supply to the brain.

Amino acids and many of the B vitamins are needed to synthesize various neurotransmitters in the brain. In addition, vitamin C is required for the synthesis of the neurotransmitter norepinephrine, and the mineral zinc is needed for functioning of the neurotransmitters norepinephrine, aspartate, and gamma-aminobutyric acid (GABA). Vitamins could possibly affect neurotransmitter binding to receptors on neurons, thereby altering neurotransmission.

Micronutrients may indirectly influence nerve impulse propagation by affecting the integrity of the myelin sheath of nerves. The myelin sheath, composed of lipids and proteins, surrounds and insulates nerve fibers and functions as a conduit in an electrical system, allowing for rapid and efficient neurotransmission. Two B vitamins, folate and vitamin B_{12}, are needed to maintain the integrity of the myelin sheath; therefore, these vitamins are important in nerve impulse propagation. Additionally, the B vitamin thiamin is required for maintenance of membrane potential and proper conductance of nerves. Furthermore, iron is required for the development of oligodendrocytes—myelin-producing cells of the brain.

Vitamin B_6, folate, and vitamin B_{12}, as well as the nutrient choline, are involved in the metabolism and reduction of homocysteine, a sulfur-containing compound produced in the metabolism of the amino acid methionine. Some studies have linked elevated levels of homocysteine with cognitive dysfunction found in dementia and Alzheimer's disease.

Consequences of Select Micronutrient Deficiencies

Thiamin

Phosphorylated forms of thiamin (vitamin B_1) are required for reactions involved in the metabolism of carbohydrates, amino acids, and lipids, and one form of the vitamin has been implicated in membrane functions of neurons and in the generation of nerve impulses. Thus, inadequate intake of thiamin can negatively affect cognition. Severe thiamin deficiency causes beriberi; the dry and wet types of beriberi involve peripheral neuropathy, whereas cerebral beriberi can lead to cell death of neurons and the clinical conditions of Wernicke's encephalopathy and Korsakoff's psychosis, especially in those who abuse alcohol.

Niacin

Niacin (vitamin B_3) is needed for a number of redox reactions (reduction—"electron gain", oxidation—"electron loss") and other reactions in the body. Severe niacin deficiency, known as pellagra, has been historically associated with poverty and consumption of a diet predominantly based on corn, which is low in bioavailable niacin. Today, the condition is uncommon but can occur in cases of chronic alcoholism and in individuals with malabsorption syndromes. Neurologic symptoms of pellagra include headache, fatigue, apathy, depression, ataxia, poor concentration, delusions, and hallucinations, which can lead to confusion, memory loss, psychosis, dementia, and death.

Pantothenic Acid

Pantothenic acid (vitamin B_5) is needed for the oxidative metabolism of glucose and fats and also for synthesis of fats, cholesterol, steroid hormones, the hormone melatonin, and the neurotransmitter acetylcholine. Pantothenic acid deficiency is very rare and has been observed only in cases of severe malnutrition. However, deficiency of this vitamin has been induced experimentally in humans by co-administering a pantothenic acid antagonist and a pantothenic acid-deficient diet. Participants in this experiment complained of headache, fatigue, insomnia, intestinal disturbances, and numbness and tingling of their hands and feet.

Experimentally induced pantothenic acid deficiency in laboratory animals has been shown to cause loss of the myelin sheath and peripheral nerve damage.

Vitamin B_6

Pyridoxal, pyridoxine, and pyridoxamine are collectively called vitamin B_6, which is required for the biosynthesis of several neurotransmitters, including GABA, dopamine, norepinephrine, and serotonin. Severe deficiency of vitamin B_6 is uncommon, but alcoholics are thought to be most at risk due to inadequate dietary intakes and impaired metabolism of the vitamin. Neurologic symptoms of severe vitamin B_6 deficiency include irritability, depression, confusion, and seizures.

Biotin

Biotin (vitamin B_7) is required for carboxylase enzymes that are important in the metabolism of fatty acids and amino acids. While overt biotin deficiency is quite rare, deficiency of the vitamin has been observed in patients on prolonged intravenous feeding (parenteral nutrition) without biotin supplementation, in individuals consuming high amounts of raw egg white containing a protein that binds biotin and prevents its absorption, and in those with inherited disorders of biotin metabolism. Neurologic symptoms of biotin deficiency include depression, lethargy, hallucinations, and numbness and tingling of the extremities.

Folate

Folate (vitamin B_9) is required for the metabolism of nucleic acids (DNA and RNA) and amino acids. The vitamin is also needed for the synthesis of several neurotransmitters, including norepinephrine, dopamine, and serotonin, and, along with vitamin B_{12}, folate is required in the breakdown of norepinephrine and dopamine. Dietary folate deficiency in the absence of vitamin B_{12} deficiency does not cause neurologic symptoms. However, individuals with genetic disorders of folate metabolism have experienced seizures and progressive neurologic deterioration.

Vitamin B_{12}

In humans, vitamin B_{12} is a required cofactor for two enzymes: methionine synthase, which is needed for the production of methionine from homocysteine, and L-methylmalonyl-CoA mutase, which is involved in crucial metabolic pathways. Vitamin B_{12} deficiency affects 10-15% of adults over the age of 60 years. It damages the myelin sheath of nerves and is frequently associated with neurological problems. Neurologic symptoms are the only clinical indicator of vitamin B_{12} deficiency in about 25% of cases.

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Continued from page 13 — Micronutrients and Cognitive Function

Such symptoms include numbness and tingling of the extremities, difficulty walking, problems with concentration, memory loss, disorientation, and dementia. Severe B_{12} deficiency is associated with pernicious anemia and, if untreated, can lead to "megaloblastic madness," characterized by delusions and hallucinations. Atrophic gastritis, an age-related condition resulting in diminished digestive factors, is often associated with decreased absorption of vitamin B_{12} from food.

Vitamin C

Vitamin C accumulates in the central nervous system, with neurons of the brain having especially high levels. Vitamin C is an important antioxidant that is required for the synthesis of the neurotransmitter norepinephrine, the reduction of metal (e.g., iron, copper) ions in the brain, and for the regeneration of vitamin E. Vitamin C deficiency causes oxidative damage to lipids and proteins in the brain. Severe vitamin C deficiency, called scurvy, is potentially fatal. In scurvy, vitamin C is retained by the brain for neuronal function, and eventual death from the disease is more likely due to lack of vitamin C for the synthesis of collagen—an important structural component of blood vessels, tendons, ligaments, and bone. Vitamin C is also required for the conversion of dietary lysine to carnitine, a compound essential for energy production in the cells' mitochondria. Hence, scurvy is characterized by fatigue and depression in addition to physical manifestations.

Vitamin D

Vitamin D is important for normal brain development and function, and vitamin D deficiency may impair cognitive abilities. Some studies in older adults have either linked lower 25-hydroxyvitamin D levels—the clinical indicator in the blood of vitamin D status—with measures of poor cognitive performance or higher 25-hydroxyvitamin D levels with measures of better cognitive performance. However, the association between 25-hydroxyvitamin D concentrations and cognitive performance is not yet clear.

Vitamin E

In the brain and other tissues, the alpha-tocopherol form of vitamin E is a key fat-soluble antioxidant that prevents lipid peroxidation and helps to maintain the integrity of cell membranes. Thus, vitamin E deficiency causes lipid peroxidation in brain tissues. Severe vitamin E deficiency results mainly in neurological symptoms, including impaired balance and coordination (ataxia), injury to the sensory nerves (peripheral neuropathy), muscle weakness (myopathy), and damage to the retina of the eye (pigmented retinopathy).

Calcium

Calcium ions are important intracellular signals that regulate a number of physiological processes, including neuronal gene expression and neuronal secretion of neurotransmitters. Normal blood levels of calcium are maintained even when dietary intake of calcium is inadequate because the skeleton provides a large reserve of the mineral. Thus, dietary calcium inadequacy primarily affects bone health.

Iodine

Iodine is required for the synthesis of thyroid hormones, which are important for myelination of the central nervous system. Iodine is critical for normal development of the brain; therefore, deficiency of this mineral during critical periods of fetal development or childhood can have deleterious effects on cognition. The most extreme cognitive effect of developmental iodine deficiency is irreversible mental retardation; milder cognitive effects include various neurodevelopmental deficits, including intellectual impairment.

Iron

Iron is an essential component of hundreds of proteins and enzymes involved in various aspects of cellular metabolism. The mineral is needed for proper development of oligodendrocytes (the brain cells that produce myelin) and for several enzymes that synthesize neurotransmitters. Accordingly, iron deficiency during various stages of brain development has negative consequences. Maternal iron deficiency during pregnancy has serious consequences for the woman and the fetus, including permanent learning and memory deficits in the offspring. Iron deficiency during childhood may be associated with impaired cognitive development.

Magnesium

Magnesium is required for more than 300 metabolic reactions, many of which are important for normal brain function. Overt magnesium deficiency has been induced experimentally and results in neurologic and muscular symptoms that include tremor, muscle spasms, and tetany (involuntary muscle contractions). According to recent surveys, many Americans do not have an adequate intake of magnesium.

Selenium

Selenium is required for glutathione peroxidases (GPx), important antioxidant enzymes in the brain and other tissues. Selenium deficiency has been associated with decreased GPx activity in the brains of laboratory animals and may be linked to a reduced antioxidant capacity in the brain.

Zinc

Zinc is present at high levels in the brain, where it has catalytic, structural, and regulatory roles in cellular metabolism. In the brain, most of the zinc ion is tightly bound to proteins, but free zinc is present in synaptic vesicles and has a role in neurotransmission mediated by glutamate and GABA. Experimentally induced zinc deficiency in humans has been shown to impair measures of mental and neurologic function. However, deficiency of the mineral during critical periods of cognitive development can be more devastating, causing congenital malformations or deficits in attention, learning, memory, and neuropsychological behavior.

Developments

Michele Erickson
LPI Director of Development

The charitable gift annuity:
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The annuity rate—locked in for life—depends on your age at the time of your gift. It's also higher than current rates for CDs and money market accounts—making a charitable gift annuity both a good way to support LPI and strengthen your retirement plans.

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Sample rates based on $25,000 CGA:

Age of annuitant	65	70	75	80	85	90
Annuity rate*	5.5%	5.8%	6.4%	7.2%	8.1%	9.5%
Annual payment	$1,375	$1,450	$1,600	$1,800	$2,025	$2,375
Charitable deduction**	$7,004	$9,014	$10,630	$12,244	$14,023	$15,420

*These rates represent the rate schedule put into effect 7/1/2010 by the American Council on Gift Annuities (ACGA) and are subject to change.
**Assumes an IRS discount rate of 3.0%.

Call or e-mail to learn more:

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Rates are subject to change. This information should not be considered or relied upon as legal advice. Before entering into a planned giving arrangement with any charitable organization, donors should seek their own professional legal and tax advice. The OSU Foundation does not engage in the marketing of services pertaining to individualized advice about estate distribution documents. Attention California residents: Payments made under a charitable gift annuity are subject to regulation by the California Insurance Department but are not insured or otherwise guaranteed by the California Life Insurance Guaranty Association. LPI

Choline

Although not considered a vitamin, choline is an essential nutrient needed for myelination of nerves, synthesis of the neurotransmitter acetylcholine, and synthesis of various structural and cell-signaling molecules, including phospholipids (phosphatidylcholine and sphingomyelin) that are important components of cell membranes. Choline deficiency during the perinatal period in laboratory animals results in persistent memory and other cognitive deficits in offspring.

Effects of Micronutrient Supplementation

Compared to the consequences of micronutrient deficiencies, considerably less is known about the cognitive effects of micronutrient supplementation. Overall, there is currently little evidence that micronutrient supplementation provides cognitive benefits related to attention, memory, or executive functions (higher-order cognitive processes that include reasoning, planning, strategic thinking, problem solving, and multitasking). Some studies, however, have reported that multivitamin/mineral supplementation may benefit subjective measures of mood and psychological well-being. Additionally, evidence that supplementation with B vitamins or antioxidant vitamins prevents age-associated cognitive decline is largely lacking, although randomized controlled trials (RCTs) of longer duration are needed.

Linus Pauling was interested in the relationship of critical micronutrients and enzymes with mental function, including mental illness. He discussed the exquisite chemical sensitivity of the brain to vitamin deficiencies and addressed the theoretical basis for micronutrient supplementation to help treat mental illness in his seminal paper, *Orthomolecular Psychiatry,* published in 1968 in *Science*.

To date, many of the RCTs of micronutrient supplementation have employed elderly subjects or individuals with pathological conditions like Alzheimer's disease. Thus, there is a need for well-designed, large-scale, long-term RCTs in healthy adults and in children. In addition, the available RCTs have used a number of different cognitive assessments; therefore, more standardized approaches would be useful to interpret evidence across studies. Studies that measure micronutrient status in blood and correlate that with cognitive function are also needed to better assess the role of micronutrients in cognition. Furthermore, intervention trials in individuals with micronutrient deficiencies are required to fully assess the role of micronutrient supplementation in populations with inadequate or marginal micronutrient status.

For more detailed information on micronutrients and cognition, see the article in the Micronutrient Information Center: http://lpi.oregonstate.edu/infocenter/cognition.html.
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Gifts in support of research efforts can be made at any time. Checks should be payable to *OSU Foundation for Linus Pauling Institute*. Information on giving is available through the OSU Foundation, **1-800-354-7281,** or by writing to the Institute.

Micronutrient Research for Optimum Health

Save the Date! October 14, 2011

Construction is nearing completion on the new Linus Pauling Science Center.

SAVE THE DATE to join us for the Building Dedication Ceremony on October 14, 2011.

Look for these informative articles inside!

Special thanks to Barbara McVicar for editorial assistance and photographs, authors of signed articles, and Dick Willoughby for the logo photograph of Linus Pauling.