

Glucosamine and Chondroitin Sulfate Study Results Announced



Dr. Clegg studies an x-ray of knee osteoarthritis.

Over 20 million Americans suffer from osteoarthritis (OA). This number is likely to double over the next two decades, as the population ages. People have become increasingly interested in CAM approaches that might slow OA's progression and reduce its pain, inflammation, and disability. NCCAM is sponsoring a number of studies in this area.

An Interest in CAM Approaches

There are conventional drug treatments that offer relief of OA pain, but they can pose problems. For example, nonsteroidal anti-inflammatory drugs (NSAIDs), a type of pain reliever, can cause gastrointestinal upset and bleeding. Also, there have been some reports of potential cardiovascular problems from the class of NSAIDs called COX-2 inhibitors (these block an enzyme in the body that stimulates inflammation).

In an interview with *CAM at the NIH*, Dr. Clegg explained why he became interested in doing the study: "I wanted to help my OA patients. I saw lots of them taking glucosamine and chondroitin sulfate alone or in combination, with no evidence to support their use. So we sought to answer the key question: Do glucosamine and/or chondroitin sulfate work to relieve the pain of osteoarthritis?"

Glucosamine and chondroitin sulfate are among the most sought-after CAM approaches for arthritis. Americans spent about \$730 million in 2004 on these products. According to the largest national survey so far of Americans' use of CAM, arthritis was among the top reasons the participants used CAM. In addition, glucosamine with or without chondroitin was among the top "nonvitamin, nonmineral, natural products" used.

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One of NCCAM's largest studies has found that, overall, glucosamine and chondroitin sulfate—alone and in combination—did not provide significant relief from pain of knee OA. However, a small group of participants with moderate-to-severe pain did experience significant relief from glucosamine combined with chondroitin sulfate.

NCCAM and the National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS), two components of the National Institutes of Health, funded this 4-year nationwide study known as the Glucosamine/chondroitin Arthritis Intervention Trial (GAIT). Researchers led by rheumatologist Daniel O. Clegg, M.D., of the University of Utah School of Medicine, Salt Lake City, conducted it at 16 sites across the United States. The results appeared in the February 23, 2006, issue of the *New England Journal of Medicine*.

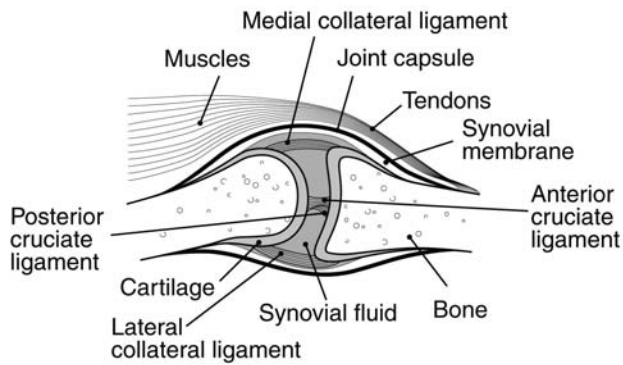
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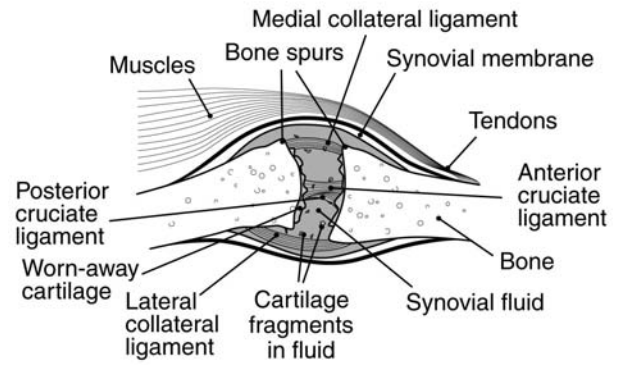


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Healthy Joint



Unhealthy Joint



Osteoarthritis...

- Is the most common form of arthritis
- Cost the American public over \$86 billion in 2004
- Is more common in women and in people who are older or obese

- Mostly affects cartilage—firm, flexible tissue that covers the ends of bones, keeps them from rubbing against each other, and absorbs impact
- Erodes cartilage
- Causes pain, swelling, stiffness, and sometimes disability

CAM at the NIH:

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A Closer Look at These Supplements

Both glucosamine and chondroitin sulfate are natural substances found in and around the cells of cartilage. For dietary supplements, glucosamine is usually obtained from the shells of shrimp, lobster, and crabs, and chondroitin sulfate from the cartilage of sharks and cattle. Both substances can also be made in the laboratory. They are sold individually, in combination with each other, and in other combinations.

Dietary supplements are not regulated by the U.S. Food and Drug Administration (FDA) in the same way as prescription drugs. Thus, Dr. Clegg's team took a novel approach (for a dietary supplement study) to increase the validity of their results. "We looked at the products on the market and were unable to identify products that met the pharmaceutical standards mandated by the trial," said Dr. Clegg. "Using current Good Manufacturing Practices, we developed glucosamine and chondroitin products that met FDA standards for pharmaceuticals."

The Study Is Launched

Over 1,500 people joined the study. All were age 40 or older and had OA of the knee, mild or moderate-to-severe knee pain, and a loss of cartilage in the affected knee. They were assigned at random to receive, for 24 weeks, either glucosamine alone, chondroitin sulfate alone, glucosamine and chondroitin sulfate combined, celecoxib, or a placebo (a "sham" treatment with no active ingredients).

When the study concluded, here is what the researchers found:

- Looking at the group of participants as a whole, there were no significant differences between any of the supplements tested and the placebo.
- For participants with mild pain, glucosamine and chondroitin sulfate alone or together did not provide significant relief compared with placebo.
- For a small group of participants with moderate-to-severe pain, glucosamine combined with chondroitin sulfate provided significant pain relief compared with placebo. However, because of this group's small size, the researchers noted that this finding should be considered preliminary and needs to be confirmed in further studies.

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First NIH Fellow in CAM Bioethics



Jon Tilburt, M.D., M.P.H.

Jon Tilburt, M.D., M.P.H., holds the first NIH Bioethics Fellowship in Complementary and Alternative Medicine, sponsored by NCCAM and the NIH Clinical Center's Department of Clinical Bioethics.

Dr. Tilburt is a graduate of Vanderbilt University School of Medicine, did his residency in internal medicine at the University of Michigan, Ann Arbor, and held a previous fellowship at the Phoebe R. Berman Bioethics Institute, Johns Hopkins University. He answered a few questions from *CAM at the NIH*.

What is bioethics?

Bioethics is the systematic study of moral questions (such as, what is or is not permissible to do and under what circumstances?) that arise in the context of the life sciences, health research, and medical care.

What do you hope to accomplish during your fellowship?

I hope to gain further skills in analyzing and presenting ethical arguments and in doing research related to ethical questions in CAM. In my experience with patients, I try to combine in every decision the patient's ethical values and the science. This fellowship position is an opportunity to learn more about how doctors, patients, and scientists can better combine science and ethical values in decisions related to CAM.

What are some prominent ethical issues involving CAM in clinical care?

A few examples are

- **Communication issues**, especially disclosure of CAM use. Patients should feel comfortable talking about CAM with their doctors, but doctors need to be

better informed and comfortable talking about CAM, too.

- **Integrating values with science.** In their daily practice, how can doctors respect choices and desires of their patients while respecting and conveying the importance of science?
- **Relationships between professionals.** To what degree are conventionally trained physicians open-minded toward CAM practitioners and treating them as valued partners in patient care?

As an example of a clinical situation, I had a patient to whom I prescribed medicine for a droop in his smile (called Bell's palsy), hoping to improve his smile. He never filled the prescription because he was worried about the side effects. When he came back to me, he had decided to go to a traditional Chinese medicine practitioner to get some herbs instead. In the case of his condition, neither conventional nor CAM treatments are greatly effective; but the treatments I prescribed had no chance of working because he had judged the risks to be too great, and I was not aware of safe CAM options for his condition. If we had discussed risks and benefits in more detail, we might have been better able to address his concerns and identify a treatment whose risk/benefit profile was more tolerable for him.

A January 2005 report from the Institute of Medicine explored a full range of ethical issues in CAM and has helped us think about some of these questions. [To find out more, see www.nap.edu/catalog/11182.html.]

What are some examples of these issues in research?

Most of the following are not unique to CAM, but CAM offers a good opportunity to revisit some of the unsettled ethical questions:

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New NACCAM Members Appointed

U.S. Health and Human Services Secretary Michael Leavitt has appointed two new members to the National Advisory Council for Complementary and Alternative Medicine (NACCAM):

Joan E.B. Fox, Ph.D., is a professor in the Department of Molecular Cardiology at the Cleveland Clinic's Lerner Research Institute. Among Dr. Fox's research interests are the mechanisms in the body by which cardiovascular diseases develop; the effects of psychological stressors on cells; and Reiki, an energy-medicine practice that originated in Japan.

Ted J. Kaptchuk, O.M.D., L.Ac., is assistant professor of medicine at Harvard Medical School and associate director of the Division for Research and Education in Complementary and Integrative Medical Therapies at Harvard's Osher Institute. He has researched widely in the field of CAM, including on therapies from traditional Chinese medicine and on the placebo effect. ❖



Calendar of Events

This calendar lists events on CAM in which NCCAM or other components of NIH are sponsors or participants and includes information available at press time.

April 2006

Distinguished Lectures in the Science of Complementary and Alternative Medicine:

April 26, 11 a.m.

"Neurobiological Correlates of Acupuncture." *Speaker:*

Bruce R. Rosen, M.D., Ph.D., Director, Athinoula A. Martinos Center for Biomedical Imaging at Massachusetts General Hospital, and Professor, Harvard Medical School.

Sponsor: NCCAM. *Location:* Masur Auditorium, Building 10, NIH, Bethesda, Maryland. This event will also be Webcast at www.videocast.nih.gov and archived for later viewing.

May 2006

North American Research Conference on Complementary and Integrative Medicine:

May 24-27. *Location:*

Edmonton, Alberta, Canada.

See www.imconsortium-conference2006.com.

June 2006

Meeting of the National Advisory Council for Complementary and Alternative Medicine:

June 8.

Location: Building 31, C Wing, 6th Floor, Conference Room 10, NIH, Bethesda, Maryland. See nccam.nih.gov/about/advisory/naccam/.

First NIH Fellow in CAM Bioethics

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- When is a therapy potentially beneficial enough to test in people?
- When are we confident a CAM therapy can be safely tested in people?
- What do we do when the way of reasoning behind a CAM treatment does not make sense to our way of scientific theory, but a long history of practice and, in some cases, a small body of research suggest that the treatment might be safe and possibly beneficial? Should we require that a CAM treatment "make sense" to us before we study it or use it?
- How can we help the research supervisors at hospitals and medical schools to fairly evaluate CAM studies?

What do you think the outlook is for integrating conventional medicine and CAM therapies in modern medical practice in the United States?

It depends. I am cautiously optimistic about a limited version of "integration."

On the one hand, it is easy to oversell some of the differences between CAM and conventional medicine. Most CAM and conventional providers are committed to do what is in the patient's best interest, even if the bodies of knowledge are different. This shared commitment may provide a common ethical ground for some integration, in both research and practice.

Also, Americans are very pragmatic. Even if they don't always agree on the theory behind something, if it seems to work (by accepted standards) they are willing to be flexible. I think this pragmatism includes large segments of CAM and conventional providers and characterizes many groups of patients.

We need to continue dialogue on what "integration" means. If it would mean wholesale acceptance and taking over of diverse health practices, I would be opposed. However, if one thinks of integrative medicine as a way to offer comprehensive whole-person medicine, which might include referrals for CAM treatments that have been proven safe and effective, I am more optimistic.

It can be difficult for many doctors in conventional medicine to find productive ways to discuss CAM therapies with their patients, and vice versa. What are some things that need to happen for this to improve?

Doctors forget things at times, not just to ask about CAM. I am hopeful that computers and electronic records will be able to help doctors by gathering information about CAM therapies and their patients' use of CAM as if these were vital signs. Then, if physicians can become more knowledgeable about CAM, patients might think it is worth discussing CAM with their doctor. ❖

New Resources

The following new NCCAM publications are available on the Web or from the NCCAM Clearinghouse (see pg. 2):

- *Meditation for Health Purposes* (nccam.nih.gov/health/meditation/)
- *An Introduction to Reiki* (nccam.nih.gov/health/reiki/)
- *Herbs at a Glance: Dandelion* (nccam.nih.gov/health/dandelion/)

NCCAM's Online Continuing Education Series has added two new lectures, originally delivered at NIH in 2005: (1) "Is Spirituality Good for Your Health?" by Anne Harrington, Ph.D., Professor for the History of Science, Harvard University, and (2) "Integrative Medicine: A Foundation for Prospective Health Care," by Ralph Snyderman, M.D., Chancellor Emeritus at Duke University and Professor of Medicine at Duke University School of Medicine. Access is free at nccam.nih.gov/videolectures/, with continuing education credits available. ❖

The Irresistible Treat That Might Help Resistance

Chocolate is irresistible—or nearly so—to many people. Could it possibly help with a health problem involving insulin resistance and blood sugar? **Michael Quon, M.D., Ph.D.**, Chief of the Diabetes Unit in NCCAM’s Division of Intramural Research, is trying to find out.

He and his colleagues have begun a study on whether dark chocolate improves insulin resistance. In a person who has insulin resistance, his body has a harder time than other people’s bodies in using glucose, a simple sugar made from carbohydrates during digestion. Insulin resistance usually has no symptoms, but may lead to diabetes. People with obesity, high blood pressure, heart disease, and/or other conditions are the ones who most often have it; getting older, lack of exercise, and a family history of diabetes can raise the risk.

CAM at the NIH asked Dr. Quon some questions about the study.

Q: What evidence is there so far that dark chocolate may have an effect on insulin resistance?

A: Right now there is very little. However, there are a number of published clinical studies showing that dark chocolate may improve blood pressure and blood vessel function in people with hypertension (high blood pressure). This may be due to a substance in cocoa called epicatechin (pronounced “eh-pih-kah-TEK-in”). Studies in our lab and others suggest that insulin resistance may explain the link between hypertension and diabetes. It’s interesting that some conventional drugs for treating hypertension also improve insulin resistance, and vice versa. Our idea is that the epicatechin in dark chocolate may lower blood pressure and improve

insulin resistance at the same time and in similar ways.

Q: Can you tell us about the preparation used in the study? Why did you use dark chocolate rather than milk chocolate?

A: The cocoa we are using is highly enriched with epicatechin. Participants consume about 900 mg of it in a cocoa drink, which has about 240 calories. In the placebo (or inactive substance) part of the trial, participants drink a cocoa that has not been enriched this way. Other forms of chocolate—such as milk chocolate—do not contain as much epicatechin as dark chocolate.



© Jose Antonio Santiso

Dark chocolate

Q: People might jump on the idea that chocolate may actually have health benefits. Is there enough evidence there for people to eat more chocolate? And are there any concerns about unwanted side effects, such as weight gain?

A: There is growing evidence that dark chocolate may have important health benefits. However, we need to find out more—it is too early to recommend that people consume more chocolate for health purposes. Also, the chocolate that is commercially available does not have consistent amounts of epicatechin, and thus consumers have no way of knowing



Dr. Quon (left, with Dr. Edward Li and Dr. Michelle Vincent) is leading NCCAM’s dark chocolate study.

which commercial chocolate, if any, may be beneficial.

Any food that has beneficial health effects may also cause weight gain if you eat too much of it. Another potential concern with chocolate is that the cocoa butter contains fats that may raise cholesterol levels. However, the major type of fat in chocolate—stearic acid—does not affect cholesterol levels, so this may be less of a concern.

At press time, this study was still recruiting volunteers within traveling distance to the NIH Clinical Center in Bethesda, Maryland (see www.clinicaltrials.gov/show/NCT00099476 or contact the NCCAM Clearinghouse, pg. 2). For more about insulin resistance, see www.diabetes.niddk.nih.gov/dm/pubs/insulinresistance. ❖



NIH has begun requiring all competing research grant applications to be submitted **electronically** via the Web portal Grants.gov (www.grants.gov), using Form SF-424 (Research and Related, or R&R, application). These changes began in December 2005 and are being phased in by grant mechanism (type of grant). See era.nih.gov/electronicreceipt.

New CTSA Program Launched

NIH has started a new program, originating from both the NIH Roadmap (nihroadmap.nih.gov) and community input. The **Institutional Clinical and Translational Science Awards (CTSA)** program will speed up advances in CAM and conventional medicine. These CTSA's will create "academic homes for the discipline of clinical and translational science" at academic health centers across the United States. Through partnerships between institutions and disciplines, the grants will support development of new methods and approaches, integrated resources, and training/mentoring. The application deadline for a planning CTSA has passed (March 2006), but there will be annual opportunities to apply for institutional CTSA's. To find out more, see nccam.nih.gov/research/announcements/premeeting.htm.

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Glucosamine and Chondroitin Sulfate Study Results Announced

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- Participants taking celecoxib experienced significant pain relief, as expected, compared with placebo. Celecoxib also provided faster relief than any of the supplements (when the supplements provided relief).

"Side effects of the supplements were minimal and mild, such as an upset stomach," said Dr. Clegg. "But a much longer period of study will be needed to fully determine the long-term effects of these products, how they work in the body, and what explains their possible clinical benefits."

Dr. Clegg is overseeing a continuing study of about one-half of the GAIT participants to find out whether these same treatments can reduce or stop the progression of OA. These results are expected in about a year.

Translating the Results Into Practice

CAM at the NIH asked Dr. Clegg what he thinks these results mean for people with OA. "Conventional treatments such as prescription drugs, graded exercise, weight loss when appropriate, physical therapy, and patient education will remain key therapies for OA," he replied. "Patients



© Frances Twitty

Water aerobics and swimming are two types of exercise that can be helpful for OA.

should talk to their health care provider about all their treatment options." He added that if they have substantial pain and are interested in glucosamine and chondroitin sulfate, they should discuss with their provider whether those

supplements would be appropriate. "People need to remember that supplements are not regulated like prescription drugs, and product quality can vary," he noted.

Stephen E. Straus, M.D., Director of NCCAM, views the study as a landmark in NCCAM's short history. "The year 2006 marks our seventh anniversary of building a portfolio of rigorous research on CAM therapies," said Dr. Straus. "This is our largest study to date. It demonstrates our commitment to study dietary supplements and other CAM therapies with well-designed research, to find out what works and what does not for compelling needs in public health. We now know that this supplement combination may offer an additional option to some patients, although much more remains to be learned about glucosamine and chondroitin sulfate."

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- National Institute of Arthritis and Musculoskeletal and Skin Diseases. *Questions and Answers About Arthritis and Rheumatic Diseases*. National Institute of Arthritis and Musculoskeletal and Skin Diseases Web site. Accessed at <http://www.niams.nih.gov/hi/topics/arthritis/artrheu.htm> on February 28, 2006.

For More Information

- Additional details about GAIT can be found on the NCCAM Web site at nccam.nih.gov/research/results/gait/.
- The NCCAM Clearinghouse (see pg. 2) provides information on CAM and on NCCAM, including publications and searches of Federal databases of scientific and medical literature. The Clearinghouse does not provide medical advice, treatment recommendations, or referrals to practitioners.
- To contact the National Institute of Arthritis and Musculoskeletal and Skin Diseases Clearinghouse, call 1-877-226-4267 (toll-free in the U.S.) or go to www.niams.nih.gov. ♦

"Research Roundup" presents examples of NCCAM-funded research recently published in peer-reviewed journals listed in the National Library of Medicine's PubMed database.

Saw Palmetto for BPH

Benign prostatic hyperplasia (BPH), also known as enlargement of the prostate, is a common complaint among older men. A plant called saw palmetto (*Serenoa repens*) is a popular CAM treatment for it. Researchers at the Osher Center for Integrative Medicine at the University of California, San Francisco, led by Stephen Bent, M.D., conducted a year-long clinical trial on the effects of saw palmetto on lower-urinary-tract symptoms of BPH. Two hundred and twenty-five men older than age 49 who had moderate-to-severe symptoms of BPH were randomized to receive either saw palmetto extract or a placebo. The investigators found no significant difference in symptoms or other outcome measures between the saw palmetto and placebo groups. The extract was generally well-tolerated. The report appeared in the February 9, 2006, issue of the *New England Journal of Medicine*.



© Larry Allain, USGS-NWRC

Yoga for Chronic Low-Back Pain

Chronic low-back pain (LBP) is a common reason that people seek medical care. Calling current treatment options "only modestly effective," Karen Sherman, Ph.D., M.P.H., and colleagues of the Group Health Cooperative in Seattle conducted a study of yoga (a mind-body therapy that involves both physical exercise and mental focus) for LBP. They chose the style of



© Krzysztof Chystowski

yoga called viniyoga, noting that some other styles may be inappropriate for back pain. Yoga was compared with two other treatments: therapeutic exercise classes and reading a self-help book. The three groups had 101 participants in total. Those in the yoga and exercise groups participated in instructor-led classes for 12 weeks and continued to practice on their own for 14 more weeks. At the end of the first 12 weeks, the LBP symptoms of all three groups had improved. Over the last 14 weeks, however, symptoms continued to improve in the yoga group only; symptoms in the other groups worsened.

The authors found that viniyoga is a safe and effective treatment for chronic LBP. The study appeared in the December 20, 2005, issue of the *Annals of Internal Medicine*.

Could Meditation Help Age-Related Mental Decline?

The cerebral cortex of the brain is involved in many complex functions, such as thought, sensory perception, language, and emotion. It thins with age, and some scientists think this may be a factor in age-related mental decline. An article in the November 28, 2005, issue of *NeuroReport* describes a preliminary study of the cortical (i.e., cortex) thickness in 20 adults who practice a type of meditation called Buddhist Insight Meditation. The researchers, led by Sara Lazar, Ph.D., of Massachusetts General Hospital, also studied a control group of 15 participants who had no meditation or yoga experience. The researchers found that cortical regions responsible for attention and sensory processing (such as auditory and visual) were thicker in meditators than in controls. In older participants (aged 40 to 50 years), only the meditators showed cortical thickness that corresponded to that of younger participants (aged 20 to 30 years) in a region that carries out higher mental, emotional, and behavioral functions.

The authors concluded that meditating regularly may change the brain's structure in ways that are important to some mental functions and could help slow declines related to aging. ❖

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Recent Announcements

Visit nccam.nih.gov/research/announcements/active.htm for more information on these and other NCCAM-funded opportunities.

Research

PAR-06-108: Developmental Centers for Research on Complementary and Alternative Medicine: Phase I Sponsor: NCCAM. These awards will encourage development of preliminary CAM research projects through partnerships between organizations focusing on CAM practices and conventional medicine institutions.

Four recent NIH **Program Announcements** invite eligible small businesses in the United States to apply for **Small Business Innovation Research** grants or **Small Business Technology Transfer** grants.

Training and Career Development

PA-06-133: NIH Pathway to Independence (PI) Award (K99/R00)

Sponsors: NCCAM and other components of NIH. This award will provide up to 5 years of support for highly promising postdoctoral research scientists.

PA-06-001: Mentored Research Scientist Development Award (K01)

Sponsors: NCCAM and other components of NIH. This initiative will support intensive, supervised career development in a variety of biomedical, behavioral, and clinical research fields. ❖

CAM at the NIH:

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NCCAM Awards Director's Fellowships for CAM Research

NCCAM has named the first two recipients of the NCCAM Director's Fellowship in Complementary and Alternative Medicine (CAM) Research from an international pool of candidates. They will prepare for careers as independent CAM investigators through 2 years' support of clinical research (studies in people), translational research (studies that bring new findings from the laboratory to clinical practice), and/or laboratory research.

"This innovative fellowship is one way that NCCAM is recruiting and training the next generation of CAM researchers. It also exemplifies our approach to integrative medicine by fostering CAM research across NIH," said Stephen E. Straus, M.D., Director of NCCAM.

The fellows will join the NIH Intramural Research Program and conduct research on CAM topics, with senior scientists from institutes and centers across NIH as their mentors. They are

- **Patrick P. McCue, Ph.D.** Dr. McCue received his doctorate in molecular and cellular biology from the University of Massachusetts in 2004. He will study the effects of chemical compounds from botanical extracts on cancer cell death under the leadership of James Phang, M.D., of the National Cancer Institute.
- **Marni N. Silverman, Ph.D.** Dr. Silverman earned her doctorate in neuroscience from Emory University in 2005. With Esther Sternberg, M.D., of the National

The National Library of Medicine's MedlinePlus Web site now includes an A-Z reference guide to herbs and other dietary supplements. See www.nlm.nih.gov/medlineplus/druginfo/herb_All.html.

Institute of Mental Health, she will study glucocorticoid resistance, a physical process that contributes to variations in people's responses to stress.

The Director's fellowship is funded in part by the Prince of Wales Foundation, which supports a wide range of causes worldwide, including research on CAM and integrative care. ❖