Supplements...

Evidence-Based Dietary Supplements™: Benign Prostate Conditions
Anthony L. Almada, MSc

Among men over the age of 50 benign prostatic hyperplasia (BPH) is the most common benign tumor condition. BPH is a condition that is defined histologically via biopsy, which can lead to progressive enlargement of the prostate gland and the development of lower urinary tract symptoms. Fifty percent of all men have BPH identifiable histologically at 60 years of age, and over two-thirds of men between the ages of 61-70 have symptomatic BPH. By the age of 80, approximately 25% of American men are treated for BPH, with greater than 300,000 surgical procedures being performed every year. Symptoms include urinary hesitancy, diminished stream, straining, incomplete emptying, interruption of the urinary stream, dribbling (presumed to be associated with urinary obstruction) and filling (irritative) symptoms, namely urgency, frequency and nocturia. Another prevalent chronic prostatic condition is chronic pelvis pain syndrome (CPPPS). This condition is marked by pelvic pain, painful ejaculation and irritation or obstruction during urination related or unrelated to pathogenic bacteria. More than 2 million U.S. doctor office visits a year are prompted by such symptoms.

Although medical and surgical treatment options are abundant, the use of dietary supplements for benign prostate conditions (BPCs) is widespread in the United States. In Europe (for example, Germany, Austria and France) plant extracts for BPCs are regulated as drugs and comprise up to half of the total number of prescriptions written for BPH. Europe has spawned a number of phytotherapeutic (plant-derived therapies) agents for BPH with most being subjected to clinical trials of varying rigor, duration and sample sizes. However, for phytotherapeutic preparations it is of paramount importance to recognize that each brand will differ in its chemical composition even if derived from the same plant due to differing methods of harvesting, storage, extraction and other manufacturing steps. Moreover, the absence of chemical equivalency suggests that...
Chair's Corner . . .

Celebrate the Past, Savor the Present, and Shape the Future

Can you name a healthy, energetic four year old (born June 1, 1998) who was conceived in Boston only seven months earlier? Answer: Nutrition in Complementary Care Dietetic Practice Group (NCC)! From my perspective, NCC’s seed was planted in May 1996 at the joint conference Food and Nutrition Beyond Borders in Canada. There, I organized a dinner with colleagues who shared my passion for functional foods—foods or food components that provide health benefits beyond basic nutrition. This marked the birth of NCC’s predecessor, the Functional Foods Interest Group (FFIG). During the evening our northern neighbors asked, “What’s ADA doing about functional foods?” I was clueless! Upon my return, my inquiries yielded little fruit. The FFIG gathered again at ADA’s 1996 and 1997 annual meetings and a 1997 JADA advertorial referenced FFIG.

What enabled NCC to get from there to here? My head swims with contributing factors: many enthusiastic volunteers with supportive work and home environments who offer varying amounts of time, rapid e-communications, consumer demand, ADA’s validation that complementary care is part of our profession’s future and generous sponsors that empowered NCC to plan and operate strategically. Each presents a potent force for action.

NCC seems to have a magnetic attraction for high-impact leaders who thrive on the cutting edge of dietetics. Many members and I marvel at how much we’ve learned through NCC. The scope of complementary care is vast—it’s more diverse than anyone can master in its entirety. I, like most members, consider myself a novice with regard to many facets of complementary care. But speaking from personal experience, the endless networking opportunities in NCC—both in-person and online—can broaden horizons, complement and guide research efforts and expand one’s comfort zone. It’s a formula for becoming a more highly valued—and compensated—professional.

Ending our fourth year with over 2,400 members, NCC’s leaders are excited about the future. We’re currently working to expand your professional tool-box and invite you to join in. NCC welcomes your participation in keeping our exemplary newsletter, Web site and Electronic Mail List as valuable tools. Our Wish List of expanded member benefits (see side bar on page 4) awaits project champions. Volunteering for NCC places the educational and networking benefits of this DPG on a higher plane both for the members individually and collectively. Please consider joining me and other NCC volunteers as together we explore the frontiers of nutrition in complementary care.

Rosalyn Franta Kulik, MS RD FADA
2002-2003 Chair

Editor's Notes . . .

Sarah Harding Laidlaw, MS, RD, MPA

Fall is in the air and that means that FNCE is just around the corner. I am sure that many of you are, like me, and are preparing for and anticipating seeing old friends and making new ones in Philadelphia. NCC has many exciting educational opportunities planned for its members (and non members as well). For a listing of what activities NCC is sponsoring or cosponsoring, turn to page 14, column 1.

As we expand and grow as a DPG (yes, our membership continues to grow!) we will see the opportunity for many more complementary offerings at FNCE including new and innovative product exhibits and activities such as yoga. Our growing DPG will help us expand our horizons within the newsletter. We will be able to offer new and differing articles and benefits for our members such as inserts to use as patient handouts and special offers from our sponsors and members themselves.

If you were unable to attend the yoga sessions at FNCE in St. Louis last year, I strongly encourage you to try to make at least one session this year. You will find that yoga is a wonderful way to relieve the tension and sore muscles developed from concentrating at the sessions and from toting the big bag of samples and educational materials!

I am looking forward to seeing many of you at Product Marketplace or the DPG showcase. I hope that you will take advantage of the opportunity to give me feedback about the newsletter—what you like and don’t like, as well as suggestions for future articles and themes. As always, I am looking for members who have ideas AND want to write. So if you are interested in contributing to the newsletter, or to the Web site for that matter, please let me know!

This issue of the newsletter provides some interesting perspectives for a predominantly female organization. The topic is men’s health and how complementary nutrition may have a positive effect on the risk of disease in men, particularly as they age. Many of my patients are asking questions about specific supplements and their use for prevention and treatment of conditions, particularly prostate disease. I am sure you will find the information as helpful and informative as I have.

Have a great fall and don’t forget to say “hi” when you stop by any one of our events. For more information about opportunities in the newsletter, contact Sarah at peaknut@wic.net or 970-241-5529.

The views expressed in this newsletter are those of the authors and do not necessarily reflect the policies and/or official positions of the American Dietetic Association.

We invite you to submit articles, news and comments. Contact us for author guidelines.

Send change-of-address notification to the American Dietetic Association, 216 W. Jackson Blvd, Ste. 800, Chicago, IL 60606-6995.

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ISSN 1524-5209
Lycopene in Men’s Health
Karen E. Todd, RD

The three leading causes of death in American men are cardiovascular disease, prostate cancer and lung cancer. All are debilitating; none is totally curable. The strongest weapons against these diseases lie not in treatment but in prevention, and new research suggests the most potent laboratory may be a room in our own homes—the kitchen.

Throughout the 1980s and 90s, epidemiologic studies revealed strong links between diets rich in fruits and vegetables and reduced risk of major chronic diseases. A food-specific protective pattern emerged in several of these, wherein tomatoes and tomato products were associated with lower risks of prostate, lung and other cancers.12 As additional studies continued to find similar results, researchers began to focus on lycopene, the carotenoid responsible for coloring tomatoes red, as the protective compound. Recently lycopene has also been associated with reduced risk of cardiovascular disease.10,19

What Is Lycopene?
Lycopene is a powerful antioxidant of the carotenoid family, the group of pigments that impart yellow, orange and red colors to fruits and vegetables. Lycopene is the most prevalent carotenoid in the Western diet and the most abundant in human serum. As an antioxidant it is able to quench reactive oxygen species that can damage DNA, proteins and fats.

Food Sources and Body Stores of Lycopene
Lycopene is found in tomatoes and tomato products, pink grapefruit, guava, watermelon and to a lesser extent, papaya. More than 85% of the lycopene in the North American diet comes from tomatoes and tomato-based products. Normally, about 10-30% of the lycopene in food is absorbed, and the remainder is excreted.10,11 Lycopene from tomato products that have been cooked is absorbed more readily than that from fresh tomatoes because processing makes lycopene more bioavailable.17 Lycopene is carried through the body by low-density lipoprotein cholesterol (LDL) and other lipoproteins. The highest concentrations are found in the testes, adrenal glands, prostate and liver.

Reduced Risk of Prostate Cancer
Prostate cancer is the most commonly occurring cancer and second leading cause of death in American men.14 The lifetime risk of being diagnosed with prostate cancer is one in six, making it even more common among men than breast cancer is among women, which is a one in eight risk. The causes of prostate cancer are unknown and treatments often have unwanted consequences including impotence.

Strong support for the role of lycopene in reducing risk of prostate cancer comes from a number of large epidemiologic studies.13-24 The best known of these are the Seventh Day Adventist Study, the Health Professionals Follow-Up Study and the Physicians’ Health Study. Risk reduction in these studies ranged from 35-50%. Interestingly, in both the Health Professionals Follow-Up Study and the Physicians’ Health Study, even higher risk reduction was seen in men who had aggressive prostate cancer (53% and 60%, respectively). Table 1 illustrates research that has linked either tomato, tomato products or lycopene intake with a reduced risk of prostate cancer. While whole tomatoes are a source of lycopene, they also contain other nutrients such as vitamin C.

Lycopene supplementation has been tested as an adjunct therapy in prostate cancer patients. A group of men were supplemented daily with 30 mg of lycopene from a tomato extract for three weeks prior to surgery. Tumors in the supplement group showed signs of regression and decreased malignancy.22 The involvement of the cancer at the surgical margin was reduced in 73% of patients given the lycopene supplements, compared to 18% of controls. A second study, also using 30 mg of lycopene per day for three weeks prior to prostatectomy, found that in the supplemented patients, prostate tissue DNA oxidative damage and PSA levels were significantly reduced.26 Although both studies were small, the findings are suggestive of a role for lycopene in prostate cancer treatment.

Table 1. Prostate Cancer Epidemiologic Studies with Statistical Significance15-24

<table>
<thead>
<tr>
<th>STUDY</th>
<th>ASSOCIATION WITH PROSTATE CANCER</th>
<th>REDUCTION IN RISK</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mills, 1989</td>
<td>Tomato intake in Adventist men</td>
<td>40%</td>
</tr>
<tr>
<td>Baldwin, 1997</td>
<td>Tomato intake in elderly California men</td>
<td>41%</td>
</tr>
<tr>
<td>Cerhan, 1998</td>
<td>Tomato intake in U.S. cohort</td>
<td>50%</td>
</tr>
<tr>
<td>Gann, 1999</td>
<td>Plasma lycopene in Physicians’ Health Study</td>
<td>44%</td>
</tr>
<tr>
<td>Jain, 1999</td>
<td>Tomato intake in Canadian men</td>
<td>36%</td>
</tr>
<tr>
<td>Tzonou, 1999</td>
<td>Cooked tomatoes</td>
<td>15%</td>
</tr>
<tr>
<td>Bosetti, 2000</td>
<td>Cooked tomatoes</td>
<td>91%</td>
</tr>
<tr>
<td></td>
<td>Raw tomatoes</td>
<td>55%</td>
</tr>
<tr>
<td>Lu, 2001</td>
<td>Plasma lycopene in U.S. men</td>
<td>83%</td>
</tr>
<tr>
<td>Giovannucci, 2002</td>
<td>Tomato product intake in male health professionals, 1992-1998</td>
<td>17%</td>
</tr>
</tbody>
</table>

Lycopene Versus Lung Cancer
Lung cancer, the leading cause of cancer deaths worldwide, occurs at twice the rate in men aged 30-54 as in women.14 While increased intakes of fruits and vegetables have been correlated with reduced risk of lung cancer, lycopene is one of the phytochemicals in fruits and vegetables that shows particular promise. In a review of epidemiologic studies, 10 studies found an inverse association between intakes of tomatoes, lycopene or lycopene status and lung cancer risk, five of which were statistically significant.2 Most of these studies adjusted for smoking history, the most important potential confounder for lung cancer.

In an analysis of pooled data from the Health Professionals Follow-Up Study and the Nurses’ Health Study, Harvard researchers found a statistically significant association between higher intakes of lycopene and reduced risk for lung cancer. Among their conclusions they stated, “Our data suggest that lycopene is an important carotenoid for protection against lung cancer, especially in current smokers.”27 The epidemiologic studies that have found a statistically significant association between tomato intake or lycopene and lung cancer are listed in Table 2.

(continued on page 8)
The United States Pharmacopeia (USP) congratulates Pharmavite for being the first to join the USP Dietary Supplement Verification Program (DSVP). Pharmavite's Nature Made® products with the USP certification mark on the label should be available in the marketplace in late fall 2002.

USP uses rigorous standards in the evaluation of manufacturing systems, product sample testing, and review of quality control manufacturing data. The DSVP is designed to build consumer confidence by helping to assure a product's quality, purity, and integrity.

For further information about USP and the Dietary Supplement Verification Program, please contact DSVP Customer Service at 301.816.8273, email dsvp@usp.org, or visit us at www.usp-dsvp.org.

NCC Wish List

Contribute to NCC from the convenience of your home. Often, expertise in complementary care is not a pre-requisite.

Volunteers wanted to…

• Establish a Speakers’ Bureau specializing in Complementary Care.
• Create a "Find-a-Complementary-Care RD" directory on NCC’s Web site.
• Develop a mentoring program.
• Form networking sub-groups representing your special interests or expertise.
• Join the Web Editorial staff. Just found someone!.
• Contribute to the NCC Newsletter or Web site, the premier information resource for those in the field and those wanting to get involved. A basic understanding of complementary care is suggested as well as an overwhelming desire to research and write on a particular topic (guidelines provided).

If you’re interested in learning more about these or suggesting other volunteer opportunities, please contact Rosalyn Franta Kulik, NCC Chair, at ncckulik@msn.com, Sarah Laidlaw, Newsletter Editor, at peaknut@wic.net, or Jocelyn Mathern, Web site Editor, at Jocelyn.Mathern@us.acatris.com.
Book Review
Healthy Eating For Life For Children.

Emphasizing the principles of vegetarian nutrition and environmentally sound food procurement practice, the book Healthy Eating For Life For Children is a fairly sound, if not sometimes slanted, reference for consumers or clients wanting to know the basics of good nutrition. For vegetarians, this book is a perfect companion, whereas those who consume foods from animal sources may be sorely disappointed at the generalizations the writers make on the benefits of a vegetarian diet as compared to the harm from an animal-protein based diet (never mind that many lean sources of animal protein are low in fat and high in B12 while dairy products contain conjugated-linoleic acid, lactoferrin, immunoglobulins and other nutrients). While there is much research to support the use of vegetarianism for healthy lifestyles, this book refers to relatively little of it and covers the topic in basically two pages. Nonetheless, the rest of the book’s content is firmly entrenched in the sound principles of nutrition with an emphasis on fruits, vegetables, legumes and whole grains. Or as the book refers to them, the “New Four Food Groups.”

After a section defining the basic nutrients, the second section covers nutrition from pregnancy to the teen years, including discussion chapters on breastfeeding, the introduction of solid foods, feeding toddlers and grade school children and includes a chapter on helping adolescents through the turbulent years. What is exceptional about this book is its inclusion of chapters on hot topics such as food allergies, ADHD and autism; how to help a child develop a healthy body image; how to help a child maintain a healthy weight; how to identify eating disorders and tips on how to find treatment; and sports nutrition. While none of these topics is covered exhaustively, the fact that they are included in a book that will be purchased no doubt by parents or guardians of younger children is beneficial because it raises their awareness of potential problems to come. Final chapters include practical materials for pulling it all together—shopping lists, cooking techniques, menus and recipes. A glossary of terms, resources list and references complete the book.

While the typical nutrition professional would find the material in this book very basic, it would make an excellent resource or adjunctive material for the nutrition professional’s client, specifically those who are vegetarian or trying to include more vegetarian style eating.

Reviewed by Tamara Schryver, MS RD, Publications Chair. Contact Tamara at RTSchryver@aol.com or 952-898-2577.

Software
HealthQuest Nutritional CD-Rom
Standard in Natural Solutions, LLC, PO Box 270165, Ft. Collins, CO 80527; 888-822-7733 or 970-204-4950 or www.hquest.com

Are you looking for an up-to-date database that provides you with information on natural and complementary medicine for your practice and patients? If so, the HealthQuest Nutritional CD-Rom may be just what the nutrition professional ordered! The HealthQuest program contains six topic areas: Health Concerns, Patient Information, Vitamins, Minerals and Specialty Nutrients, Herbal Nutrients and Natural Foods, Health Tests and Drug/Nutrient Interactions and Depletions. There is also a search button that helps further define what you or your patients may be interested in knowing more about.

In the Health Concerns sections there are over 300 health conditions that include signs and symptoms, possible causes, nutrient applications, dietary and lifestyle applications and related notes for each condition. Patient Information has two sections: 1) Patient Fact Sheets that can be used as patient education handouts which define the clinical applications and research related to particular nutrient combinations; and 2) Wellness Information including special diets and other patient handouts. The Vitamins, Minerals and Specialty Nutrients section covers functions, effects of a nutrient deficiency, clinical applications/research, nutrient tidbits, RDAs and contraindications, which include toxicology. Commonly used herbs and information about natural foods are detailed under the topic heading of Herbal Nutrients and Natural Foods. The Health Tests has two sections: 1) Laboratory Tests - evaluation of lab results for optimal health; and 2) Questionnaires which can be inputted directly on the computer or copies made and given to patients. Information from the health test section can be graphed and analyzed with nutrient support recommendations. In the Drug/Nutrient Interactions and Depletions section there are 1693 drugs listed with adverse reactions to herbs.

The HealthQuest program appears to put a considerable amount of useful information at the nutrition professional’s fingertips in a concise and easy to learn and use format.

There are two versions of the software available—an Multiuser version that allows links to other PCs and their users and a Single-User version. The Multiuser version has editable and customizable features, which allows customized inserts into the original document. For NCC members Standard in Natural Solutions, LLC is offering special pricing. The Multiuser version is available for $495.00, a price break of $100.00 and the Single-User version for $350.00, a price break of $100. For more information, or to request a DEMO disk for $10, please call 888-822-7733, 970-204-4950 or go to their Web site www.hquest.com.

Reviewed by Sarah Harding Laidlaw, MS RD MPA, newsletter editor. Contact Sarah at 970-241-5529 or peaknut@wic.net.
It is necessary to inform and query the membership regarding any proposed changes to the Dietetic Practice Group Governing Documents. The following changes have been recommended to the current structure of the Executive Committee as a result of the new strategic plan. Please provide comments via phone/email to Susan Pitman at 202-973-5800 or pitmanNCC@hotmail.com. The comment period will close September 30, 2002 and the final version will be posted on the NCC Web site www.ComplementaryNutrition.org.

Article II - Mission

Current: Section 1. Mission. The American Dietetic Association (ADA) is the advocate of the dietetics profession serving the public through the promotion of optimal nutrition, health and well being. NCC, a professional interest group of ADA, promotes responsible, science-based use of complementary care in the practice of dietetics.

Revised: Section 1. Mission. Nutrition in Complementary Care (NCC) is a specialty group of dietetics professionals (DP) that promotes the integration of conventional nutrition practices with evidence-based alternatives through education, research and practice.

Current: Section 2. Vision. Members of NCC will serve as leaders to increase public knowledge of science-based complementary care.

Revised: Section 2. Vision. NCC bridges conventional and emerging nutrition choices.

Article VI - Other Officials

Current: Section 1. The appointed officials will consist of Committee Chairs and Project Leaders. All officials will take office when the elected officers of ADA assume their offices. Officials will lead standing committees as specified in Section 2 of Article IX. All officials will work closely with the Executive Committee and within applicable Bylaws, Policies and Procedures of ADA and NCC. All appointed officials shall be current members of NCC. Except under special circumstances, each official shall be willing and able to communicate via an electronic mail system and facsimile.

Revised: Section 1. The appointed officials will consist of Operating Chairs, Committee Chairs and Project Leaders. All officials will take office when the elected officers of ADA assume their offices. Officials will lead standing committees as specified in Section 2 of Article IX. All officials will work closely with the Executive Committee and within applicable Bylaws, Policies and Procedures of ADA and NCC. All appointed officials shall be current members of NCC. Except under special circumstances, each official shall be willing and able to communicate via an electronic mail system and facsimile.

Current: Section 2. Committee Chairs shall serve for one (1) year unless otherwise specified, being appointed by the Chair or the Chair-elect to serve during the Chair-elect’s term as Chair. Committee Chairs shall be approved by the Executive Committee. A Committee Chair may be reappointed.

Functions. A Committee Chair will:
A. report to the Executive Committee and submit written reports to the Executive Committee as designated by the NCC Chair.
B. submit a program of work and projected budget to the Executive Committee at the beginning of his/her service.
C. perform functions as described in relevant sections of this Article and in Article IX of these Governing Documents and in NCC's Policies and Procedures.
D. coordinate the work of the Committee and Project leader(s) within the Committee.

Revised: Section 2. Operating Chairs are voting members of the Executive Committee and are appointed by the NCC Executive Committee. Operating Chairs will provide direction for NCC. Each Operating Chair position will serve a two-year term and may be reappointed for additional one-(1) or two-(2) year terms. Operating Chairs consist of Publications Chair, Liaison Chair, Member Services Chair and Content Chair.
C. Member Services Chair. The Member Services Chair has overall responsibility for facilitating and managing additional programs and projects beyond the NCC newsletter and NCC Web site that provide direct member benefits. Activities include, but are not limited to the following: Electronic Mail List (EML); Continuing Professional Education programs; Mentoring Program; Find-a-Complementary-Care-RD program; New Product/Service Development.

D. Content Chair. The Content Chair oversees the identification and provision of technical resources in ways that further NCC’s mission and strategic plan. Identifies and appoints content leaders/experts for various NCC projects including, but not limited to: legislative testimony, fact sheets, reviewers for position papers. The Content Chair accepts overall responsibility for supplying, in response to requests to NCC, authors, editors and reviewers when such requests are in line with NCC’s Program of Work.

Current: Section 3. Project Leaders shall be appointed by Committee Chairs with approval by the NCC Chair, Chair-elect or by the Executive Committee. Project Leaders shall serve for the duration of the project.

Functions. A Project Leader will:
A. report to the Committee Chair.
B. submit a project proposal and projected budget to the Committee Chair and the Executive Committee.
C. implement and complete the work of the assigned project.

Revised: Section 3. Committee Chairs shall serve for one (1) year unless otherwise specified, being appointed by the Chair, the Chair-elect to serve during the Chair-elect’s term as Chair or the Operating Chair. A Committee Chair may be reappointed.

Functions. A Committee Chair will:
A. report to the designated Operating Chair and submit written reports as designated by the Operating Chair.
B. submit a program of work and projected budget to the Operating Chair at the beginning of his/her service.
C. perform functions as described in relevant sections of this Article and in Article IX of these Governing Documents and in NCC’s Policies and Procedures.
D. coordinate the work of the Committee and Project leader(s) within the Committee.

Current: Section 4. Publications Chair. The Publications Chair will be appointed by the Executive Committee to serve a term of two (2) years and may be reappointed for additional one- (1) or two- (2) year terms. The Publications Chair will assure that the official publication of NCC will be developed, published and issued at least quarterly in keeping with Article XI in these Governing Documents. The Publications Chair will receive assistance as desired from the Education Committee regarding documents designed to receive Continuing Education approval. The Publications Chair will oversee or provide guidance during the development, production and distribution of other DPG publications. All publications will be consistent with applicable Bylaws, Policies and Procedures of ADA and NCC.

Revised: Section 4. Project Leaders shall be appointed by Operating or Committee Chairs with approval by the NCC Chair, Chair-elect or by the Executive Committee. Project Leaders shall serve for the duration of the project.

Functions. A Project Leader will:
A. report to the Operating Chair or Committee Chair.
B. submit a project proposal and projected budget to the Committee Chair and the Executive Committee.
C. implement and complete the work of the assigned project.

Article VIII - Governance

Current: Section 2. Composition. The Executive Committee will consist of the Chair, Chair-elect, Immediate Past Chair, Treasurer, Secretary, Nominating Committee Chair, Publications Chair, Liaison Chair, Member Services Chair and Content Chair.

Article IX – Standing Committees

Current: Section 2. General. Standing Committees shall be designated by the Chair or Executive Committee and approved by a majority vote of the Executive Committee as needed to conduct NCC activities. The Chair or Executive Committee shall appoint Task Forces as needed to assist in achieving the mission of NCC.

Revised: Section 2. General. Standing Committees shall be designated by the Chair or Executive Committee and approved by a majority vote of the Executive Committee as needed to conduct NCC activities. The Chair, Operating Chair or Executive Committee shall appoint Task Forces as needed to help further the mission of NCC.
Potential Benefits in Cardiovascular Health

Cardiovascular disease (CVD) is the leading cause of death among men of all races and ethnic groups in the U.S., ranging from about 28% of deaths among Native American men to almost 39% of deaths in white men. While the incidence in post-menopausal women equals that in men, it also remains true that men face CVD at younger ages than women and that the incidence in men still exceeds that in women. Prevention is preferable to treatment, since death is often the first "symptom" of disease. In fact, 50% of men who die suddenly from coronary heart disease have shown no prior symptoms.

Laboratory evidence and a small intervention study have suggested that lycopene helps protect low density lipoprotein cholesterol (LDL) against oxidation, which is believed to be an important step in atherosclerosis. Epidemiological studies that have explored the potential protective effects of tomato-based products and/or lycopene have shown fairly consistent benefits across a wide range of cancers, especially prostate, lung and stomach. Similar benefits in CVD are beginning to surface as research continues.

### Table 2. Lung Cancer Epidemiologic Studies with Statistical Significance 27-32

<table>
<thead>
<tr>
<th>STUDY</th>
<th>PROTECTIVE FACTOR</th>
<th>REDUCTION IN RISK</th>
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<tr>
<td>Bond, 1987</td>
<td>Tomato intake</td>
<td>58%</td>
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<tr>
<td>Le Marchand, 1989</td>
<td>Tomato intake</td>
<td>57% in men</td>
</tr>
<tr>
<td></td>
<td></td>
<td>73% in women</td>
</tr>
<tr>
<td>Forman, 1992</td>
<td>Tomato intake</td>
<td>58%</td>
</tr>
<tr>
<td>Agudo, 1997</td>
<td>Tomato intake</td>
<td>55%</td>
</tr>
<tr>
<td>Li, 1997</td>
<td>Plasma lycopene</td>
<td>63% in whites</td>
</tr>
<tr>
<td></td>
<td></td>
<td>88% in African-Americans</td>
</tr>
<tr>
<td>Michaud, 2000</td>
<td>Lycopene intake</td>
<td>37% in current smokers</td>
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### Table 3. Lycopene and CVD Epidemiologic Studies with Statistical Significance 4-10

<table>
<thead>
<tr>
<th>1ST AUTHOR</th>
<th>MAJOR FINDINGS</th>
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<tbody>
<tr>
<td>Kohlmeir, 1997</td>
<td>Adipose tissue lycopene associated with lower risk</td>
</tr>
<tr>
<td>Kristenson, 1997</td>
<td>Low serum lycopene associated with increased mortality from heart disease</td>
</tr>
<tr>
<td>Schmidt, 1997</td>
<td>Lower serum lycopene in high risk individuals</td>
</tr>
<tr>
<td>Klipstein-Grobusch, 2000</td>
<td>Higher serum lycopene associated with 45% lower risk of atherosclerosis</td>
</tr>
<tr>
<td>Rissanen, 2000</td>
<td>Low plasma lycopene associated with 17% increase in carotid artery intima-media thickness</td>
</tr>
<tr>
<td>Rissanen, 2001</td>
<td>Lower serum lycopene levels associated with a 3-fold increased risk of acute coronary event or stroke</td>
</tr>
<tr>
<td>Gianetti, 2002</td>
<td>Plasma lycopene had an inverse association with intima-media thickness</td>
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In the Health Professionals Follow-up Study the intake levels associated with the highest protection for prostate cancer were 10 or more servings per week of tomatoes or tomato-based products, translating to an average of about 6.5 mg lycopene per day. Intakes of lycopene in the United States vary widely. There is evidence that as many as half the population may have low lycopene intakes of under 3.6 mg per day.

(continued on page 9)
References


different products will lack bioequivalency. To this effect, this review will mention specific brand names where appropriate, as indicated by published original research within reviewed journals.

**BPH**

**Saw palmetto (Serenoa repens; Sabal serrulata; saw palmetto)**

The berry (fruit) of this “dwarf” palm (which grows in abundance in the southeastern US) has been the subject of hundreds of basic and clinical research studies and is the most thoroughly researched natural therapy for BPH. The most widely studied extract is called Permixon® (Pierre Fabre Medicament, France; not sold in the US), which is a hexane extract. The components frequently standardized for content include a variety of long chain fatty acids, phytosterols and long chain alcohols. As for many natural products the exact mechanism of action is unknown but is suggested to involve anti-inflammatory or anti-androgenic activity, inhibitory effects toward peptide growth factors and inhibition of the enzyme 5-alpha-reductase (5AR), which converts testosterone into dihydrotestosterone (DHT; a steroidal prostate growth factor). This latter proposed mechanism is displayed by the BPH drug finasteride (Proscar®).

Of the many clinical trials that have been conducted with *Serenoa* extracts/Permixon, the most commonly reported dose is 160 mg twice daily. The largest study to date was a double blind multi-center study within nine European countries, enrolling 1,098 men (age range: 49-88 yrs.) with BPH diagnosed by a digital rectal exam. The positive control was finasteride (5mg/day). After an average of 26 weeks of follow up, improvements in validated symptom scores and peak urinary flow rate were equal between the Permixon and finasteride groups. Because finasteride is most effective in men with large prostate volumes, this study does not unequivocally indicate that Permixon is bioequivalent to finasteride in BPH per se. However, this subset of men comprises less than one third of those with BPH.

The longest trial to date was an 11 country, European, double-blind, multi-center study, which randomized 704 men to receive Permixon (320 mg/day) or the alpha-adrenergic receptor blocker tamsulosin (Flomax®). This drug is used for the symptomatic management of lower urinary tract symptoms. After one year of intervention, both groups showed equal improvements in symptoms scores but only the Permixon group showed a drop in prostate volume, which was significantly different from the tamsulosin group that showed an increase in this parameter. The tamsulosin group also showed a significantly greater frequency of ejaculation disorders.

The primary weakness of the previous two studies is the absence of a placebo control group, given the strong placebo effect and intermittent improvements characteristic of BPH. However, a recent Cochrane Collaboration systematic review/meta-analysis performed on 24 published trials concluded that *Serenoa* repens extracts improve urinary symptoms and flow measures in men with BPH. Additionally, they found it to produce improvements in urinary symptoms and flow measure similar to that of finasteride, yet with fewer side effects and less costs. The long-term safety and efficacy, and its influence on progression of BPH, remains enigmatic. Note that clinical trials with finasteride have been conducted over a four year intervention period.

**Pygeum (Prunus africanaum; African plum tree)**

Relative to *Serenoa* extracts/Permixon, the quality and number of well-controlled clinical studies with this African tree bark extract are notably inferior. The most widely tested branded preparation is Tadenan® (DEBAT, France; not available in U.S.), a chloroform extract standardized to pyrophoril, short and long chain fatty acids and long chain alcohols (a composition similar to *Serenoa* repens extracts). The purported mechanisms of action include inhibition of leukotriene synthesis/anti-inflammatory action and stabilization of bladder cell and organelle membranes. The frequent dosage is 100-200 mg/day. Of the placebo-controlled studies that have been published, only a few were published in English language journals. A recent systematic review and meta-analysis identified 31 clinical trials on Pygeum. Of these, 14 were excluded because they lacked a control group (placebo or positive control). Only 11 compared Pygeum to placebo alone. The authors found a modest positive effect of Pygeum upon urinary flow, residual urine volume and overall symptoms but none of the studies used validated BPH symptom questionnaires. In addition, none of the studies had intervention periods exceeding four months. Lastly, none of the studies compared Pygeum to alpha-antagonists (like tamsulosin) or 5-alpha-reductase inhibitors (like finasteride).

**Phytosterols/Beta-sitosterol**

Plant sterols are among the constituents present in both *Serenoa* and Pygeum extracts. Beta-sitosterol (BSS) esters are used as hypolipidemic agents in table spreads (for example, Take Control® margarine). BSS has been postulated to exert palliative effects in BPH through anti-inflammatory or growth factor response-modifying effects. Several clinical trials have been performed with various BSS compositions. In a study reported in Lancet, German researchers performed a multi-center double blind study that randomized 200 patients to receive three times daily either placebo or a phytosterol mixture (Harzol®, Hoyer, Germany). Harzol was comprised of 10 mg of BSS and 0.1 mg of BSS-D-glucoside, along with a total of 10 mg of other phytosterols (campesterol stigmasterol and their glucosides), for six months. Note: a product available in the US called Moducare® (Essential Phytosterolins, Inc., Canada) is identical to the Harzol used in this study. After six months, scores on standardized symptom questionnaires within the Harzol group were significantly superior to placebo, in addition to urodynamic and residual volume measurements. Prostatic volume appeared to be uninfluenced.

A second multi-center double blind study in Germany randomized 177 symptomatic BPH subjects to receive either a phytosterol preparation containing a minimum 70% BSS (65 mg of BSS) or placebo, twice daily for six months. Urinary symptom scores (using a validated questionnaire) and peak urinary flow rate showed significant and dramatic improvements in the BSS group compared to placebo.

Unlike the innovator preparations Permixon and Tadenan, there are various BSS products, which makes comparisons between studies challenging. Given the relatively small body of evidence supporting BSS, a lack of comparator trials against agents like finasteride or tamsulosin and lack of trials extending beyond six months, BSS appears to be a phytotherapeutic choice less compelling than Permixon or Tadenan.

**CPPS**

**Quercetin**

Quercetin is a flavonoid found in abundance within the diet, residing in large quantities within onions, red grape products, tea and apples. It has moderate anti-inflammatory and antioxidant activity, demonstrated primarily in *in vitro* studies. It is widely believed to exert anti-allergic effects despite the absence of systematic clinical trials verifying this activity. In a 30 day placebo-controlled, double blind trial with 30 men presenting with NIH category III prostatitis syndromes (chronic abacterial prostatitis and prostatodynia), 500 mg of quercetin twice daily produced significant improvements in symptoms during the first week of treatment. These results are consistent with a Cochrane Collaboration review which concluded that there was evidence for the efficacy of quercetin in treating CPPS.

(continued on page 11)
improvements in a validated symptom questionnaire, relative to placebo. One subject receiving quercetin reported a headache while another reported mild tingling of the extremities, both symptoms resolved after stopping supplementation. Other open label studies have been performed by the same investigative group with different variants of a formulation marketed as Prosta-Q™ (Farr Laboratories, California). One study cited the inclusion of the plant proteolytic enzymes papain and bromelain as antioxidants, despite any data indicating this in their paper. In a more recent study the currently marketed formulation, which still contains 500 mg of quercetin per capsule but has added zinc and undisclosed amounts of non-standardized cranberry and saw palmetto berry powders (along with bromelain and papain), treatment produced a reduction in the prostatic fluid prostaglandin E2. This is suggestive of an anti-inflammatory effect. Alternatively, quercetin may be displaying antibacterial action exerted against "cryptic" prostatic bacterial infections that often go undetected. The available data do not warrant purchase of the high expense Prosta-Q product and suggest that quercetin is the primary, if not the only, active ingredient.

Take Home Message

The widespread use, and perhaps misinformed use, of dietary supplements intended to elicit a therapeutic or palliative effect in chronic benign conditions of the prostate warrants a vigilant monitoring of the biomedical literature and product claims. In a recent analysis of a cross section of six commercially available Serenoa repens products, wide variances in the fatty acid content were observed. While this may not be reflective of other prostate/phytotherapeutic products, the nutrition professional integrating complementary medicine and dietary supplements into their practice is encouraged to seek out branded products that adhere to good manufacturing practice guidelines and uniform ingredient supply. In addition, dietary supplements for the treatment of BPH should be supported by product-specific clinical science.

Disclosure: IMAGINutrition is a consultant to Essential Phytosterolins, Inc., the North American marketers of Moducare®.

References:

The prostate functions as an exocrine gland that contributes to semen and is called the male accessory sex organ. In contrast, the testes is an endocrine (and exocrine) gland, because it secretes sex steroid hormones in the blood. The prostate functions under the control of testosterone.

Testosterone is secreted by the interstitial (Leydig) cells of the testes. The brain is a target organ for this hormone as it contains testosterone receptors. One of the effects of testosterone in the brain is the suppression of the secretion of luteinizing hormone (LH). The negative feedback circle is closed as LH stimulates the testosterone secretion. Testosterone is in fact not the mediator, but its derivatives are. Testosterone can be converted into active metabolites such as dihydrotestosterone (DHT) by the enzyme 5-alpha-reductase. DHT is needed for the development and maintenance of the prostate and other tissues (penis, spongy urethra and scrotum). FIGURE 1

Alternatively, testosterone may be converted to 17-beta-estradiol, usually regarded as the female sex steroid. The enzyme aromatase is responsible for this conversion. Estradiol formed from testosterone in the brain is required for the negative feedback effects of testosterone on LH secretion. This feedback mechanism is one factor in maintaining relatively constant levels of androgen secretion from the testes. In general, this secretion of testosterone and androgens declines only gradually and to varying degrees in aging men. The causes of this age-related change in testicular function are currently not known.

Benign prostate hyperplasia (BPH)*

Benign prostate hyperplasia (enlargement of the prostate) or BPH and its related symptoms are very common among aging men leading some to suggest that it is concomitant with aging. Currently, prostate enlargement is considered a chronic, progressive condition. Autopsy data indicate that anatomic or microscopic evidence of BPH is present in 40% of men aged 50 to 60 and 90% of men aged 80 to 90 years. An enlarged prostate may lead to a set of symptoms summarized by the term prostatism, which includes frequency, urgency, dribbling, hesitancy, nocturia and diminished urine flow. The etiology of BPH is still unclear, but it appears to represent a multifactorial process. Prostate enlargement is influenced mainly by androgens. The metabolite of testosterone, DHT, supports abnormal growth of the prostate. Although testosterone secretion generally declines with age, DHT is often found at increased levels in men with enlarged prostate. 5-alpha-reductase inhibitors are believed to work on the prostate by reducing the volume of the gland, specifically the glandular epithelium in the transition zone of the prostate.2,3

Lower urinary tract symptoms are due to a heightened tone of the prostatic smooth muscle, which is controlled by the sympathetic nervous system. Alpha receptor blockers are believed to simply reduce the tone of the smooth muscle in the area of the bladder neck, prostate and prostatic capsule. However, it is now known that a-receptor blockers also exert effects on other areas of the body where receptors are found such as blood vessels, the spinal cord and the detrusor muscle (the external muscular layer of the bladder).

A Role for Flax Lignans

In recent years, many animal model studies and human clinical trials have suggested that flaxseed lignans may have important beneficial health effects. Lignans are a group of polyphenolic compounds containing a 2,3-dibenzylbutane skeleton. Antioxidant properties are established for these compounds. Over 200 lignans have been identified and they are widely distributed in plants and woody tissues, but flaxseed is the richest source providing 75–200 times more plant lignans than any other source. The main lignan in flaxseed is secoisolariciresinol diglucoside (SDG). Plant lignans are known to have antioxidant properties and are considered to be phytoestrogens. But in the case of SDG, it needs to be converted to the so-called mammalian lignans enterolactone and enterodiol that exert the antiestrogenic effects. The human intestinal bacteria are believed to be responsible for this pathway, composed of de-glucosylation, demethylation and de-hydroxylation.

A few studies have reported the levels of lignans found in prostatic fluids compared to the presence of isoflavone metabolites. Table 1 presents the results of these studies with insight on the levels of isoflavones and lignans in prostatic fluids with a daily, habitual diet (a diet not supplemented with soy or flaxseed). (continued on page 13)
(continued from page 12)

Table 1. Mean concentrations of isoflavonoids and lignans in prostatic fluids (ng/ml) 4

<table>
<thead>
<tr>
<th></th>
<th>Daidzein</th>
<th>Equol</th>
<th>Enterodiol</th>
<th>Enterolactone</th>
</tr>
</thead>
<tbody>
<tr>
<td>Manchester, UK</td>
<td>11.3</td>
<td>0.5</td>
<td>2.6</td>
<td>20.3</td>
</tr>
<tr>
<td>Lisbon, Portugal</td>
<td>4.6</td>
<td>1.7</td>
<td>13.5</td>
<td>162.0</td>
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<tr>
<td>Hong Kong</td>
<td>70.0</td>
<td>171.6</td>
<td>1.6</td>
<td>31.0</td>
</tr>
<tr>
<td>Beijing, PR China</td>
<td>24.3</td>
<td>29.2</td>
<td>6.6</td>
<td>32.9</td>
</tr>
</tbody>
</table>

Depending on the typical diet —soy, fiber rich or vegetarian, the specific phytoestrogens can be located in the prostate fluids, indicating that flax lignans are in fact bioavailable and metabolized into active mammalian lignans in the general population. Furthermore, it is of interest that the concentration of enterolactone in human semen is 2.5-25 times higher than in blood plasma. This finding suggests an accumulation of lignan metabolites in prostate tissue.

The mechanisms by which flax lignans may act in prostate tissue have been studied in vitro and in animal models rather than in clinical trials in men at this time. The mechanisms are generally related to estrogenic or antiestrogenic effects. One effect that has been confirmed is the inhibition of the aromatase system. Mäkelä et al. concluded that enterodiol and enterolactone were inhibitors of the aromatase enzyme. Enterolactone appeared to be a stronger aromatase inhibitor than enterodiol.

Enterodiol and enterolactone were also found to inhibit 5-alpha-reductase in prostate tissue homogenates. The transformation of testosterone into the more potent DHT may therefore be reduced influencing the prostate size. Research in this area is too premature to conclude whether lignan metabolites also modulate other effects for other alpha-receptor blockers (see above under BPH) in other areas of the body.

Sex hormone binding globulin (SHBG) is the major carrier protein for steroid hormones. It has a high affinity to androgenic and estrogenic hormones, but the most preferred ligand of SHBG is in fact DHT. Target tissues are equipped with receptors for SHBG, which make them more than only carrier proteins. SHBG was shown to be an allosteric protein in which the protein-receptor interaction depends on the occupancy of steroid binding site and the kind of bound ligand. Therefore, nonsteroidal ligands of SHBG are of great interest while they may interfere with the mechanism by which the key hormones act. For this purpose, flax lignans have been studied. Enterolactone and enterodiol were both found to have a binding affinity for SHBG. The parent plant lignan secoisolariciresinol aglucone and matairesinol had even a higher affinity to SHBG. The authors concluded that these lignans met the structural criteria for binding. This finding might be another explanation of the modulating effects of physiological concentrations of flax lignans in prostate enlargement.

Take Home Message
Prostate enlargement or benign prostate hyperplasia is common in the aging male population, leading to many inconveniences in the early stages of this condition. Flax lignans may help prevent prostate enlargement by three mechanisms: 1) inhibition of aromatase; 2) inhibition of 5-alpha-reductase; or 3) by binding to SHBG.

For clients looking to improve their prostate health, flax lignans may be a natural way to help prevent BPH and other negative effects of aging by helping to regulate the hormone production involved in good prostate health. There are no official recommendations on lignan intake at this time. However, one recent human pilot study tested 30 grams of ground flaxseed (approximately 3 rounded tablespoons) per day in conjunction with a fat restricted diet (approximately 3 rounded tablespoons) per day in conjunction with a fat restricted diet and found that this influenced several biomarkers associated with prostatic neoplasia. Significant decreases in testosterone were observed. Whole and ground flaxseed will contain lignans, but flax oil is relatively devoid of lignan content due to processing. Ground flaxseed may be the easiest to recommend because whole flaxseed has a sharp spiculum and therefore has the potential to cause intestinal perforation. The Flax Council of Canada offers many helpful suggestions on how to incorporate flax into a daily diet, including recipes. Their website is http://www.flaxcouncil.ca/

Whatever supplement your patients choose to use for reducing the risk of BPH or its complications, one aspect that is paramount is getting men to see a physician and other health care providers on a regular basis.

Marian Verbruggen, PhD, is currently the R&D Director of Acatris Holding B.V., manufacturer’s of natural soy, fenugreek and flax ingredients for the food and dietary supplement industry. Contact Marian at Marian.Verbruggen@nl.acatris.com; or 31-183-446-435.

Visit www.complementarynutrition.org for a client handout written by flax specialist, Jane Rheinhardt-Martin, RD.

References:

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Quaker Oats
Tropicana Products
Be on the cutting edge; don’t miss these exciting events sponsored by NCC during the annual Food and Nutrition Conference and Exhibition (FNCE) in Philadelphia, PA October 19-22, 2002. All activities will be held at the Marriott unless otherwise noted.

Friday, 10/18
6:00 - 9:00 PM
NCC Executive Committee meeting, Part 1 (Grand Ballroom, Salon J)

Saturday, 10/19
8:00 AM-1:00 PM
NCC Executive Committee meeting, Part 2 (Room 303)
3:00 - 5:00 PM
3:30 - 4:30 PM
Yoga CPE session (Rooms 407 - 409). Co-sponsored by American Specialty Health, Inc. (Healthyroads.com)

Sunday, 10/20
6:00 - 7:00 AM
Yoga CPE session (Rooms 407 - 409). Co-sponsored by American Health Specialties, Inc.
9:00 AM - 3:30 PM
Product MarketPlace
5:30 - 6:30 PM
Yoga CPE session (Rooms 407 - 409). Co-sponsored by American Health Specialties, Inc.
6:30 - 8:30 PM
Networking reception with NCC/DBC/NE/students (2nd floor of Union League Club: 4 blocks from convention center). Sponsored by Nature Made Nutritional Products.

Monday, 10/21
6:00 - 7:00 AM
Yoga CPE session (NOTE different place: Rooms 304 - 306). Co-sponsored by American Health Specialties, Inc.
6:15 - 7:30 AM
NCC-CV-Healthy Functional Foods business breakfast meeting co-sponsored by Eggland’s Best, International Tree Nut Council, Kashi Company, McNeil Nutritionals, Quaker Oats, Tropicana Products
9:30 - 11:30 AM
DPG showcase
1:30 - 3:00 PM
4:00 – 5:00 PM
Book Signing: NCC’s Ruth DeBusk will be signing copies of her book *Genetics: The Nutrition Connection* in the ADA Bookmart.
5:30 - 6:30 PM
Yoga CPE session (Rooms 407 - 409). Co-sponsored by American Health Specialties, Inc.

Tuesday, 10/22
6:00 - 7:00 AM
Yoga CPE session (Rooms 407 - 409). Co-sponsored by American Health Specialties, Inc.

See you there!

Awards and Accolades

The following NCC members have been recognized for their service to their community and or to the American Dietetic Association. Please join us in congratulating them.

**Barbara Ann Hughes**, PhD, RD, FADA. NCC Content Chair.

Barbara received the Southeast Regional Trustee Award at the National Association of Local Boards of Health (NALBOH), meeting in New Orleans on July 10, 2002. The award recognizes outstanding contributions of time and energy in supporting state and/or local public health issues.

Barbara Ann also received the 2002 Women in Business awards, given by The Business Journal on August 8, 2002 in Raleigh, NC because of distinguished career and exemplary community service.

**Lynn Hoggard**, Media Excellence

**M. Patricia Fuhrman**, Excellence in Practice Awards for Clinical Nutrition
Introduction

Two years ago NCC launched a series on genetics and its growing importance to nutrition therapy. The series began with a CPE article that discussed the emerging awareness of the connection between genetics and nutrition therapy and provided an overview of fundamental genetic principles and terminology. This article also included a variety of conditions in which genetics played a prominent role in developing effective nutrition therapies.

The past two years have seen major advances in genetic research and its growing importance to health care. The driving force has been the Human Genome Project, the original goal of which was to identify each nucleotide in the human genome. The Project has consistently exceeded its goals and has regularly expanded its vision to include goals that are directly applicable to understanding health and disease processes. Research now includes identifying the protein products of each gene and the functions of those proteins to the overall workings of the organism, uncovering the details of protein/protein interactions and understanding the mechanisms by which environmental signals are transmitted to the DNA to effect changes in genetic outcomes.

Current research effort is concentrating on details such as these, focusing on the least complicated situations before tackling more complex issues. A predicted early clinical application has been the use of DNA sequencing identification to determine an individual’s unique genotype, which is the arrangement of DNA nucleotides that distinguishes one member of a species from another member of the same species. In human beings such genotypic profiling is being used to develop diagnostic assays. For example, it is now possible to associate nucleotide sequences with a disease state or to determine an individual’s unique profile with respect to the genes that code for drug-metabolizing enzymes. These types of genetic assays form the basis for medical diagnoses that direct therapeutic decisions. Medical diagnostic and pharmacological applications are likely to continue to dominate the early on clinical applications of genetic research.

In contrast, advances in applying genetics to nutrition therapy have been much slower but are being driven by the advances in medical diagnostics. We are fast approaching the time when it’s possible to analyze the genetic material of individuals and determine the diseases for which they’re susceptible. Nutrition professionals should expect clients to come to with genotypes in hand and for those diseases that are diet-and-lifestyle-related, we will need to design a therapeutic approach that will at least lower their susceptibility—if not prevent disease development altogether. It’s situations like these where nutrition professionals will be essential. As nutrition research and genetic research continue to progress and the interaction between nutrients and genes becomes better understood, expect gene-directed therapeutic approaches to become commonplace and an ever-expanding set of research-based information to be available upon which specific therapies can be designed. The nutrition professional of the future will have the tools to be effective in preventing disease and in ameliorating existing disease. Genotypic profiling will provide the “heads up” data for preventing disease or for differentiating among several disorders that may manifest similarly but respond differently therapeutically. A basic understanding of genetics and a thorough understanding of biochemistry and metabolism and of how nutrients can be used to alter genetic outcomes will be essential in designing targeted nutrition therapies.

In this up date the focus will be on reviewing fundamental genetic principles of particular importance to using gene-directed nutrition therapy, on providing background information on technologies commonly used in nutrition-related research and on exploring expected applications of genetics to nutrition therapy. For a more thorough review of basic genetic principles or of the genetics-nutrition connection, readers can refer to the list of additional resources found at the end of this article. Here the focus is on updating nutrition professionals on where the field of gene-directed nutrition therapy stands at present and on developing a framework of the types of therapeutic approaches that are expected. The omega-3 fatty acids have been chosen to illustrate some of the key approaches.

Genetic Basics

The genetic material is composed of DNA with its four component nucleotides: adenine (A), cytosine (C), guanine (G) and thymine (T). DNA contains the information to make all of the proteins that carry out the work of the cells. Various types of proteins are needed: enzymes, transporters, receptors, hormones, communicators, structural proteins, antibodies and so on. Each individual’s unique information is encoded in the sequence of the four nucleotides. The decoding process is stepwise, with the information in DNA being transcribed into messenger RNA (mRNA) and then translated into the amino acid sequence of the encoded protein.

Not all of the DNA encodes information that results in a protein being synthesized. The sequences of nucleotides that do code for proteins are called genes and genes have a common organization. There’s the coding region itself that’s ultimately translated into protein. Upstream from the coding region is the regulatory region where the RNA polymerase attaches and initiates the process of transcribing the DNA into mRNA. Further from the initiation site are nucleotide sequences that are involved in enhancing or repressing transcription. These sequences bind protein transcription factors that can enhance the binding of the polymerase to the promoter and increase the rate of transcription and protein production or they can interfere with polymerase binding and thereby inhibit transcription. Transcription factors have two different binding domains: the DNA-binding domain and a transcription-activating domain, which binds other proteins or cofactors such as nutrients, hormones, metabolites and other such messages. Binding of a messenger molecule to a transcription factor changes its shape (conformation) and allows it to bind to the DNA and exert its positive or negative effect on gene expression.

Regulating gene expression by enhancing or repressing transcription is an important mechanism in an organism’s ability to respond to its environment. To do so, there must be communication between extracellular stimuli and the genetic material and this communication is mediated by a series of complex signaling cascades, a process called signal transduction. The end result of the signal transduction process is that information from the environment is communicated to the DNA in the interior of the cell and results in altered gene expression so that the amount of protein produced is increased or decreased.

Changes in the amount of a protein produced can occur at a number of levels, from changes in transcription rate to increased stability of messenger RNA (making it longer-lived) to post-translational processing of the protein into its active form. Regulating transcription is a major control point in gene expression and transcription factors are potent effectors of this process. These factors are of particular interest to nutrition professionals because several nutrients have the ability to bind to transcription factors and in this way, alter gene expression.

Gene-directed nutrition therapy is also called nutritional genomics and (continued on page 16)
nutrigenomics. The distinction between genetics and genomics has been confusing for many. Genetics is a field in transition, evolving as scientific progress is made. To some the term genetics refers to an earlier stage in the evolution of the field, a simpler time when the relationship between a gene and its effect was described as one gene, one protein, one disease. Genomics has a broader context encompassing all the genes in an organism, their interaction with each other, their interaction with the environment in which the organism finds itself and the interaction of the various proteins that are produced. It remains to be seen whether the term genomics will give way to genomics for everyday use. As one longtime genetic researcher remarked recently, ‘You say “to-may-to”; I say “to-mah-to”. For now, genetics and genomics are frequently used interchangeably. The key point is understanding that the genetic material underlies the biochemistry and metabolism of each organism and is directly linked to the functional abilities of an organism. Further, the organism has mechanisms for monitoring its environment, sensing signals that require a physiological response and transmitting those signals to the genetic material in order to bring about the needed response.

Key Genetic Technologies

Two technologies that are routinely used in genetic research that should be included within the basic genetics vocabulary of nutrition professionals are transgenic organism technology and diagnostic assays based on single nucleotide polymorphism technology.

Transgenic Organisms

One of the most useful systems for understanding human gene/protein/disease associations is the transgenic mouse, which is constructed using genetic engineering techniques. Laboratory mice are specially bred strains that have been studied extensively and are commonly used as model systems sufficiently similar to the genetic makeup of humans so that findings in transgenic mice can often be extrapolated to humans. The genetic material of laboratory mice is manipulated so that the mice have more than the usual amount of a particular gene (overexpression) or one or both copies of a gene have been mutated (or knocked out, hence the name knockout mice). The impact of this manipulation of the genes on the function of the organism (for example, biochemically, physiologically, behaviorally) is then observed. Experiments using transgenic mice, which are genetically altered mice, have provided valuable information about the function of many genes and how the expression of those genes is regulated.

As just one example of the effective application of a transgenic mouse model to gene-nutrient associations, the effect of omega-3 fatty acids on colon carcinogenesis was studied in this system. Protein kinase C beta II (PKCbetaII) is known to promote colon carcinogenesis in humans and it’s thought to do so by inhibiting gene expression of transforming growth factor beta receptor type II (TGFbetaRII) in the epithelial cells of the colon. Normally, transforming growth factor beta (TGF-beta) inhibits the growth of intestinal epithelial cells. This action requires the binding of TGF-beta to TGFbetaRII receptors. Transgenic mice in which PKCbetaII was overexpressed developed colonic hyperplasia, increased colon carcinogenesis and repression of TGFbetaRII receptor expression. Nutrition intervention with dietary omega-3 fatty acids inhibited colonic PKCbetaII signal transduction, which in turn released the inhibition on the expression of TGFbetaRII receptors and allowed inhibition of colonic cell proliferation by TGF-beta. These data suggest that the mechanism by which omega-3 fatty acids protect against colon cancer is through their action on PKCbetaII signaling.

In two unrelated but equally interesting experiments, knockout mice were used to examine the effect of the omega-3 fatty acid docosahexaenoic acid (DHA) in genetically-related diseases. In the first study, researchers investigated whether DHA could prevent the development of colon polyps in mice with a mutation in the adenomatous polyposis coli (APC) gene. Damage to this gene in humans is responsible for one of the more common forms of colorectal cancer. The control mice developed numerous polyps but the DHA-treated mice had significantly fewer polyps, suggesting the DHA can inhibit intestinal polyposis.

In the second study, individuals with cystic fibrosis (CF) had been reported as having deficient plasma omega-3 fatty acid levels. Researchers were interested in determining whether such deficiency was correlated with a defect in the cystic fibrosis transmembrane conductance regulator gene (CFTR) and if so, whether restoring DHA would improve the CF phenotype. Using knockout mice deficient for CFTR, the researchers found that the membranes of organs typically affected by CF had an imbalance in omega-3 and omega-6 fatty acids. When DHA was fed to these mice, the lipid imbalance was corrected and the phenotype improved.

The transgenic mouse system can also be used to ask questions about how dietary ingredients affect gene expression. Recently this system was used to investigate the mechanism by which dietary soy can protect against atherosclerosis. Scientists knew from cell culture work that certain peptides in soy stimulated the production of LDL receptors, presumably by increasing gene expression. Such a mechanism would explain soy’s hypocholesterolemic and antiatherosclerotic effects, but direct evidence was lacking. By using transgenic mice that lacked LDL receptors, researchers expected to find that soy was ineffective in preventing atherosclerosis. Instead, mice fed a control diet of casein/lactalbumin developed atherosclerosis as expected but those fed soy protein isolate did not. These data suggest that inhibition of atherosclerosis by soy protein is independent of the LDL receptor pathway.

Single Nucleotide Polymorphisms (SNPs)

A polymorphism is a common variation of a gene. Technically, to be considered a polymorphism the change must be common enough to occur in greater than 1% of a population. The change can involve one or many nucleotides in the DNA. If just a single base is changed, the polymorphism is referred to as a single nucleotide polymorphism or “SNP” (pronounced “snip”). SNPs are believed to be responsible for the subtle differences among members of a species; they’re what make us all human beings but quite different individually in terms of how we look, metabolize our food and so on.

SNPs are the basis for the disease diagnostic and genotypic profiling assays. Among the earliest applications of SNPs to health care has been the ability to determine the variant of key drug metabolizing enzymes in an individual. Many of the negative side effects of drugs that patients experience result from a mismatch between the drug and the genetically-determined metabolic machinery of the patient. Being able to determine an individual’s genotype allows the physician to decide whether a particular drug will be helpful to an individual, of no help or even harmful.

Ultimately SNPs can be used to distinguish variants in key metabolic enzymes and determine nutrients that would be most applicable, which will not only direct nutritional therapy but can potentially guide an individual in matching food choices to genetic capability. Before that point is reached however, researchers will need to
identify SNPs that pertain to metabolic enzymes and associate them with particular nutrients. For now, SNPs are being sought that correlate with susceptibilities to some of today’s major diet-and-lifestyle disorders, such as cardiovascular disease, diabetes and osteoporosis. Several have been identified and already at least three laboratories are offering genotype profiling with associated diet-and-lifestyle advice based on an individual’s genotype.

**Integrating Genetics Into Nutrition Therapy**

If genetic research continues to progress at its current rapid pace, the expectation is that nutrition professionals will soon be integrating genetics into therapeutic approaches. What kinds of useful findings are likely and how will nutrition professionals translate the findings into effective therapies? At this point we have more questions than answers, but it’s not too early to begin building a framework that gets us thinking about how to convert this research into useful applications. Studies are in progress that ask how nutrients, as food or dietary supplements, might be used to address metabolic limitations resulting from genetic defects or how nutrients communicate the need for alterations in gene expression. Predictable applications of gene-directed nutrition therapy occur at two levels: the biochemical/metabolic level where nutritional intervention can compensate for defective genes and their proteins and the DNA level where nutrients can alter gene expression in response to the organism’s needs. Just a few of the wide variety of the directions that gene-oriented nutrition research is taking are discussed below.

**Metabolic Applications**

Nutrients have long been used to compensate for defective enzymatic activity. Vitamin C is an obvious example; the lack of a single enzyme leads to an absolute requirement for this vitamin in humans. The omega-6 and omega-3 polyunsaturated fatty acids are essential for humans because of the lack of an enzyme that can incorporate a double bond beyond carbon nine in the fatty acid chain. Similarly, certain amino acids are essential. Each of these nutrients must be provided by the diet in sufficient quantities. Other familiar examples of the use of nutrition therapy to compensate for metabolic defects include therapies designed to prevent the accumulation of harmful metabolites. These defects include phenylketonuria, maple syrup urine disease, galactosemia and so on—the classical single gene disorders that affect metabolic pathways and for which nutrition therapy has long been helpful.

Researchers are also investigating more subtle changes where the genetic defect leads to altered rather than absent activity. As research into the connection between genes and nutrients progresses, it’s becoming obvious that although all humans may require a particular nutrient such as a particular vitamin, everyone does not require the same level of that vitamin. In fact, for some genetic constitutions, mega doses of particular vitamins may be required. This realization was thoughtfully put forth in an extensive review by Ames and colleagues. They examined some 50 human diseases in which a faulty gene resulted in a defective enzyme that had a decreased affinity for its nutrient cofactor. The affinity was sufficiently low that the rate of reaction of the enzyme was lowered to the point where it was not meeting the body’s needs and negative health consequences resulted. A high dose of the cofactor was required to restore enzymatic activity to normal levels. By so doing, the disease state was either relieved or greatly improved. This review underscores the need for nutrition therapy to take into account the genetically-determined needs of each individual.

Beyond the single gene disorders and their resulting metabolic limitations, nutrition therapy is being used for a variety of metabolic deficiencies or imbalances, some directly related to genetic defects and others not so directly. Examples include generalized approaches such as the use of omega-3 fatty acids to alter the lipid composition of cell membranes and enhance receptor-ligand binding or to decrease synthesis of pro-inflammatory eicosanoids in chronic inflammatory disorders. (A ligand is like the substrate for a receptor, the molecule that fits the receptor and causes a response, whether it’s to get transported across a membrane or trigger a signaling cascade from the outside of the cell to the interior.)

**Gene Expression Applications**

Another predictable type of gene-nutrient interaction is the role of nutrients as sensors that communicate environmental signals to the genetic material through their binding to transcription factors, which in turn can positively or negatively affect the rate of transcription of DNA into protein. In light of the importance of transcription factors to the regulation of gene expression, several lines of research are focusing on what nutrients affect transcription, the mechanism by which control is accomplished and the nature of the signaling cascades that ultimately translate the environmental stimuli into nutrient-associated changes in gene expression mediated through transcription factors.

Among the growing number of transcription factors that are directly related to nutrient regulation are the nuclear receptors, which include the peroxisome proliferator-activated receptors (PPARs). These are important factors in controlling gene expression and the omega-3 fatty acids are natural ligands that bind to the PPARs that in turn bind to the DNA and affect gene expression.

**Peroxisome Proliferator-activated Receptors (PPARs)**

The peroxisome proliferator-activated receptors (PPARs) are a family of nuclear transcription factors that belong to the steroid receptor superfamily. There are multiple isoforms of the PPARs encoded by different genes and active in different tissues. They function as lipid sensors and act to regulate lipid and lipoprotein metabolism, glucose homeostasis and cell proliferation and differentiation, particularly adipocytes and the formation of foam cells from monocytes. Like other nuclear receptors, the PPAR transcription factors require the binding of a ligand to the ligand-activating domain in order to enable the DNA-binding domain to bind tightly to the DNA and promote gene expression. The omega-3 and omega-6 fatty acids are among the natural ligands of these transcription factors. Synthetic ligands such as the fibrates and thiazolidinediones can also bind and are useful for treating dyslipidemia and dysglycemia.

Before the PPARs can bind to DNA however, they must first bind to the retinoid X receptor (RXR) to form a 2-subunit protein complex (“heterodimer”) of PPAR-RXR. RXRs are also ligand-activated transcription factors and bind retinoids, which are derived from retinol (vitamin A), another example of gene-nutrient interaction. Once the heterodimer is formed with the RXR and PPAR ligands attached, it can bind to the DNA. Binding causes increased gene expression related to fatty acid oxidation and decreased gene expression related to fatty acid synthesis. The PPARs also have a negative effect on the expression of proinflammatory genes that produce cytokines (inflammatory mediators), metalloproteases and acute-
phase proteins. The obvious application to nutrition is the potential for using essential fatty acids to modulate PPAR transcriptional control, both positive and negative. The omega-3 family of essential fatty acids already promotes anti-inflammation by serving as precursors for the synthesis of the anti-inflammatory eicosanoids. A second, enhancing effect could potentially be achieved by increasing the amount of omega-3 PPAR ligand to turn off transcription of the pro-inflammatory cytokine genes.

Sterol Regulatory Element Binding Proteins (SREBPs)

SREBPs are also transcription factors that belong to the steroid receptor superfamily. Two genes encode the three major isoforms. They regulate several genes involved in cholesterol homeostasis and fatty acid and triglyceride synthesis. These transcription factors are normally sequestered in the endoplasmic reticulum (ER). When cellular sterol levels drop, the SREBPs are released from the ER and enter the nucleus where they activate the transcription of various genes in the fatty acid and cholesterol metabolic pathways. Among the genes that the SREBPs regulate are delta-6-desaturase and fatty acid synthase. Delta-6-desaturase is a pivotal enzyme shared between the omega-6 and omega-3 pathways. The enzyme is under feedback inhibition by dietary, highly unsaturated fatty acids but by a different mechanism. In this instance omega-3 fatty acids have been found to suppress the expression of SREBP itself, thereby limiting the pro-transcriptional effect on fatty acid synthase. The SREBPs promise to be an interesting set of factors in that one of the isoforms (SREBP-1c) appears to be a major factor in increasing the expression of lipogenic genes in response to carbohydrate feeding. Practical applications may include the use of omega-3 fatty acids to suppress the lipogenesis that results from high carbohydrate diets.

References


Useful Overviews of Key Topics


(continued on page 19)


Ruth DeBusk, PhD, RD is a geneticist and registered dietitian who works in the area of gene-directed nutrition therapy as applied to digestive disorders and their associated cancers. She is the author of the forthcoming book Genetics: The Nutrition Connection to be released at the Food and Nutrition Conference and Exhibition in Philadelphia. Contact Dr. DeBusk at RDeBuskRD@aol.com or 850-562-3261

Questions:
T/F 1. Genetics is an important tool in the future of nutrition therapy.
T/F 2. The Humane Genome Project, the driving force behind genetics, is ahead of schedule.
T/F 3. A phenotype is the arrangement of DNA nucleotides that distinguishes one member of a species from another member of the same species.
T/F 4. Genetic assays make it possible to associate nucleotide sequences with a disease state or to determine an individual’s unique profile with respect to the genes that code for drug-metabolizing enzymes.
T/F 5. Advances in applying genetic information to the field of nutrition therapy have moved quickly.
T/F 6. Adenine (A), cytosine (C), guanine (G) and tyrosine (T) are the four component nucleotides of DNA.
T/F 7. The information in DNA is transcribed into messenger RNA (mRNA) and then translated into the amino acid sequence of the encoded protein.
T/F 8. Protein transcription factors enhance the binding of the polymerase to the promoter and increase the rate of transcription and protein production as well as interfering with polymerase binding and thereby increasing transcription.
T/F 9. Currently the terms genetics and genomics are used interchangeably.
T/F 10. Transgenic mice are mice that have been bred with either genes that over exhibit a certain characteristic or have a mutated gene (knock out mice) that is intended to mimic human disease states.

T/F 11. Single nucleotide polymorphisms (SNPs) involve a change in one or many nucleotides in the DNA are result in the uniqueness between members of a species.
T/F 12. Nutrition therapy will be unable to address single gene disorders and their resulting metabolic limitations.
T/F 13. PPARs and SREBPs are transcription factors that can have altered activity by various nutrients.
T/F 14. PPARs work independently to bind to DNA and promote gene expression.
T/F 15. SREBP-1c appears to be a major factor in increasing the expression of lipogenic genes in response to carbohydrate feeding.

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2002–2003 CONTACT INFORMATION

Sarah Harding Laidlaw, MS, RD, MPA
P.O. Box 23089
Glade Park, CO 81523–0089