Focused on Excellence

An NCCAM Update

Russ Mason, M.S.

Fifteen (15) years ago alternative and complementary therapies were not only marginalized as methods of care but there also was a great deal of suspicion and distrust within the allopathic medical community regarding their efficacy and safety. As Ralph Moss, Ph.D.—a founding member of the Office of Alternative Medicine (AOM)—stated: “Before we started, do you know what alternative medicine meant? Tijuana! No university or medical school would touch alternative medicine with a ten-foot pole. Look where we are today!”¹

Since its founding in 1992, the National Center for Complementary and Alternative Medicine (NCCAM; the AOM’s successor) has provided more than \$200 million to fund research into alternative and complementary therapies, including support for clinical trials on alternative and complementary medicine (ACM) protocols.

In October 2005, the NCCAM announced the funding of three new U.S. Centers of Excellence for the study of ACM. Two of the three centers—those at Mount Sinai Hospital, New York City, and the University of Maryland, Baltimore—will explore therapies used in Traditional Chinese Medicine (TCM), including acupuncture and Chinese herbal mixtures. The third Center of Excellence—at Temple University, Philadelphia, Pennsylvania—will study an innovative and relatively unexplored type of energy medicine called millimeter wave therapy.

When he announced the new centers, Stephen E. Straus, M.D., the NCCAM’s director, stated: “We are excited by the addition of these centers to our research program and the unique collaborations and approaches they bring to studies of [ACM] practices. [These] centers will strengthen our research portfolio for major health problems.”²

The three Centers of Excellence each have been promised 5 years of financial support for their research initiatives; in turn, the researchers will strive to identify the potential benefits and underlying mechanisms of the respective ACM practices being studied.

The Center for Mechanisms Underlying Millimeter Wave Therapy

Millimeter wave therapy is a noninvasive, painless form of energy medicine that is applied to the skin via a small electronic device about the size of a thick book. The signal is directed to an

appropriate area with a small hose. At the present time, the only site in the United States to have such a device is Temple University Medical Center, although the device is widely used in Eastern Europe.

Marvin C. Ziskin, M.D., a professor of radiology and medical physics at Temple University, first learned about the therapy in the early 1990s when he was visiting the former Soviet Union. Richard J. Fox—the chairperson of the Temple University board of trustees at that time—was with Dr. Ziskin. Mr. Fox was impressed with millimeter wave therapy and ended up funding the establishment of the Center for Biomedical Physics at the University in 1992. Dr. Ziskin, who says he has a “skeptical personality,” was unsure about the therapy’s effectiveness because the reports he had seen only cited positive results. However, his interest in millimeter wave therapy was piqued.³

“Although there were many studies of millimeter wave therapy in the Russian literature, their research doesn’t go through the same scrutiny as ours,” Dr. Ziskin said.³ And so, during the 10 years after his first learning about the therapy, he and his international team of scientists examined the glowing claims via critical scientific evaluation. The scientists’ goal was to find out how millimeter waves affect biologic conditions and to discover if there were side-effects that had not been documented.

Millimeter waves are similar to microwaves although millimeter waves are somewhat shorter and have a higher frequency. While microwaves have somewhere around an 11-cm wavelength and a 2.5-gigahertz (GHz) frequency, millimeter waves measure between 4 and 7 millimeters and have a frequency of between 40 and 60 GHz.

When used as a therapy, millimeter waves are applied at such a low intensity that the patient has no sensation of pain. The therapy generally consists of placing the millimeter-wave generator at the surface of the skin, where the device is kept for approximately 15 minutes; this is done once a day, every day, for 2 weeks, according to Dr. Ziskin.

“The Russian medical community is extremely welcoming of new technologies such as the millimeter wave technology, because pharmaceutical supplies are not always available. They are desperate to help patients,” Dr. Ziskin noted. In addition, it seemed from the reports coming out of that country that millimeter wave therapy did indeed help patients. “These reports—to a Western physician—were astoundingly good; for a wide range of conditions, the Russians were claiming 95 percent cure rates.”

To Contact the Principal Investigators

Marvin C. Ziskin, M.D.

Center for Biomedical Physics
Temple University School of Medicine
3420 North Broad Street
Philadelphia, PA 19140
Phone: (215) 707-4259
Fax: (215) 707-4324
E-mail: ziskin@temple.edu

Brian M. Berman, M.D.

Center for Integrative Medicine
Kernan Hospital Mansion
2200 Kernan Drive,
Baltimore, MD 21207-6697
Phone: (410) 448-6871
Fax: (410) 448-6875
E-mail: bberman@compmed.umm.edu

Xiu-Min Li, M.D.

Center For Immunobiology
Mount Sinai Medical Center
One Gustave L. Levy Place
New York, N.Y. 10029
E-mail: xiu-min.li@mssm.edu
Phone: (212) 241-5548

Dr. Ziskin's inquiries about the efficacy of millimeter waves have already begun to support at least some of the Russians' claims. "We have seen positive results in pain relief," he said, adding that patients in acute pain and those with some forms of chronic pain can benefit from millimeter waves. He also said: "We are now looking into the relief of neuropathic pain, which arises from nerves being damaged. This condition is painful and difficult to treat, so we are hopeful that this therapy might prove beneficial as a treatment for neuropathic pain. We found that millimeter waves did increase cytokine and endogenous opioid release."

The nature of millimeter wave theory is not yet fully understood despite a variety of both in-vitro and in-vivo studies. For example, the specific mechanisms by which millimeter wave irradiation enhances T-cell function is not yet clear, and yet T-cell immunity has been seen to improve with therapy.

In some instances, studies showed that pretreating mice with naloxone, a narcotic antagonist, may block the antipruritic and hypoalgesic effects of millimeter wave therapy. This suggests that endogenous opioids are released by the millimeter waves, and the resulting hypoalgesia is a direct result of such irradiation. Despite the obvious therapeutic effects, it remains unclear as to how the keratinocytes, the main constituents of the epidermis, absorb the millimeter wave energy.³

"We found that millimeter waves reduce pain in laboratory animals, stimulate the immune system, and slow the progression of skin melanomas, without damage to the skin or other harmful side-effects. It is a painless, noninvasive, easily tolerated therapy," said Dr. Ziskin.³

The new grant will fund three major projects at the University:³

1. Stanislav Alexeev, Ph.D., will lead a team to examine how millimeter waves interact physically with the skin. This informa-

Marvin C. Ziskin, M.D., Temple University.

tion is intended to help determine the intensity and frequency of millimeter waves that may work best for treating different health conditions.

2. Mahendra Logani, Ph.D., will lead a team to investigate the mechanisms by which millimeter waves and anticancer pharmaceuticals affect the immune system. The researchers hope that the findings that emerge from the study will be used to make chemotherapy more effective and more tolerable via a combination of pharmaceuticals and

millimeter wave therapy.

3. Alexander Radziewsky, M.D., Ph.D., will lead a team to explore how well millimeter wave treatment can relieve nerve pain and intense itching.

"We want to find out exactly what happens in the body during and after exposure to millimeter waves, an obligatory step before the treatment can be introduced in people," said Dr. Ziskin.³ Eastern European doctors apply millimeter waves directly to skin lesions and acupuncture points. It is also common to beam millimeter waves onto a diseased organ or a painful joint.

"Applying the waves to points on the skin with the highest density of nerves appears to work best. Using this approach, under strict double-blind conditions, we've produced evidence of pain relief in experimental animal models as well as in a small group of human volunteers," Dr. Ziskin stated.³

Dr. Ziskin has expressed optimism regarding millimeter wave therapy: "I was initially highly skeptical of millimeter waves doing anything," he said and then added "but now I am convinced—at least by the laboratory experiments—that there are some true effects. Will this be clinically useful? I think it will find its place in the range of treatments that are available."

And, he observed: "The biological effects of millimeter waves are real."³

The Center for Arthritis and Traditional Chinese Medicine

"More than 20 million Americans have osteoarthritis," says Stephen I. Katz, M.D., Ph.D., director of the National Institute of Arthritis and Musculoskeletal and Skin Diseases of the National Institutes of Health. "This disease is one of the most frequent causes of physical disability among adults. Thus, seeking an effective means of decreasing osteoarthritis pain and increasing function is of critical importance."⁴

That is the task that has been undertaken by the NCCAM Center of Excellence at the University of Maryland School of Medicine, associated with the Center for Integrative Medicine at

the Kernan Hospital Mansion, Baltimore, Maryland. The Center for Arthritis and Traditional Chinese Medicine will use its NCCAM funds to investigate the use of TCM approaches—specifically, acupuncture and herbs—in the treatment of arthritis. Specifically, the center's researchers will conduct a clinical trial of an 11-herb Chinese formula known as *Huo-Luo-Xiao-Ling* (HLXL) for treating osteoarthritis (OA) of the knee, assess acupuncture's effects on inflammatory pain in an animal model, and study the efficacy of HLXL in an animal model of autoimmune arthritis.

Heading this effort will be Brian M. Berman, M.D., a professor of family medicine and director of the Center for Integrative Medicine. Originally trained in family medicine and pain management, as well as in complementary medical approaches such as acupuncture, Dr. Berman has dedicated his career to evaluating the efficacy, safety and cost effectiveness of alternative and complementary therapies.

Dr. Berman is particularly noted for his landmark research study, published in the *Annals of Internal Medicine*,⁵ which proved acupuncture to be a safe and effective therapy in the treatment of arthritis. The study, one of the largest clinical trials on acupuncture ever done, was funded in part by NCCAM and has been hailed as a model for how scientific testing can evaluate alternative therapies. Commenting on the Berman study, Dr. Straus stated: "For the first time, a clinical trial with sufficient rigor, size and duration has shown that acupuncture reduces the pain and functional impairment of osteoarthritis of the knee."⁴

The proposal involves three projects that will investigate the safety, efficacy and mechanism of action of acupuncture and a traditional Chinese herbal formula used to treat arthritis.⁶

1. A randomized, placebo-controlled, double-blind, phase II, dose-escalation clinical trial to find an optimally effective, safe, and tolerable dosage of HLXL Dan, for use as an adjunct to treatment of patients who have OA of the knee.
2. A trial to investigate the mechanism of action of electroacupuncture (EA), which was previously shown by investigators at the Center for Integrative Medicine to be safe and effective for treating knee OA. (See box entitled Electroacupuncture.)⁷ This study is based on prior studies⁸ that show that EA produces a prolonged anti-inflammatory and antihyperalgesic effect. This project is directly based on the hypothesis that the mechanism of EA's therapeutic action originates with the release of neuropeptides from the hypothalamus–pituitary–adrenal gland axis.

Electroacupuncture

Electroacupuncture is similar to traditional acupuncture because the same meridian points are stimulated by needles during treatment. In electroacupuncture, however, the needles are attached, via small clips, to a device that generates continuous electric pulses. The device is used to modulate the frequency and intensity of the impulse being delivered relative to the condition being treated.

Electroacupuncture uses two needles at a time so that the impulses can pass from one needle to the other. Several pairs of needle can use for stimulation simultaneously are used typically for no more than 30 minutes at a time.^a

^aFrom ref. 7.

3. An investigation of the antiarthritic effect of HLXL that will test the hypothesis that "the protective/beneficial effect of HLXL in arthritis involves selective modulation of the level and type of (Th1/Th2) T-cell responses to the pathogenic or regulatory determinants within the disease-related antigen (mycobacterial hsp65–Bhsp65)."⁶

The Center for Integrative Medicine—and thus the Center for Arthritis and Traditional Chinese Medicine as well—will be helped by three cores: (1) a Data Management & Statistical Analysis Core will support the design, conduct, and analysis of each projects and present essential information to a Data Safety and Monitoring Board. (2) A Botanical Core will establish quality assurance to cover all aspects of production, including source materials, extraction, standardization, and herbal products' formulation. (3) An Administrative Core will optimize synergy among the projects and give general support and oversight to the Centers.⁶

The Center for Chinese Herbal Therapy

The third NCCAM Center of Excellence project is being led by Xiu-Min Li, M.D., at the Mount Sinai School of Medicine. Dr. Li and her colleagues are investigating an oral combination of three Chinese herbal extracts from Ling-Zhi (*Ganoderma lucidum*), Ku-Shen (radix of *Sophora flavescens*) and Gan-Cao (radix of *Glycyrrhiza uralensis*). This combination is called ASHMI, which is an acronym for "antiasthma herbal medicine intervention." Dr. Li and her colleagues are hopeful that ASHMI will be as effective as conventional medications such as corticosteroids in alleviating

Three Centers of Excellence at-a-Glance

Center	Institution	First-year funding total	Principal investigator
Center for Mechanisms Underlying Millimeter Wave Therapy	Temple University School of Medicine Philadelphia, Pennsylvania	\$1,025,895	Marvin C. Ziskin, M.D.
Center for Arthritis and Traditional Chinese Medicine	University of Maryland Baltimore, Maryland	\$1,197,651	Brian M. Berman, M.D.
Center for Chinese Herbal Therapy	Mount Sinai School of Medicine New York, New York	\$1,144,274	Xiu-Min Li, M.D.

asthma symptoms but without the severe nervous and cardiovascular side-effects associated with pharmaceuticals.⁹

Dr. Li's previous research has focused on food allergy and allergic asthma, including research on immunopathogenic mechanisms underlying food allergy and assessments of various therapies for allergic diseases.

Along with Dr. Li, the other researchers involved in the new NCCAM center—from the Weifang Asthma Hospital and Weifang School of Medicine in Beijing, China and the Mount Sinai School of Medicine in New York City—are investigating alternatives to the corticosteroids used in Western asthma treatment. While corticosteroids can be effective, they do have side-effects—such as greater susceptibility to infections due to immune suppression and reduced growth velocity. This limitation has convinced Dr. Li and her colleagues that there is a need for an asthma treatment that is gentler and less toxic.

ASHMI's formulation excludes *Ma Huang*, which is used in many herbal asthma remedies internationally. That is because *Ma Huang* (*Ephedra distachya*) is a source of ephedrine and ephedrine has been associated with adverse effects on the cardiovascular and central nervous systems. U.S. dietary supplements containing more than 10 mg of ephedrine alkaloids are prohibited here, although the ban does not involve *Ma Huang* itself.

ASHMI was originally developed as a simplified version of a 14-herb formula (MSSM-002), which the same team had investigated, finding that the formula reduced asthma symptoms in a mouse model. Prepared by the Weifang Pharmaceutical Manufacturing Factory, the formula was developed based on the actions of the individual herbs in MSSM-002, and according to formulation guidelines of TCM.

A recent trial on the effectiveness of ASHMI conducted by Dr. Li's group involved 91 subjects with moderate-to-severe persistent asthma.¹⁰ They were hospitalized for the 4-week trial.

Forty-six (46) of the people with asthma were randomly assigned to receive 12 ASHMI capsules per day. Each capsule contained 0.3 g of a dried aqueous extract. The total daily dosage of extracts was equivalent to 20 g of raw *Ling-Zhi*, 9 g of *Ku-Shen*, and 3 g of *Gan-Cao*. The subjects in this group also received placebo tablets that resembled oral prednisone ones.

The 46 people in the placebo group (considered as placebo relative to the ASHMI formula) group took 20 mg of prednisone per day plus placebo capsules that looked like the ASHMI ones. The researchers measured participants' lung function, serum cortisol, cytokine and immunoglobulin E levels at baseline and after treatment. The patients were also monitored for side-effects.

The effects of prednisone on lung function were slightly but significantly greater than those produced by ASHMI. Unlike pred-

nisone, however, ASHMI had no adverse effects on adrenal function and had a beneficial effect on TH1 and TH2 cytokine levels.

In addition, the subjects who received ASHMI experienced less gastric discomfort compared to those receiving prednisone; and only the prednisone group had significant weight gain after 4 weeks of treatment.

"Taken together, the findings of this study show that ASHMI is effective and well-tolerated in nonsteroidal-dependent patients with moderate-severe persistent asthma,"⁹ the researchers wrote. The mechanisms underlying ASHMI's effects remain unknown but are likely to be the result of synergistic or additive effects of the formula's constituents.

Dr. Li and her team hope that ASHMI may prove to be a worthwhile asthma treatment option for patients who are sensitive to conventional pharmaceutical preparations. At this early stage in her research, she said that the results look quite promising. □

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