The new head of alternative medicine at NIH faces what may be a superhuman task: evaluating unconventional treatments—and pleasing both believers and skeptics

Stephen Straus's Impossible Job

ALTERNATIVE MEDICINE

This special focus looks at the challenges of evaluating alternative therapies and integrating them into mainstream medical practice.

▶ **NIH'S NEW CENTER**

MEDICAL SCHOOLS

Why in the world would a respected researcher like Stephen Straus leave a topflight lab at the National Institutes of Health to run NIH's new National Center for Complementary and Alternative Medicine (NCCAM)? After all, the center's predecessor, the Office of Alternative Medicine (OAM), was a child of politics that was widely denounced by mainstream researchers. Conceived by Senator Tom Harkin (D–IA), a die-hard fan of alternative medicine and ranking Democrat on the subcommittee that approves the entire NIH budget, the office was earmarked into existence in 1992. It soon gained a reputation as a counterculture enclave for pseudoscience. After just 2 years, the office's first director resigned in protest. Harkin, he claimed, had stacked the advisory board with credulous advocates and was meddling in OAM affairs.

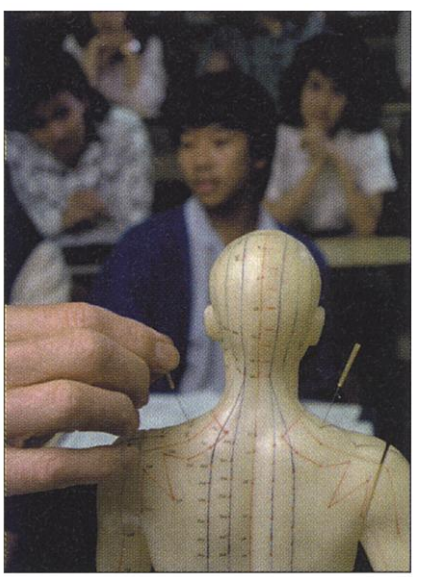
The office's reputation didn't improve under the tenure of the next director, a homeopathic physician. High-profile scientists continued to condemn OAM for sponsoring inconclusive research and bestowing prestige on practices that sometimes resembled "witchcraft." In 1997, former presidential science adviser D. Allan Bromley and others urged Congress to abolish the office. Instead, Harkin kept boosting its budget, from an initial $2 million to nearly $70 million this year. And in 1998, he succeeded—over the objections of then–NIH director Harold Varmus—in elevating the office to a full-fledged center with its own authority to award research grants.

So, last fall, when Varmus recruited Straus, a battle-hardened mainstream clinical investigator, to head up the new center, even critics of OAM lauded the choice. But they and even some of his colleagues wondered why Straus accepted. "It takes guts to take on a job like this," says Anthony Komaroff, a former collaborator with Straus and physician at Harvard Medical School in Boston.

Some, like Komaroff, think Straus has the right combination of receptiveness to new ideas and scientific rigor to pull it off. A longtime NIH physician and virologist, the soft-spoken Straus has strong scientific credentials earned during his studies of infectious diseases, from AIDS to herpes. And from his high-profile research on chronic fatigue syndrome, Straus is no stranger to controversy.

Even so, Straus faces formidable challenges. His goal is to bring scientific rigor to a field that many of his peers would just as soon see disappear. His reputation, and that of the center, will hinge on how well he can do that. Straus will need a deft political touch to avoid the ire of alternative medicine advocates—including those who hold NIH's purse strings in Congress—yet also engage first-rate scientists in evaluating these untested therapies. Indeed, some doubt that anyone can succeed. NCCAM "is a political creation, through pressures of congressional believers and deluded supporters," says Wallace Sampson of Stanford University, a longtime critic of alternative medicine. "Unless Straus plays footsie with them, he will not last."

So why did Straus agree to put himself in this hornet's nest? He says he was attracted to the chance to have a bigger impact on public health than he could as a bench scientist and lab director. He says he relishes the challenge. And his job, he enthusiastically explains, is to marshal the best science to figure out which of these therapies work and which don't, and then inform the American public, whose judgment he thinks is vastly underestimated. Therapies that work should be incorporated into mainstream medicine, Straus says; as for those that don't, the public needs to know that, too.



Making a point. Acupuncture classes are gaining popularity in medical schools.

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Big business

Scientific rigor is sorely needed in this enormously popular but largely unscrutinized field. Alternative medicine—loosely defined as treatments and practices not commonly taught in medical schools, not generally used in hospitals, or covered by insurance companies—is big business. Americans spent $27 billion on unproven remedies in 1997. St. John's Wort, a herb taken for depression, alone racked up an estimated $400 million in U.S. sales last year. According to a 1998 study in *The Journal of the American Medical Association (JAMA)*, 42% of Americans have tried some sort of alternative medicine, from megavitamins to energy healing, up from 34% in 1990.

Most of these substances and treatments have not been tested for either safety or efficacy. Thanks to heavy lobbying by the supplements industry, the 1994 Dietary Supplement Health and Education Act classifies botanicals as a kind of food supplement; these are not regulated by the Food and Drug Administration (FDA). As a result, manufacturers do not have to demonstrate that their products work or even that they are safe. Nor are they required to report adverse effects. Instead, the FDA must prove a danger before a supplement can be banned. For most, the risks and benefits are simply unknown.

Straus, 53, has the kind of training necessary to get answers. During his 23 years at the National Institute of Allergy and Infectious Diseases (NIAID)—including 8 years

as chief of the Laboratory of Clinical Investigation—Straus has investigated a range of diseases, a track record that has earned him the respect of NIH institute directors, Varmus says. That's a "key ingredient" in making this job work, adds Varmus, as most of the center's clinical trials are done in collaboration with other institutes.

MAJOR CLINICAL TRIALS FUNDED BY NCCAM

Study	Institution	Randomized	Placebo	Double Blind	No. of Patients	Length	Cost	Co-funder (millions)
Acupuncture for knee arthritis	University of Maryland School of Medicine	X	X	X	570	4 years	$2.5	
Ginkgo biloba to prevent dementia	University of Pittsburgh School of Medicine	X	X	X	3000	6 years	$15	NIA, NHLBI, NINDS
Glucosamine and chondroitin sulfate for knee arthritis	University of Utah School of Medicine	X	X	X	1000	4 years	$6.6	NIAMS
St. John's Wort for depression	Duke University	X	X	X	330	3 years	$4.3	NIMH, ODS
Shark cartilage for lung cancer	M. D. Anderson Cancer Center	X	X	X	500	5 years	$2.5	NCI
Gonzalez Protocol for pancreatic cancer	Columbia-Presbyterian	X			90	5 years	$1.4	NCI
Saw palmetto extract in benign prostatic hyperplasia	Veterans Affairs Medical Center, San Francisco	X	X	X	224	3 years	$1.8	NIDDK

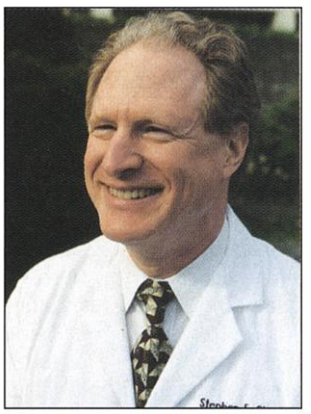
Equally important for relations with the wider scientific community, Straus wants to allay fears of NIH-sponsored quackery. In his warm bedside manner, Straus insists he is not an advocate of alternative therapies, only an advocate of good science. He doesn't practice alternative medicine, nor does he take any. The closest he has come to prior hands-on experience with the field was a clinical trial he designed and participated in to investigate whether capsaicin, the active component of hot peppers, might help against herpes simplex virus. (It didn't.)

Yet Straus does not reject alternative practices out of hand. As a physician, he sometimes referred his patients with chronic fatigue syndrome and acute postherpetic pain to hypnosis, acupuncture, and other practices if they weren't satisfied with his standard care. To Straus, respect for patients and different practices is key. "He seriously listens to people, and he's got a scientific ability to think how to assess these problems without being contentious or confrontational," says John La Montagne, deputy director of NIAID. "He really is an ideal person for this job."

Straus has also weathered the intense scrutiny of his peers and the wrath of advocates. While he was principal investigator for a clinical trial of an experimental drug for hepatitis B, called fialuridine, five of 15 patients in a related trial died from liver or pancreatic damage. The FDA sent letters to Straus and several other investigators, accusing them of not reporting side effects promptly and understating "foreseeable risks." (Panels appointed by NIH and the Institute of Medicine found no wrongdoing, and NIH praised the trial as "the best of current practice.")

On the flip side, when Straus was investigating chronic fatigue syndrome, he concluded that the disease has a psychological component. This finding enraged some advocates, who unsuccessfully tried to get him sacked. But Straus refused to budge from his scientific principles. Notes La Montagne: "He gained in credibility and stature because of that."

Straus says the experience taught him a valuable lesson: Keep advocates plugged into the research. "I learned that one needs to listen to advocates and incorporate them into the research process, rather than marginalize them, because they're far better as partners than as your adversaries."



All smiles. Stephen Straus says talking straight to both camps is the answer.

Science or quackery?

The kinds of therapies Straus is charged with investigating—from homeopathy to shark cartilage to coffee enemas—would make many of his colleagues smirk. But where others might despair of ever designing a rigorous study of, say, energy healing, Straus sees room for creative clinical design. At the top of Straus's list of therapies to study are those that are widely used and for which there is some preliminary evidence that they work. Straus is most enthusiastic about clinical trials of compounds, such as botanicals or shark cartilage, because these can be tested in double-blind, placebo-controlled trials—the height of scientific rigor. Large clinical trials (see table) take up 21% of NCCAM's 2000 budget. The beauty of these types of studies, Straus says, is that "we don't have to reinvent the wheel. We can take what has worked, has been rigorous, and has given the best and most definitive answers."

Yet principles aside, Straus also has to follow the mandate of Congress—and some of its, well, less-than-scientific members. NCCAM is stuck funding a 5-year, $1.4 million trial of an unusual protocol designed to treat terminal pancreatic cancer by physician Nicolas Gonzalez. The so-called Gonzalez Protocol—a hodgepodge of pancreatic enzymes, coffee enemas, and up to 150 dietary supplements a day—caught the attention of Representative Dan Burton (R–IN), who in 1998 encouraged the National Cancer Institute (NCI) to study it. Even though Straus considers the evidence just an "aggregate of interesting anecdotes," he defends the trial—albeit lukewarmly. "I'm more comfortable and find it easier to approach and fund things that already make a lot more sense to me," he admits. "But the mandate here is … to be willing to take more risks for things that are novel."

NCCAM's other trials are more firmly grounded in science. For example, following up on a 1997 lead published in *JAMA*, NCCAM is co-funding with the National Institute on Aging a 6-year trial of an extract of *Ginkgo biloba* to prevent age-related dementia. Researchers from the University of Pittsburgh School of Medicine will coordinate the trial, which will include 3000 people in four clinical centers. Just like any other NIH trial, the Pittsburgh team was chosen as the principal investigators by peer review, says

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Richard Nahin, NCCAM's director of Extramural Research Training and Review.

Another of the large trials already under way is a 4-year study of glucosamine and chondroitin—substances found in and around the cells of cartilage—for treating pain related to osteoarthritis of the knee. NCCAM and NCI are also supporting a phase III clinical trial of shark cartilage for advanced lung cancer. All patients will receive standard chemotherapy, but half will also take the shark extract. The other half will be given a placebo, and the researchers will then compare survival rates between the groups.

Straus is confident these trials will be informative. As an example, he points to recent studies of St. John's Wort, funded by other institutions, that show both the potential and the danger of this botanical. In an 8-week trial of 263 patients with moderate depression, St. John's Wort was more effective than a placebo—and just as effective as a standard drug, according to a trial by researchers from the Bezirkskrankenhaus in Landshut, Germany. But a small NIH study showed that taking St. John's Wort reduces the efficiency of a widely used AIDS drug. Without the study, Straus says, AIDS patients would not have been aware of this danger.

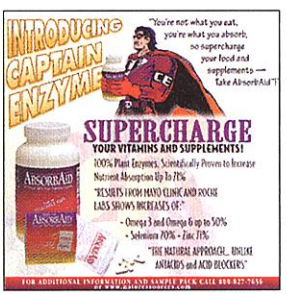
Popular appeal. Some 42% of Americans have tried alternative medicine.

Even straightforward trials such as these face unusual hurdles that are not encountered when testing conventional drugs. Foremost is the quality and consistency of the product being tested. Sometimes the active ingredient may not even be known. Often unknown is the bioavailability and shelf life of the compound, or basic toxicological data. To help glean information about safety, efficacy, and biological action, NCCAM last fall began to co-fund (with the Office of Dietary Supplements, ODS) two botanical centers, one at the University of California, Los Angeles, and one at the University of Illinois, Chicago. Both will analyze botanicals for active ingredients and test their effects on everything from fighting tumors to lowering cholesterol. NCCAM also funds nine other centers that conduct research on alternative medicine for various conditions, such as arthritis, or groups, such as children.

Investigating the implausible

Trials that don't involve drugs are even harder to design. "If you're studying massage therapy, obviously you can't do a double-blind, randomized control trial," Straus says. "But massage can be compared to other kinds of physical interventions or other standard care." But what's usual care for massage? In setting up a trial on the efficacy of alternative therapies for lower back pain, for example, researchers at the Center for Alternative Medicine Research and Education at Beth Israel Deaconess Medical Center in Boston struggled to standardize treatments given in acupuncture, massage, and chiropractic.

Straus emphasizes that large, expensive trials begin only after smaller studies have shown evidence that a therapy might work—barring congressional interference, of course. To that end, 22% of NCCAM's budget is funding investigator-initiated grants on such topics as the role of meditation in coronary heart disease and the effect of high-dose vitamin E on arteriosclerosis.



But the center isn't limited to the merely plausible. Earlier this year, NCCAM's advisory board, which includes advocates and a range of alternative medicine practitioners, unanimously approved a proposal to investigate what they call "frontier medicine." This includes therapies for which there are no plausible biological mechanisms, such as magnets, energy healing, and homeopathy. The rationale is that the public uses these therapies despite a lack of rigorous evidence for whether or not they work.

Not surprisingly, frontier medicine serves as a lightning rod for all the complaints people have about the center and alternative medicine in general. This kind of science isn't worth any time or money, and it attracts charlatans, says Stanford's Sampson. "NCCAM serves as an employment agency for opportunists and a source for aberrant and biased science. As long as the money is there from ideologues, there are people who will go after it," he says. "The present situation is a scientific disgrace."

The ever-optimistic Straus defends the program, saying it holds "exciting new opportunities." And he is willing to invest $600,000 for each of three exploratory grants. "We're not funding quacks," Straus says. "We will fund experienced investigators at institutions with track records in research." Straus does concede that it could be tough to find top-notch investigators who want to spend their time probing the implausible.

Balancing act

In taking this job, many observers say, Straus is walking a tightrope. Skeptical scientists and powerful supporters of alternative medicine will both be measuring his performance by their own criteria. In addition to Harkin's sway over the NIH budget, Representative Burton is also a hard-nosed supporter of alternative medicine; over the past 2 1/2 years he has held at least 10 hearings on alternative medicine to urge NIH to examine alternative remedies such as EDTA chelation therapy for cardiovascular disease.

Many advocates swear by therapies that have not been scientifically shown to work, and these groups "are likely to make a lot of noise if the studies do not support their value," Harvard's Komaroff predicts. At the same time, Straus is spending public funds on research that some accomplished scientists think is pointless. But Straus claims he isn't worried. He insists he can maintain credibility with both scientists and advocates by talking straight to both of them and letting solid science speak for itself.

In some cases, alternative remedies won't pan out, and Straus is confident that the public will respond to a conclusive thumbs down—despite the massive marketing and hype pumped out by an essentially unregulated industry. If other alternative treatments hold up to serious scrutiny, Straus hopes to integrate them into mainstream medical practice. That's why NCCAM is funding fellowships and training grants for established medical schools (see p. 1571).

Meanwhile, NCCAM is growing by leaps and bounds. The senior staff has doubled since November, and Straus is setting up an intramural research program. Congressional supporters would like to see even more growth; in March, for instance, Harkin called NIH's funding for alternative research "woefully inadequate." But Straus is cautious about upping the budget too fast. To spend $80 million on solid research this year, he told *Science*, would have been difficult. His goal is for NCCAM to become more critical rather than less, and to some extent, he says that requires "maturation of the scientific community."

–ERIK STOKSTAD