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WHITE HOUSE COMMISSION
on
COMPLEMENTARY and ALTERNATIVE MEDICINE POLICY

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Meeting Topic II:
CAM: Research Challenges

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Volume III

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C O N T E N T S

Meeting Topic II:
CAM: Research Challenges

CONTENTS (continued)

CONTENTS (continued)

PROCEEDINGS

[8:00 a.m.]

DR. GORDON: Good morning. Nice to have you. Our other commissioners are coming in momentarily. Thank you for being so prompt.

Before we begin each morning, we just sit quietly for a moment and gather ourselves in the space.

[Moment of silence observed.]

Panel V: Research Methodology

DR. GORDON: Thank you. This is the second day of the panels on research. This first panel is on research methodology. We will begin with John Chabot.

Presenter: John A. Chabot, M.D.

DR. CHABOT: Good morning. I am a surgeon, which may be unique in this group. That gives me a bit of perspective that other people don't have. I came to alternative medicine, to an interest in alternative medicine, through research, rather than the other way around. I suspect most people you will be hearing from developed an interest in alternative medicine first, and then developed a research focus there.

What happened to me was, several years ago, the

director of our Comprehensive Cancer Center, Karen Antman, was approached by the NCI to look at designing a trial to study the protocol used by Nick Gonzalez to treat various cancer patients, and specifically we were asked to think about pancreatic cancer.

Karen approached me, as our local pancreatic cancer person, and said, would you consider it. At that point, I had no personal experience with alternative medicine treatments or any specific interest. I looked through Nick Gonzalez's data and became much more interested.

Initially, I looked at it from a very skeptical perspective. His results were so remarkable, in fact, that I was completely suspicious. As I went through his data and his information, became more and more convinced that the pilot trial that he had done under the auspices of the NCI was both valid and important.

He, over several years, treated 11 pancreatic cancer patients with a regime that he had developed from historical data. The regimen primarily consists of very high-dose pancreatic enzyme supplements in conjunction with a very rigorous nutritional program that is highly,

highly specific, day to day, highly specific dietary regime that leaves very little room for deviation. It includes fresh juices, prepared on the day. It includes micronutrient supplements. It includes cleansing and cathartic regimes at specified time intervals.

The data on those first 11 patients demonstrated a 17-month median survival for patients with advanced pancreatic cancer. In looking through the data records, it became clear to me that these, in fact, were all patients with documented pancreatic adenocarcinoma, and it was advanced disease. So the initial skeptical thought being, well, these aren't real cases, I certainly convinced myself that these were patients who had real cases of pancreatic adenocarcinoma.

The longest surviving patient in that group, I actually interviewed. Because he had a very limited disease remaining, he asked me if I would consider re-operating on him. He was four and a half years out from his original disease, was deemed unresectable initially, had been on the regimen for four and a half years and had what appeared to be very limited disease by all measurements.

I was interviewing him to get data, but he eventually convinced me to do an operation on him, and I found him, at that point, to still have unresectable, poorly differentiated pancreatic adenocarcinoma.

With that in mind, the treatment became a very real potential therapy for advanced pancreatic cancer, in my mind, and we set about designing a trial. We put together a standard, randomized trial to compare Gemcitabine, which is the standard chemotherapeutic agent for advanced pancreatic cancer with the Gonzalez regimen. It was funded by the NCI, and we worked to get it through our various internal regulatory bodies, the Institutional Review Board and the Cancer Committee.

That represents an important hurdle, I think, in trying to do these trials, because just as there are strong advocates of alternative medicine, there are strong biases against alternative medicine and working through those committees is a chore when you are trying to do this sort of trial. We were successful. We designed a good trial. Scientifically, it was valid, and we made it through the regulatory committees.

The initial year of the trial, we had a huge

interest. There was a fair bit of publicity about this, none of it solicited by us, but with a lot of press involvement in these sort of trials. We were on TV and in the newspapers. We had huge numbers of patients call with interest. Many, many, many of the patients did not fit the eligibility criteria we had set, which are really very narrow. Those patients who did fit the eligibility criteria, there were almost none of them who were willing to enroll in a randomized trial.

In the first year, we randomized three patients into the trial, despite a huge interest, enough patients to easily fit into the pattern where we would expect to be able to complete the trial. It became very clear that we would never collect adequate numbers of patients to come to a conclusion.

So that, we then got the research group back together, tried to make a decision, and did come to a conclusion that we could do this trial in a non-randomized fashion by carefully stratifying the critical variables. We went to the literature and confirmed that the two critical variables in determining anticipated survival in patients with pancreatic cancer were extent

of disease, basically volume of disease, and the patient's ability to eat.

With those two critical variables, we redesigned the trial, resubmitted it for approvals, and we are now running a trial where patients can choose which therapy they receive, whether it is a chemotherapy-based treatment or the Gonzalez regimen, and we are stratifying those two important variables to generate a control group as well as the experimental group.

We now are accruing patients regularly. From a practicality perspective, this trial, I think, will effectively collect the appropriate number of patients for us to draw a conclusion. In the absence of a randomized design, there are obvious pitfalls here in drawing conclusions from the data once it is generated, the randomized design being much easier to eliminate biases.

So that is where we stand today in my experience over the last two and a half years with this particular trial. Now knowing a bit about alternative medicine, I have come up with several observations, and I think they can only be called observations at this point.

Among those people that we have screened for this protocol, the bias toward alternative therapy is very, very strong.

The vast majority of people who call with interest are only interested in alternative medicine approaches. Patients who express interest in this protocol are generally healthier than the overall population of patients that I see in my practice with advanced pancreatic cancer. The way this protocol, and, I suspect, many are designed, the patients who meet the eligibility criteria are clearly healthier than the general population of advanced pancreatic cancer patients.

One has to be very careful coming to any conclusions comparing these patients with the general population of pancreatic cancer patients.

I will stop at my third observation. The effects of psychosocial support and delivering hope to these patients is not insignificant. In the absence of a blinded, randomized trial, separating these effects from the physiologic and pharmacologic effects will be a major challenge in trial design.

DR. GORDON: Thank you very much, Dr. Chabot.

Marcia Angell.

Presenter: Marcia Angell, M.D.

DR. ANGELL: Thank you for inviting me to address you this morning.

CAM is an umbrella term for a large number of disparate practices based, often, on very different theories. They include homeopathy, therapeutic touch, naturopathy, chiropractic, acupuncture, and on and on. Many of them have very little in common, except for the fact that they are practiced, largely, in the absence of good scientific evidence to support their use. More about that later.

Because CAM consists of such disparate practices, it makes no sense to imagine that a single research methodology would apply to all of them. A clinical trial of acupuncture, for example, presents different methodologic problems from a trial of an herbal remedy.

The former would require particular attention to the selection of a comparison group, or more likely comparison groups, whereas the latter, a trial of an

herbal remedy, would require particular attention to the composition of the product being tested.

Still less, does it make sense to imagine that we need a brand new methodology to study CAM. The problems in designing trials of new drug combinations to treat leukemia, for example, are not all that different from the problems in studying herbal remedies. The problems in studying fetal cell transplantation for Parkinson's disease are similar to those of studying acupuncture.

Almost none of these methodologic problems are insoluble. For years, scientists have managed to devise valid, sometimes quite ingenious, ways to study potential new remedies, and there is nothing qualitatively different about CAM.

Despite some differences in the details of research methodology, the overarching approach must be the same, the application of the scientific method. This means formulating a hypothesis that can be tested. It is no good to have a hypothesis that can't be tested, designing a study that will actually test it, collecting verifiable data, and drawing those conclusions, and only

those conclusions, that follow from the data.

The hallmark of the scientific method is its utter reliance on evidence. No evidence, no conclusions. In the case of proposed medical treatments, CAM or otherwise, randomized, controlled clinical trials are usually required, not always but usually. That is because they eliminate or reduce biases that stem from confounding variables, variations and uncertainties in natural history, the placebo effect, and the expectations of researchers and subjects.

Needless to say, the condition that is being studied must be precisely defined, and the outcomes precisely defined, so that a study can be replicated.

I want to emphasize that the scientific method is not one of a number of options. It is the only way to answer questions about the natural world, and the human body is a part of nature. It is not a cultural or Western phenomenon, it is universal.

True, it has emerged and been applied at different rates in different parts of the world, but that is mostly a reflection of economic conditions. Whenever countries can afford to adopt what is sometimes called

Western medicine, they do. Medical care in Japan, for example, is not much different from medical care in the United States. Even in China, Western medicine is replacing traditional practices.

Now, I would like to say a few words about the questions you posed to this panel. Many of them, I think, are in the form of, have you stopped beating your wife, in the sense that they are based on a dubious premise. The premise is that there is something different about studying CAM that will require modification of current methodologies.

Let me highlight two of the implied differences because they are, in fact, not different at all. You seem to suggest CAM is unique in involving multiple interventions and complex systems. That is simply not true. The standard treatment of diabetes or childhood leukemia, for example, involves multiple interventions and complex systems.

Many standard drugs, such as digitalis, were derived from complex botanicals. It is important, nonetheless, that the various components of treatment regimens be sorted out so that the contributions of each

are identified.

You also imply that CAM is different because it requires individualization of treatment, but in standard medicine, good doctors have always been ready to select or modify treatment according to individual response. What is not possible, in general -- there are exceptions -- but what is not possible in general, is to evaluate the safety and effectiveness of new treatments in individuals. That requires a sample of a population, and the population can be chosen to be as diverse or as homogeneous as possible. It depends on what you want to find out.

Fortunately, humans are more similar than they are different. So that, a beta blocker or a healthy diet tend to work in everyone in much the same way, although not in the identical way. The fact is that there are not two kinds of medicine, CAM and standard medicine. There is only medicine that has been adequately tested, and medicine that hasn't; medicine that works, and medicine that may or may not work.

In general, CAM falls into the second category. Standard medicine falls into both. I don't want to imply

for a second that all standard practices have been scientifically tested.

This would be a good time to say a few words about the German Commission E monographs, since they are often considered a source of scientific evidence on herbal remedies. Commission E was established by the German Government in 1978 to evaluate the safety and effectiveness of herbal remedies. Over the years, it issued its findings in a series of 380 monographs, now collected together and translated.

Here is the shocker. They contain not a single citation to any research study. The introduction to the English translation of the compendium states that, "Only in conflicts or cases of disputes to the medical act can an attorney or scientific organization view these references."

Even then, the references might not be there, since, "Some of the materials upon which the monographs were based were unpublished studies of proprietary products from manufacturers in Germany." In fact, it is acknowledged that many of the monographs are based only on materials supplied by the KP, an organization of

German manufacturers.

Now, no one should accept ex-cathedra pronouncements about scientific research, no matter what the source, without having access to the evidence on which they are based. In this case, it seems the opinions are not just those of an unbiased governmental body, but also of the industry that gains from favorable evaluations.

One should also be wary of accepting the notion that there is a gold mine of scientific information sequestered in another language. Since science is universal, and English is a lingua franca of science, that is highly unlikely.

In summary, we need to get on with the job of testing CAM treatments rigorously, because millions of people are taking remedies for which there is little or no evidence. Tradition, testimonials, and speculation are no substitute. This has been demonstrated repeatedly throughout medical history. What seemed true, and sometimes had seemed true for millennia, often proved false.

The spectacular advances in clinical medicine

during the 20th century correlated with the growing acceptance of the need to demonstrate scientifically. Whether biologically implausible remedies should be tested is arguable, since we don't have the resources to test everything.

I have come to believe, somewhat reluctantly, that even biologically implausible remedies should be tested for safety and effectiveness if, and only if, they are already being widely used. If they are shown, and any other remedy is shown, to be effective and reasonably safe, they should be incorporated into clinical practice, regardless of whether they originate as CAM, but there are no shortcuts and there should be no free passes.

Thank you.

DR. GORDON: Thank you very much.

Jennifer Jacobs.

Presenter: Jennifer Jacobs, M.D., M.P.H.

DR. JACOBS: I would like to thank the Commission for inviting me here today. I am going to be speaking from the perspective of a physician who has been using homeopathy in my practice for almost 25 years, and also a researcher in the area of homeopathic medicine.

Homeopathy has long been an enigma, due largely to the high dilutions of the medicines that are used. While the mechanism of action of homeopathy is not known, nearly 200 years of anecdotal evidence from all parts of the world has convinced many patients as well as physicians of its efficacy.

In France, 33 percent of medical doctors use homeopathy in their practices, while in India, it is used by up to half of the population. In that United States, 3.4 percent of the population used homeopathy in 1997, which was a five-fold increase since 1990.

Homeopathy is based on the "principle of similars," first described by Samuel Hahnemann in the late 18th century. Substances that have been found to cause certain symptoms in someone who is healthy are used to treat those same symptoms in someone who is sick.

Another important tenet of homeopathy is individualization, whereby each person is treated with a specific remedy which fits his or her unique pattern of physical, emotional, and mental symptoms. For this reason, different people with the same diagnosis may receive one of several different homeopathic medicines.

Homeopathy has been found to be extremely safe, due to the low concentrations of active substances, as well as efficacious in many clinical trials. A meta-analysis published in "The Lancet" in 1997, established clearly the efficacy of homeopathy when compared to placebo. The investigators also found, however, that many studies had not been replicated, something that has changed since the time of that meta analysis publication.

Homeopathy has also been found to be cost effective, reducing by more than half the use of conventional medicines in those physicians who use it. In France, where homeopathy is included in the national health system, medical costs have been estimated to be 15 to 25 percent lower for homeopathic physicians. The average cost of a bottle of 100 homeopathic tablets in the United States is $5 to $10.

There are many barriers, both political and methodological, to carrying out good homeopathic research. Many of these things also apply to other areas of CAM research. The first is funding. Funding has been limited by the fact that homeopathic medicines are generic and cannot be patented. Thus, there are no

profits to be made from investments in research. Because of this, sample sizes have been relatively small in homeopathic trials, which means that only large differences can be detected between treatment groups.

In the childhood diarrhea research that I carried out, p values in the range of 0.03 to 0.05 were found in individual studies of 87 to 125 patients. However, when these studies were combined to yield more than 200 patients, the p value drops to 0.002. If enough money is available for enough subjects, even small differences in effects can be found to be statistically significant, as is the case for many highly marketed allopathic drugs.

Unlike other CAM modalities, homeopathy lends itself well to conventional, randomized, placebo-controlled trials, the RCT, which is the gold standard, as we have heard. This is because homeopathy is prescribed on sugar pills. However, the individualized nature of homeopathic practice makes a strict application of RCT methodology difficult. Unlike trials in conventional medicine, all patients with the same illnesses are not prescribed the same medicine in

homeopathy.

Several strategies have been used to incorporate individualization into the RCT study design. These include individualizing the treatment each subject receives, and comparing the outcome of the homeopathic group, as a whole, to placebo; limiting study subjects only to those who fit a specific remedy picture; and using combination remedies that contain the most common medicines for a specific illness.

Another area of importance is outcome measures. It is important that outcome measures reflect the holistic nature of CAM practices. In conventional medical research, often one or two specific parameters are looked at, such as a blood pressure measurement or a blood test. You do not really see the effect of the intervention on the patient as a whole.

This can be solved by using already existing symptom scores, such as the Kupperman Menopausal Index for hot flashes. More globally, quality-of-life indicators, such as the SF-36 Health Survey, can be used to evaluate subjective feelings as well as limitations of work, social activities, and general health status.

Other outcomes, such as days of missed school or work, the cost of medical care, and patient satisfaction, are all important in evaluating CAM modalities.

The use of placebo is an area of controversy in CAM research, but it is necessary to establish efficacy, especially for therapies such as homeopathy, which are thought be some to be nothing but placebo. However, there are ways to use placebo to minimize the ethical difficulties. One is to limit the time of the study to the shortest possible to measure a clinical effect and to offer all patients the opportunity to receive active treatment at the end of the study.

Once the efficacy of homeopathy is established firmly, the use of placebo can be eliminated by randomizing subjects to receive either conventional medical care or homeopathy. This would give a more accurate representation of what homeopathy has to offer in actual clinical practice. Longitudinal studies of homeopathic patients over several years, should document the preventative as well as curative aspects of this modality, as well as cost analysis.

There is now adequate evidence-based research

to justify the use of homeopathy in several conditions, yet the belief structures of scientists continue to block its widespread application. Many critics have stated that no matter how many clinical trials are published, they will never accept homeopathy until its mechanism of action is understood. This, in my view, is foolhardy, as there are many drugs in modern medicine which were used for many years before their mechanism was understood.

It is also chauvinistic for us to think that we understand everything there is to know about science at this point in history. Homeopathy does work, most likely on a subatomic or a subtle energy level that has not yet been elucidated.

My first recommendation to the Commission is that the government establish an initiative to find out how homeopathy works. This could revolutionize our understanding of health and disease, as well as open the door to other new healing strategies.

Modern medicine is at an impasse; $425 billion per year are spent treating the six leading illnesses, and costs continue to rise. Drug costs now exceed $100 billion per year, and are predicted to reach nearly $400

billion by 2010.

Recent studies have shown that adverse reactions to allopathic drugs, used as directed, is the fourth leading cause of death in hospitals. One survey showed that more than half of all physicians said they would not do it again, when asked about their decision to go into medicine.

In the 1999 special issues on alternative medicine, the editors of JAMA wrote: "There is no alternative medicine. There is only scientifically proven, evidence-based medicine, supported by solid data, or unproven medicine for which evidence is lacking."

Homeopathy deserves the kind of careful, unbiased evaluation that is necessary to establish its legitimacy. The Commission should charge the government agencies to thoroughly investigate homeopathy, so that it can become available within the health care system to anyone who wants it.

Well-funded research into clinical efficacy and cost effectiveness should demonstrate that homeopathy is a low-cost way to provide health care to a wide segment of our population. It may also make them healthier.

Thank you.

DR. GORDON: Thank you very much.

Alex White.

Presenter: B. Alex White, D.D.S., Dr.P.H.

DR. WHITE: Good morning. My name is Alex White, and I appreciate the invitation to come and talk with you today.

I serve as the principal investigator of the Oregon Center for Complementary and Alternative Medicine, which is based in Portland, Oregon, part of Kaiser Permanente. It is a collaboration of four complementary and alternative medicine schools in Portland, as well as the Oregon Health Sciences University.

What I would like to talk to you about this morning are some of the experiences and learnings from about two years together. Many of the recommendations that I will talk with you about this morning are in your packet, and some of the background materials as well.

I should give a bit of a disclaimer. I work for Kaiser, but I am not representing Kaiser. I am representing the Oregon Center, so my comments should be taken in that context.

We are fortunate, actually, in Portland to be able to have this institutional collaboration with the College of Chiropractic Care, Oriental Medicine, Massage, and Naturopathy, as well as the Oregon Health Sciences University School of Medicine and Dentistry. Together with those institutions and Kaiser at the Center for Health Research, we put together a center grant that is supported by the National Center for Complementary and Alternative Medicine.

I would like to talk, generally, about three areas: first, is research; the second is research methods; and the third is infrastructure. I think some of the themes I would like to talk about with you are some themes that you have heard from the other speakers. So that is a good thing.

I think the fundamental and most important thing that we need to focus on is doing good science. Without good science, places like Kaiser and other payers, other practitioners, are not going to incorporate CAM therapies into routine clinical care. That shouldn't in and of itself be the goal of science, but it should certainly be to improve the health and health care of our

members, and research is an important tool to do that. But it has got to be based on good science.

We go through processes that use science and make recommendations for additions to the formulary for deciding what new technologies to cover. Those decisions are based, among other things, on good science. Certainly, politics and other things come into play in that process, but science is the critical feature of each of those processes. So we need to conduct good science on those products and processes, looking at particular diseases, particular conditions that need to be addressed.

We also need to expand, I think, the research to include factors that may influence that process. We need to understand what it is about practitioners and patient characteristics that influence good outcomes, to understand what it is about theories and beliefs and ideas about how things work that may or may not influence the process and outcomes of care.

We also need good research on outcomes. I think, as was highlighted by the other speakers, we need measures of outcomes that are going to reflect what is

important to the patients who receive that care, as well as to the practitioners who are providing that care. They are broader than what are most used as clinical measures of outcomes. I think clinical measures are an important part of assessing CAM therapies, but we also need to look at things like economics. We need to look at psychosocial impact of CAM therapies on health beliefs and, simply, quality of life.

We need research that is going to help us integrate CAM therapies into health plans or into routine and conventional medical care. For example, we need research that is going to demonstrate product safety. Not only is it important to demonstrate safety, but we need to develop some standardization within natural products. We need to look at good manufacturing processes.

We have got efforts afoot at Kaiser to try to identify products that we can include in our formulary, and one of the problems that we run into continually is, can we get good standardized products of high quality, and it is very difficult to do that. So I think research and efforts that can begin to introduce that information,

and the evidence is an important part for enhancing CAM therapies.

We also need to think about research more broadly than simply clinical research, and think about, certainly, mechanistic and biobehavioral research, but as well to think about health services research, to think about cost and cost effectiveness, and to begin to look at how CAM therapies can be integrated within conventional care settings.

The second area I would like to talk about is research development. While I agree with the other speakers, that many of the methods that we need to evaluate CAM therapies are in place now, there are, I think, unique parts about CAM that we need to evaluate, whether the current methods will be able to capture the important features of CAM therapy.

For example, we have developed as part of our CAM Center, this huge packet of questionnaires. We refer to it as "death by questionnaire." The members who are willing to participate literally spend hours filling out questionnaires.

It is not that we are trying to kill them, but

what we are trying to do is to see if there are aspects of individual members who are participating in our studies that make them more or less receptive to CAM therapies; not only does the CAM therapy work, but is there something about the mindset that people bring to clinical trials. Certainly, I think that is true in conventional medicine, and perhaps even more important in CAM therapy.

If we are asking a person to be randomized to a trial where there is acupuncture, there is chiropractic care, there is massage, and there is conventional care, can we really believe that they are willing to be randomized to each of those arms, and if not, do they have inherent preferences about which one they would like to be in; are there ways that we can design clinical trials in the randomization process to account for preferences in practitioner and patient beliefs about certain therapies.

I think one of the important parts that we need to work on in research development is understanding the mechanisms of action of CAM therapies to get the bio markers and other ways of assessing what it is that we

are doing to members, and how is it that they have come to benefit from these therapies.

Finally, the infrastructure. As I mentioned earlier, in Portland, we are very fortunate to have these collaborations established, but I will tell you that it has taken a lot of time and effort. There are people who are participating with us that are following on the next panel, and perhaps that will come up. I will tell you that it is a major investment of time and effort.

There is lots of enthusiasm within the CAM community in Portland to participate in our clinical trials. The problem is that many of the folks don't have the necessary research training and experience to do that. Many of the institutions are geared toward providing education and training clinicians, and not conducting research.

So there is infrastructure, not only in providing training and education for new CAM practitioners, but also providing infrastructure and training to institutions to allow them to participate in NIH trials. When we began this process, many of institutions had no idea what indirect costs were and how

you come up with a negotiated rate with HHS. For us, it is the lifeblood of what we do, and that is just part of our operating business. So I think there are some very fundamental things that need to be established within the CAM community to support CAM research.

Secondly, as I mentioned earlier, the training of new researchers in the area, that is going to come up in the next panel, but I think it is really important to talk about it in the context of research as well. NCCAM and other places at NIH support training grants for new investigators. I also think it is important to think about the role that CAM centers can play in supporting and building a cadre of investigators who can either be collaborators or turn into principal investigators.

At our center, we have made a significant effort to try to include people who do not have doctoral degrees, massage therapists, acupuncturists, and others, who have come to appreciate research methods, who will never be principal investigators on NIH-funded grants, but who will understand the scientific process, who will learn to ask important questions, who will begin to evaluate their clinical practice in clinical ways, and

can collaborate with us in developing new protocols that answer questions that are important to them.

Through that process of developing a cadre of perhaps non-principal investigators, but certainly investigators, we believe we can advance CAM science in important ways because we can work with the community in answering questions and addressing issues that are important to that community.

The final point about infrastructure I would like to make is that many of the CAM centers, I think, have had success in developing these Phase 2 trials, or trials that establish whether or not a CAM therapy is efficacious, but as we begin to think about moving trials into larger trials, I think the journalizability issue is important. The CAM therapies are going to need to be evaluated in multi-site clinical trials, looking at the impact of culture, looking at the impact of geography and preferences, in whether or not these interventions work.

That requires a substantial amount of investment, and infrastructure beyond what we have in place in Portland and other CAM centers, but infrastructure on a national level that allows us to do

many of the trials that are supported, for example, by NCI or NHLBI, that we are able to provide an infrastructure to do a national study looking at chronic pain and to have support to do that.

Let me just close by reiterating again that I think the research in CAM and the evidence base for CAM is less well developed than it is in other areas, and that research is an important way, the only way, I think, that we can advance CAM therapy. The objective, then, is to assure the best possible science, and as Marcia Angell said, adhering to the good scientific method and developing hypotheses that can be tested.

I do think that there are some areas we need to explore and understand, whether these research methods can be applied directly to CAM, or whether we need to tweak the methods to understand how it is and what it is about CAM that we are trying to evaluate, and making sure that we are not missing some important parts of CAM therapy in improving the health of people who use CAM. Thank you.

DR. GORDON: Thank you very much.

Bruce Rabin.

Presenter: Bruce Rabin, M.D., Ph.D.

DR. RABIN: I want to thank you for the opportunity to address some issues regarding research methodology in complementary and alternative medicine.

First, I would like to comment on a small, uncontrolled, unscientific research effort at the University of Pittsburgh Medical Center Health System regarding terminology. As you all are aware, the terms "complementary and alternative," and "complementary and integrative" have, on occasion, elicited not very subtle reactions, both pro and con, from the public and health care workers.

Therefore, we conducted a consumer survey for an indication of what patients seeing physicians in our health system preferred our program to be called. As a result of this survey, we call our program the Health Enhancement Program. Our program, which is a top-down, trustee-driven, approved program by the trustees of the Health Center, will incorporate validated alternative approaches and components of behavioral medicine, and conduct research studies to determine the appropriateness of modalities not yet validated.

I am a psychoneuroimmunologist, and I work with the mind-body connection, the subject the panel was asked to address. I study the effect of psychologic stress on the brain, how the brain's response to stress alters the function of the immune system, and how altered immune function influences health. I will briefly comment on three areas of research concerns related to mind-body interactions: safety; standardization; and controls.

Safety. Mind-body interactions often promote enhanced coping with stress. Massage is a modality utilized for this. Massage is unlikely to cause harm when applied by well-trained hands that have received the appropriate certification from the appropriately certified schools of massage.

Imagine feeling tired with some lower-back pain, just the conditions that massage can help a patient with. That is, unless the patient has multiple myeloma with destructive bone lesions, and as a result of too vigorous a massage, suffers a bone fracture. Certainly, a technique can be safe. However, only if the subject and the technique are properly matched. In the example, they were not.

What if the same patient had sought a therapeutic touch practitioner for their tiredness and low-back pain. Certainly, there would be no concern of fracture, only the concern of time lost before proper treatment was provided. I cannot emphasize strongly enough, due to the increasing numbers of patients seeking non-standard approaches to health, that it is essential to have proper medical evaluation before embarking on a procedure that superficially may appear to be safe but that may do harm or delay proper treatment.

How will research into the formulation and implementation of guidelines for safety be established? I suggest the answer lies in traditional and non-traditional practitioners working together to merge their specialized skills into a consumer safety program. Formation of collaborative panels of experts is encouraged to develop such guidelines.

Standardization. Many arguments take place regarding the appropriateness of standardization of alternative modalities. Alternative practitioners claim their techniques cannot be standardized because different patients require adaptation of the modality to the

characteristics of the particular patient.

Traditional practitioners desire standardization within large-scale clinical trials to determine the effectiveness of a procedure. Both approaches are correct, indicating the complexity of the subject. However, my concerns regarding standardization addresses the recipient of the treatment, not the treatment itself, and this was just alluded to by Dr. White.

Applying the same modality to individuals of different personalities and emotional characteristics may yield different outcomes, as we do not know the personality characteristics of someone who is likely to experience a placebo effect.

Certainly, the mind-body health connection may decrease the symptoms of disease because the patient is made to feel better and tolerates their condition better. However, we also need to determine whether having an enhanced sense of well-being has an effect on the pathologic basis of disease by altering the concentration of stress hormones in tissue and plasma.

Cell trafficking patterns, adhesion molecule

concentrations, protein synthesis, and even stem cell maturation, may be altered by effects on catecholamine and glucocorticoid plasma concentrations as a result of belief in an alternative modality a patient is experiencing.

Meaningful research is not going to occur through study of non-standardized approaches of individual patients and anecdotal reports. Large studies of standardized approaches in well-characterized patients are needed.

Some of the characteristics of subjects we are concerned about that may influence these sympathetic nervous system and hypothalamic pituitary adrenal axis responses to alternative interventions, and may contribute to understanding why the interventions work for some individuals and not others, are: Is the subject high or low in optimism, anger, hostility, a sense of humor, perceived stress, social support, religiosity or spiritualism, and physical fitness; has the subject tried and been disappointed in traditional medical care; is the subject high or low in their opinion of CAM; does the patient have a good relationship with their physician, or

have they been dissatisfied with their physician; does the subject practice meditation or yoga; does the subject expect the procedure to work.

Knowing what works and in who it works is essential. A patient requesting acupuncture who has characteristics that are found, through proper research, unlikely to be associated with a therapeutic response, can be directed to a therapy more likely to provide a therapeutic response, thereby saving time and money for both the patient and health care practitioner.

For example, would research find that a subject who was high in hostility, low in optimism, low in expectations of a possible outcome from a procedure, sedentary, and lacking a sense of humor, be a likely responder to acupuncture.

Controls. Whenever possible, control groups should be studied to provide a means of evaluating CAM treatments, alone or in combination with conventional treatments, and compared to standard treatments or to no treatment.

Certainly, blinding a practitioner or a subject to whether or not actual massage or acupuncture was being

applied is difficult. However, in the area of mind-body interventions, institutional review board requirements are also a problem.

For example, assume that a study is being performed of the effects of a stress-coping program on the progression of MRI-documented plaque size in the central nervous system of patients with multiple sclerosis. Patients are recruited to the study and sign an informed consent appropriately indicating that they will either receive the intervention or be randomized to a weightless control group.

However, the control group obviously knows that they are a control group, and that if the intervention works, they will be able to participate once the study is completed. This expectation and knowing that they are part of a study may produce a positive placebo effect.

The proper control would be patients who did not know that they were part of a study, believing the MRI was being done as part of routine management. However, that could be deceptive and not allowed.

Thus, proper research studies of the influence of mind-body medicine on alteration of the course of

disease may require a modification of IRB criteria or the design of innovative clinical trials that are developed by meaningful collaboration between alternative practitioners and well-trained clinical trial interventionists.

In conclusion, in the absence of strong, empirical data to support many CAM interventions, it is important for CAM clinics and practitioners to put a mechanism in place to systematically obtain baseline and objective outcome data on the clinical condition of the patients they treat. Subjective outcomes, without knowing that the course of a disease has been modified, will not help to end to the differences between traditional and non-traditional practitioners.

Detailed assessment of the patient's course of disease, including changes in symptoms, objective disease measures, and laboratory parameters, should be monitored and recorded in accord with guidelines that will allow the data to be published in peer-reviewed journals.

As I have stated, collaboration between traditional and complementary practitioners is needed to enhance the safety, standardization, and use of proper

controls for studies to establish the appropriateness of integration of CAM into conventional health care.

CAM practices have a past, present, and future. The health care industry, the academic community, and CAM practitioners in and out of the academic world, should advocate for and pursue advances in the practices of scientific and humanistic medicine. This will occur through open communication and mutual respect.

At present, the public both demands access to and frequently utilizes CAM treatments. These treatments appear to offer something that patients want and presumably may not be receiving from mainstream medicine. Both patients and CAM practitioners believe that the good in these treatments usually clearly outweighs their potential for harm.

The challenge is, therefore, to offer such treatments to patients while carefully monitoring their use, subjecting CAM treatments to empirical study, using accepted methods of scientific inquiry, and making every effort not to mislead patients or the public. Thank you.

Panel Discussion

DR. GORDON: Thank you all very much. I really

appreciate the thoughtfulness of testimony.

One of the things I thought we might do is send you all copies of each other's testimony, plus a couple of papers that we have from Andrew Vickers at Memorial Sloan-Kettering that might be interesting on the same subject, because we really feel this is an ongoing dialogue.

I also just wanted to thank you, John Chabot, personally for your work with the Gonzalez trial, and also with a patient of mine who consulted you. I just wanted to say that publicly.

DR. CHABOT: Thank you.

DR. GORDON: Questions. Tieraona first, then Dean, and then Wayne.

DR. LOW DOG: It is hard to know who to ask questions because you were all so good. Anybody who would like to answer, but perhaps Dr. Angell.

Thirty years ago, we were confronted with a similar sort of situation with OTC remedies when, basically, we had no randomized trials. There was very little evidence of benefit, yet all these products were out on the market. They got a group of experts together

to try to sift through if there was a reasonable certainty of safety or a reasonable certainty of efficacy.

Keeping in mind that these are for minor self-limiting conditions -- I'm not talking about heart failure or things like that -- under the current situation that we have with DSHEA, would you be in support of a group such as the National Academy of Science or another group, an expert group, trying to set up a panel that would look at things that seem to have a reasonable degree of safety or a reasonable degree of efficacy for minor conditions, which, many of these supplements are used for? Do you think that that would be a step in the right direction, or not?

DR. ANGELL: Well, as some of the speakers said yesterday, I think the major problem is DSHEA itself and the herbal remedies, the dietary supplements, the so-called dietary supplements, should be subjected to the same standard as any drug. That is, the manufacturers should be required to show safety and efficacy before they are marketed, and not afterwards.

As for panels, if a panel gets together, an

expert panel, and looks at the scientific evidence that is out there, I am all in favor of that, of sifting through it, but panels tend to take on a life of their own and go beyond the evidence that is out there, and then it becomes ex-cathedral pronouncements, and they are of no particular value. You can't reach a conclusion without the evidence.

DR. LOW DOG: I guess my problem always comes to things such as chamomile tea, which you can get at the village in or an restaurant. We had it last night.

At what point do all things have to be tested for safety and efficacy, when some of them are not foods but they are clearly not the potent medications which so many companies do sell?

DR. ANGELL: What is the medicine and what is the food, you are saying. Obviously, that is going to be a fairly fuzzy boundary. I think the first question is, is the substance in the thing that is labeled as having the substance in it. So there are two different questions. There is standardization. There are standards of purity and concentration and so forth, and there is effectiveness.

If the chamomile tea really is chamomile tea, it would depend on what evidence is out there -- and I don't know -- about any adverse reactions and so forth, but you can get silly about this. I agree with you. You have to draw the line in a sensible place.

DR. GORDON: Let me just go through the list and make sure I have everybody. I have Dean, Wayne, Ming, Joe Pizzorno, George DeVries, and George Bernier, and Joe Fins.

Dean.

DR. ORNISH: I also want to thank the panel for its very eloquent testimony, and to say that I think many of us are of like mind, but I also have questions because one of our charges is to make policy recommendations. We hear from a number of people that there should be an increase in funding or there should be an increase in research. So this first question is directed to Dr. Angell.

Do you support an increase in funding for the National Center for Complementary and Alternative Medicine?

DR. ANGELL: I have a problem with that center

to begin with, because I don't believe that there should be two kinds of medicine. I think that CAM practices for which there is preliminary evidence, a lot of anecdotes, well-documented anecdotes, or CAM practices that are already in widespread use, need to be studied. That you need a new center to do it, I think, is arguable, and I would argue against that.

The current institutes can study any kind of treatment they want for any kind of scientific question they want. And so, if the hypothesis is that homeopathy is good for heart disease or whatever, being more specific than that, then I would think that it would be studied within the National Institute of Heart, Lung, and Blood.

So I think that this increases the separateness of it. It is as though there were two kinds of medicine, which I argued against in my statement. Instead, there ought to be medicine that has been tested, and medicine that hasn't, and it ought to be all in there together.

DR. ORNISH: I have quoted your statement many times, because I agree with it in theory, but in practice, if that were true, then those studies would

already be out there. We have heard from a number of people, almost as a refrain, that in the conventional institutes, the NHLBI or whomever, at least certainly in the past, it has been very difficult to get studies funded that are not within the conventional paradigm, and for that matter difficult to get them published in leading journals like the New England Journal and others, or that they are held to a different standard.

De facto, if it were possible to get these studies funded at the conventional institutes, there would be a much broader literature already out there. People say, well, these interventions don't have any science, but then it is very hard to get these studies funded.

DR. JACOBS: Can I just make a comment as a researcher in the field? And that is, the whole area of research and funding changed dramatically with the establishment of what was then the Office of Alternative Medicine.

Before, when I was knocking on the doors at the University, people thought I was some kind of lunatic. Once the OAM was established and there were calls for

paper and there were funds available, all of a sudden, people were willing to collaborate and to take it seriously.

I agree with you that none of the research that we have in the past, and very little of it in the past 10 years, would exist if it hadn't been for the NIH office. I think it is very important that it grow, because even with the small amount of funding it has now and so many different modalities, a good homeopathic research study in otitis media, which is one of the areas that it is reputed to be good for, we have estimated would cost $3- to $5 million. That is maybe a tenth of the budget of the whole NIH centers. So clearly, we need more funding.

DR. ANGELL: The way research is funded and the attention that different things get has to do with a lot of factors, one of which is the public concern about the ailment or the treatment. You could name almost any disease or any treatment that somebody would argue had been underfunded at some time. For a while, people thought that breast cancer was underfunded. Now people argue that prostrate cancer is relatively underfunded.

So that there is always a group that would like

to see more money put into something. The problem with talking about CAM in general, as I said at the outset, it is so disparate, and not everything can be funded. There is usually some prior probability that it might work.

One would say that the claims of a large study of St. John's wort are very much higher than the claims of a large study of therapeutic touch. So, which of those things are you talking about?

You can always complain that something is being underfunded. Scientific knowledge changes. So that, for a while, everything is going into AIDS because it is, scientifically, so interesting, and then it switches.

I don't see why one should bundle all of the CAM practices together and say it should be treated separately and specially.

DR. RABIN: The problem is not the institutes; the problem is the reviewers in the process. For those with, that I am sure many of us had, years of experience on study sections, there are biases which come into the review process.

To make a level playing field, this institute was created, but once the playing field is level and

there is fair review and qualified reviewers of CAM procedure on study sections, or study sections set up for this within the existing institutes, then this may not be a problem, but I think right now, there certainly is a bias. We dealt with that in psychoneuroimmunology for many years, until we were able to get adequate reviewers on study sections.

DR. ORNISH: Just one follow-up question.

DR. GORDON: Quick, because we have a lot of other people.

DR. ORNISH: Then, why don't we come back if there is time.

DR. GORDON: Okay, great. Thank you.

Wayne.

DR. JONAS: How many questions?

DR. GORDON: One.

DR. JONAS: One question?

DR. GORDON: One per person.

DR. JONAS: All right, one per person.

I want to thank the panel. I thought this was an excellent series of presentations. I thought it was very consistent with the previous presentations that we

had, and I am supposed to be heading up one of the discussion groups on research methodology a little later in the day, and from what I can tell, it is going to be extremely easy because there appears to be a consensus that we have good research methods that now exist, that we want to use good research methods, and we just need to start applying them to these areas and letting science take its course.

I want to especially thank Dr. White for pointing out the variety of research methods that exist for different purposes and that are good. I think it is important that we look at and use all those research methods for those different purposes.

Let me mention that there was a third methodology conference that was held, you may not have known about, that may be of interest on histomology, which did not get published at the OAM.

Which question to pick.

DR. GORDON: Like Gertrude Stein, right?

DR. JONAS: Yes, that's right.

The only area that I don't think, really, has been addressed is the plausibility issue, and Dr. Angell,

you addressed that. I was pleasantly surprised and pleased to see that you were willing to say, if there is no plausibility but if it is largely used by the public, we probably need to investigate it in some way. I think we are coming even closer on that issue, and could perhaps set up some criteria to decide when those conditions exist.

I would like to ask Dr. Chabot why a randomized, controlled trial was decided on in the first place. When I was getting my evidence-based medicine training up at McMaster University, and Dr. Sackett was up there saying, this is what you do, and this when you do a randomized, controlled trial, et cetera, the example they always used, when you do not need a randomized, controlled trial, was pancreatic cancer. I taught that for years to my students. Yet, when we actually have the opportunity to do an integrative therapy for pancreatic cancer, that is the first thing that is attempted.

I am just wondering what the background, and why was it that that was selected as something that needed to be done at the time.

DR. CHABOT: I think the best answer to that

goes back to your first comment, plausibility. When you look into the treatment, identifying physiologic relationships that should allow this treatment to be explained, I can't come up with a mechanism.

So we then have to go back to, how can we be absolutely sure we are going to come to a conclusion based strictly on empiricism that this works, and I think the best trial designed to do that is the trial design that eliminates all bias. A randomized trial is certainly the easiest way to do that, and the way that is most unimpeachable when you present the data.

In thinking about presenting this information, once we have collected the data, there are ardent supporters and vigorous antagonists to this treatment in particular. My hope was to develop absolutely unimpeachable data to bring both of those camps together and say, yes, this is the answer. A randomized trial is the way to do that. As we went forward, it became quite clear that we were not going to come up with any data if we insisted on that design.

The new design will be attacked when the data becomes available, and there will then still be ongoing

discussion: Well, I can't accept it because of this; because the control group wasn't quite right; because this patient didn't match that patient quite perfectly; because we disagree on what the stratification should be. In order to get the trial done, I think we have to accept that.

DR. JONAS: It was really patient preferences that didn't allow you to do the controlled trial, right? They just wouldn't be randomized into it.

DR. CHABOT: Correct.

DR. JONAS: My understanding from the case you presented is that it looks like it doesn't actually cure the cancer in any case. The cancer was still there, and just something else was going on that allowed these people to live longer. Is that correct?

DR. CHABOT: That particular individual, certainly. The other explanation for this phenomenon is selection bias, which, it is very clear in running this trial now for a couple of years, that this patient population is different, and therefore the control group we select has to be selected very, very carefully. Again, randomizing is the easiest way to do that, but

hopefully not the only way.

DR. JONAS: [Off mike] -- that it was belief and plausibility that prevented this trial, because I looked at this data from Nicholas Gonzalez when I first came to the OAM, actually, and also was impressed that there was something there and it ought to be looked at. I was severely resisted at the NIH until there was some gentle congressional influence, which then, finally motivated the NCI to fund it.

Whether that turns out to be worthwhile or not, who knows, but I just thought I would illustrate that for the Commission.

DR. GORDON: Ming.

DR. TIAN: A question for Dr. Angell.

Thank you very much for your presentation. You mentioned that methodology, you think there must be one standard. I just wanted to share information with you about NIH research on acupuncture. In 1974, NIH did fund an acupuncture study using double-blind study to evaluate the efficacy of lower-back pain. Unfortunately, after a three- or four-year study, the conclusion was that in the control group it was 45 percent is effective, and in the

treated group, it was 55.

So the conclusion was acupuncture was not effective, it was placebo. That was pure, scientific design, until 1997, which, it was sponsored by Dr. Jonas -- the second meeting was November -- that they then reviewed all the data and noticed that methodology is quite important. Now acupuncture is positively accepted because of a lot of scientific evidence to show it works.

My question for you is, do you think we should develop methodology for CAM? For instance, like acupuncture, there are no such sham points. Is that necessary to develop the methodology?

DR. ANGELL: I'm not sure I understand the question. You are saying that there are no acupuncture points that are not valid, according to the theory of acupuncture?

DR. TIAN: No. My question is, if we use traditional methodology to evaluate acupuncture, we might fail, so we have to be very careful to at least use a newly developed methodology and have a well-controlled group to study.

DR. ANGELL: I can't speak to the details of

this because I am not quite sure about the study that you are talking or what you are alluding to, but when I said the same methodology, what I meant was the application of the scientific method, to have a hypothesis, that this will, in this condition, do this to; to have verifiable outcome measures; to collect verifiable data; to draw the conclusions based on the data.

Within that overall requirement for the application of the scientific method, of course there will be differences in the details of the methodology, depending on the question that you are asking and the modality that you are testing. There has to be.

In something like, I gave the example of, fetal stem transplantation for Parkinson's disease, there is a lot of trouble knowing what the control group should be, what the sham procedure should be, whether it is ethical, for one thing, to do a sham procedure.

So there can be difficulties, but I don't think they are unique in CAM. I am not persuaded that they are unique.

DR. GORDON: Thank you.

Joe.

DR. PIZZORNO: Dr. Angell, you present an interesting challenge, because on the one hand, I agree with most of what you have to say and believe that science is indeed the pathway, not so much that we prove our efficacy, but by which the practice of medicine gets better.

On the other hand, we seem to live in very different worlds, and I hear some perspectives from you of CAM being simply modalities or therapies, which is a gross simplification. I also hear your perspective about what conventional medicine is that is not, apparently, shared by most of the patients out there who are choosing to go to CAM professionals.

I think one of the big challenges here is that what really differentiates natural medicine from conventional medicine is more of a philosophical approach to our patients, how we think and interact with each other. That, I think, needs to be tested, and I think that that different approach to the patient, which is much more patient-centric than disease-centric, is why patients come to see us.

Is there some way we could design a study to

look at that very factor, not the theories, because, like you say, there is lots of research that can be done there, but rather the different experience that patients have going to conventional versus CAM providers, and learn from that about ways in which we can improve medicine?

DR. ANGELL: Well, if that is a general area that you would like to study, then you have to develop a hypothesis that can be tested, and design a trial that will test it, and collect verifiable data, and draw the conclusions, and only those conclusions, that flow from the data, just as you would if you were testing anything else, but you have to give me, not a vague hypothesis, but a specific hypothesis that can be tested.

DR. GORDON: Alex White, and also Bruce Rabin, you addressed this some in your testimony, so we would welcome hearing from you.

DR. WHITE: At the Oregon Center of Complementary and Alternative Medicine, we don't get at this directly, but I do think we get at some of the issues that you have highlighted.

Developing an acupuncture protocol was actually

very difficult because many of the people with whom we are working, when we ask them to develop a standardized protocol that can be used in a clinical trial, it is incomprehensible. It is not something that they are used to doing. It is an individualized treatment approach. The acupuncture points are modified based on patient response and examination, and if we ask them to identify 20 points that can be used in a trial: Why would I do that, because it doesn't make sense; My colleagues wouldn't believe it.

What we have tried to do in designing our trial is to provide some flexibility in our studies, with some core acupuncture points, but allowing there to be individualized within the context of the clinical trial.

In particular, one of our studies is actually evaluating more of the system approach. We have a trial that looks at traditional Chinese medicine and naturopathy for women who have multiple medical problems and chronic facial pain. We haven't specified that X,Y, and Z happens within the context of that trial. We would rather randomly assign these women to these particular intervention arms.

Within the context, we know what happens and we have tried to put some balance on it, but it generally is evaluating the system of care rather than a particular intervention.

The hypothesis is different because the hypothesis then becomes not whether acupuncture point X,Y, or Z is the right point, but rather, is the system approach and the holistic approach important. That is what we are testing, essentially, rather than the individual components that may make up traditional Chinese medicine or naturopathy.

DR. RABIN: I wonder if part of the study which you are suggesting, looking at interaction between patient and practitioner, wasn't already done historically.

There was a time when the patient went to the physician. The physician knew about the family, the personal problems, the work problems, the stressors in their lives, and that interaction had, possibly, a positive effect on health, and that is gone. The time is gone where practitioners can get to know the patients like that.

I think history would say that you are correct, that reestablishment of that relationship -- and a lot of what you are doing and the beneficial effect of what you are doing, is reestablishing that relationship -- it would be extremely important to take a look at it again. If it indeed is shown through the proper scientific studies to be important, to try and reestablish that.

DR. GORDON: Joe Fins is next -- no, I'm sorry, George is next.

DR. BERNIER: Thank you, sir.

DR. GORDON: Thank you. I stand corrected.

DR. BERNIER: I have a question for Dr. Jacobs.

In the minds of many, evidenced here today and in a lot of the discussion that has happened over the last year, many people believe that it will be the clinical trial, one way or another, that provides the answer for a lot of the issues that are being discussed.

In your statement, you indicate that an important tenet of homeopathy is individualization, whereby each person is treated with a specific remedy which fits his or her unique pattern of physical, emotional, and mental symptoms. For this reason,

different people with the same diagnosis may receive one or several different homeopathic remedies. The implication is that it can never be tested by the conventional clinical trial way.

It makes me think of Dr. Bernie Fisher, who, back in the 60s and 70s was able to start a program, whereby surgeons, present company excepted, at that time, weren't terribly interested in finding out what would happen to a population of 100 people. They were just focusing on one.

That is a long-winded question. I guess what I want to ask is, looking down the road, can you see really valid clinical trials being conducted on a regular basis to test homeopathy?

DR. JACOBS: Well, actually, there have been many clinical trials that I believe are valid that have tested homeopathy. There are several ways to do this. I actually mentioned these in my comments, but perhaps I was talking fast. The studies that I have done have all been RCTs, where patients are randomized to either receive a homeopathic medicine or a placebo.

So we are testing the patients as a whole who

received homeopathy, even though they may have received different individualized medicines, versus the patients who received the placebo. This, of course, has been criticized. In some circles it is seen as what they call the "black box effect," whereas, you put people through a certain system and compare that to placebo.

There are other ways that the RCT has been adapted to homeopathy. One is by selecting only patients who fit a specific homeopathic remedy picture for a specific disease. There is a study of fibrositis that was done in England in the late 1980s, where only patients were prescreened to see which ones fit the remedy picture for Rus Tox, which is a homeopathic remedy which is commonly given for arthritic and rheumatic conditions.

And so, only those patients were enrolled in the trial, and those patients then were compared to placebo.

And then, the third approach is to use homeopathic combination remedies, which are those that are sold over the counter. You can buy them in health food stores today, teething tablets, homeopathic cold

medicines, where they have the five or six most common homeopathic medicines for a particular illness.

In our diarrhea research, we found that 80 percent of the children had only five remedies that were indicated, five different remedies were indicated in 80 percent of the children. Theoretically, a combination medicine with those five medicines should help 80 percent of people. So a trial could be done of that combination versus placebo.

I think this is true for other areas of CAM research, too. There are ways to use individualization and still stay true to the RCT methodology. I think it is very important because it is the gold standard that we do this.

DR. GORDON: Please, John.

DR. CHABOT: May I make a very brief comment? Dr. Bernier's allusion to surgical research opens the opportunity here.

I think, in many ways, the history of surgical evolution and research is somewhat similar to the current dilemma in CAM research, in that, the surgeon-patient relationship is very, very individual. The intervention

is considered massive. The thought of randomizing between an operation and medicine, most patients will usually favor taking a pill rather than undergoing an operation.

But thinking about current surgery for breast cancer is the ideal example. There were strong advocates of mutilating operations in the past who felt fervently that the right operation to do was a radical mastectomy for breast cancer, and the only operation to do. It is only through long years of well-designed and implemented clinical trials that most women now undergo breast conservation surgery for breast cancer.

Very difficult to do; it took a long time, and it was only through good science that we have achieved the state where amputations for breast cancer are not done.

DR. GORDON: Thank you.

Joe Fins. We are already over time, and I want to do our best to give the three people who haven't had a chance to ask questions the chance. So, Joe, please.

DR. FINS: Dr. Angell, and the panel, thank you all for your comments. I want to follow up Dean's

question to its logic or illogical conclusion.

When he asked whether you would want to increase funding for the NCCAM, you said no, but based on what you have said, if there would good hypotheses that were worthy of extramural funding, you would say that would be appropriate.

I think there is an implicit statement or idea in what you said about the value of integrating these studies in the other institutes because it would foster integration, but at the same time, there are biases in the other institutes against these kinds of hypotheses and some of the questions that are out of the Cunian paradigm that they are used to living in.

So in an ideal world, we would have it dispersed through all the institutes, maybe a quota system of certain kinds of funding. But, practically, how do we get there from here? If the term is not "complementary and alternative," but it is "integrative medicine," how do we have an integrative research system on the federal level, and maybe seeing NCCAM as a transition item into a more integrative approach? How do we get there from here?

DR. ANGELL: Well, it may, in fact, turn out to be a transition, although any organization to become dedicated to its survival. So that, I am not so sure that it, in fact, would play out to be a transition.

Here again, the implication of your question is that CAM is all one thing. I think there is often resistance to a new type of treatment that is proposed. We just heard about lumpectomy versus mastectomy; tremendous resistance, but as the science comes out -- and it may be very slow at first, and there may be biases that have to be overcome -- the successes will make the next one easier, and the next one will be easier. That is just the way clinical science progresses. You can't do all overnight.

Some of the CAM treatments, and I think the herbal remedies are the most promising, will turn out to work, to be confirmed in scientific testing, and will be incorporated within standard medicine. Others will die, and should die.

So I don't want to see it marginalized by being lumped together. I want to see it treated on its merits.

DR. FINS: The implication here is that

separate is not equal, and that the maturation of the field will be when investigators, who maybe today are considered CAM investigators, are applying to the other institutes for funding and they are viable.

DR. GORDON: One thing I want to point out that Steve reminded me of, is that there is considerable and increasing cofunding of some of these studies by NCCAM and some of the other institutes. So I think that is an important development.

DR. WHITE: I would just add to that that it is not only the support of research itself, but it is support of education and training, and creating a cadre of CAM researchers, which I think is important. It is a sort of Catch-22. I think the ability of other institutes to take risks on funding CAM -- "risks" might not be the right word, but my sense is that some directors would say that it is a risk -- of funding CAM therapies is because there is not good science.

Well, you are not going to get good science until you get the funding, so which do you do first, to the extent to which good science, then, will lead other institutes to feel like it is less risky, that there is a

clear methodological basis for these therapies. I think that NCCAM goes beyond simply funding research, that the infrastructure piece is the education and training, developing a cadre, developing a research agenda in CAM.

I certainly agree that CAM is not a uniform therapy, but there are things go beyond simply funding RO-1s.

DR. ANGELL: Except that advocacy should not get ahead of the science.

DR. WHITE: I would agree with that.

DR. GORDON: Bill.

DR. FAIR: I, too, would like to thank the panel. Having, until recently, spent 16 years at Memorial Sloan-Kettering, I know Nick very well and was impressed by the tremendous practice that he had. I also had the opportunity to review his manuscript and submission to a journal, not the one it was subsequently published in, and the problems that we had were several, and I wanted to know whether you had surmounted these problems.

First of all, was, out of this huge practice, he had 11 patients that he reported on. Quite honestly,

we could never get the denominator of the patients that he saw.

Secondly, the Kanusky Performance Status was not listed adequately. Across the board, almost any clinical study in oncology, as you well know, the best predictor of response, is going to be the Kanusky Performance Status going into the study. That is almost axiomatic.

The third was, he was using his hair analysis to alter the treatment. I think that that was pretty much put to rest. You can't judge the effect of cancer therapy by hair analysis.

So my questions were, have you been able to sort this out? As a surgeon, I would like to say one other thing to support what you said. It has often been said that had we waited until all the mechanisms and the responses and what flavored it and what inhibited the immune response before doing a transplant, we would still be waiting to do the first kidney transplant.

So I think this goes along with what Dr. Angell said, sometimes you don't have perfection when you do things. Typical surgical analysis: Just don't stand

there, do something. So I think that sometimes we have to do these studies, even if we don't have what would fit the perfect statistical study, and obviously that is what you are doing there.

DR. CHABOT: First, let me address the hair analysis. It has no role in the clinical trial. It has been demonstrated not to be effective. It was never part of the clinical trial and has no role in guiding therapy.

I do not know the denominator for those 11 patients. The two answers to this, the 17-month median in 11 patients, it is either selection bias, which is a very real possibility, or it works. There aren't very many other plausible answers to this question.

I think that my review of the data convinces me that they were real patients, they had the correct disease, they had the correct stage of disease, they were followed carefully and the data are good data. But selection bias is a very real possibility and I think that is the concern that you raise.

To try to go back and answer that question, look at that pilot trial and think about how many patients did 11 come from, I think we would still be

arguing about this, whether it is real or not. So we just designed a trial to answer that question. That very specific hypothesis really is, is this selection bias, or is this a real phenomenon.

DR. FAIR: We were just asking, okay, Nick, in the course of a year, how many patients did you see with pancreatic cancer; you have been doing this for X number of years, so X times X should give us the denominator, and it was not possible to get that information.

DR. CHABOT: Today, Nick is not seeing any patients with pancreatic cancer. He is referring all of them to the trial, and we are screening them all. If they don't meet our screening criteria and enter the trial, then they are free to see Nick independently, but Nick will not see patients with pancreatic cancer without referring them to the trial.

I do believe completely that he is following that course of action.

DR. GORDON: I just want to say something to everybody. We are already 10 minutes over. One of the things that we might do is begin the small groups during lunch time, if that is all right.

No, not all right? I'm sorry?

Okay. So not as good to do that. So let's just have the last two questions, and then we will move on. Effie next.

DR. CHOW: I want to thank the panel, also. I have some comments, and I would like some comments from the panel. We don't like the term "CAM" either. It is a dilemma within itself, but using CAM, the dimensions that is very different, maybe you folks can reduce that difference, is that many of the therapies utilize energetic concepts, prahna, manna, toth [ph], chi, qi, whatever, and goes back to Xioming's comment, there are no sham points in acupuncture. In touch, there is no sham touch, either.

I think your psychoneuroimmunology is kind of related to that very closely, and perhaps you could help us with this. How do we then control the studies? For example, in distant healing, we haven't mentioned distant healing. There is a great interest in that now, and it is very effective; spirituality.

The thought is that once you think it, it is so. So, how do you measure that? Dr. Samuel Rosen, the

famous audio-larynologist did a research on acupuncture. He used deep acupuncture for real acupuncture, and superficial acupuncture for a sham. There, he lost his control already, if we knew what acupuncture was, really.

Yet, they got results with the group. They could talk behind them and they could hear, but their audiograms didn't show any change. So, what about measurement tools, et cetera? I throw this out. It is a real dilemma for us.

DR. RABIN: It is a very important question, and, I think if we look at Michael Meaney's work, a question that begins in utero. Certainly, we know from non-human primate studies that if a pregnant monkey is undergoing high levels of stress, that the personality characteristics, the response of the offspring, the immune system function, is permanently changed.

The Michael Meaney studies on touching and stroking animals, and how that permanently changes the function of the HPA access. We are learning that different personality characteristics in adults are associated with different activities of the HPA access, and different activities of the locus cerelius.

I think we are dealing with a very exciting area where we are beginning to learn that the wiring patterns of the brain, that the hormonal milieu that the brain produces with different emotional states have physiological effects. Certainly, with our new understanding of why individuals develop atherosclerotic disease and adherence of monocytes to endothelium, and migration of monocytes into the subendothelial tissue, we begin to realize that the hormonal composition of an individual is associated with the disease.

Now, we spent a lot of time looking at stress and anxiety states. We have spent very little time looking at relaxation and spiritualism and stress coping, and the hormonal alterations that that produces. If you say to somebody, like you are indicating, "You are the product of distant healing," there are most likely hormonal alterations occurring in the individuals which will be associated with the different health outcomes.

We really need to begin to look at these interactions, at the hormonal response to both well-being as well as stress, to look at what it does, not only to immune system function, but to a variety of physiologic

functions. Placebos work for a reason.

The investigators are not putting in grants to do this. We don't need separate institutes for this. What we need are researchers who put in excellent grants. If you put in excellent grants with the proper controls and the proper data analysis, these should be funded. We do need to remove biases from study sections, but the money is there, certainly, if we have the qualified investigators.

As has been indicated, we need to stimulate more individuals to work in this area to understand these mechanisms. There are powerful effects. We know that from epidemiologic studies. We do need to learn more about mechanisms, and we need the proper trials.

DR. CHOW: Do you feel you have the mechanisms in place, or do you think they need to be more developed?

DR. RABIN: We are beginning to learn about some of the mechanisms, but we can only study what we know. Certainly, we can study the sympathetic nervous system and the HPA access, and we can look at substance P and neural peptide Y. There are probably other systems out there that modify the hormonal response to stress,

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the hormonal response to relaxation and health effects.

I don't think we know everything. We started off with a few cytokines, and now there are 40 or 50. Every day, there are more cytokines. There are many things yet to be discovered. We have to do that to get

DR. GORDON: Thank you. I think, as you can see from our response, we could probably go on all day. I really appreciate, we all appreciate, your coming and your presentations, and we hope we will be able to continue the dialogue. Thank you very much.

[Applause.]

Panel VI: Training of Conventional and CAM Investigators

MS. CHANG: We are going to move right into our next session, so if Commissioners can stay where you are. There will be a break after this session, we promise.

Nancy Pearson and Neal West, who are sharing some time, Robert Blanks, Russell Phillips, and Richard Hammerschlag, if you could join us at the speakers' table. Thank you.

DR. GORDON: Good morning, everyone. We will begin with Nancy Pearson, please.

Presenter: Nancy Pearson, Ph.D.

DR. PEARSON: Thank you. Good morning, and thank you for inviting Dr. West and myself to participate in this panel.

During the next several minutes, we would like to briefly describe NCCAM's training initiatives for conventional and CAM investigators. I will describe NCCAM's National Research Service Award program, or NRSA, for research training, Dr. West will describe NCCAM's Career Development Award programs.

NCCAM's ability to achieve its research goals is dependent on the availability of a critical mass of skilled investigators, both from the CAM and the conventional research communities. These goals are consistent with the NRSA program. To quote from an NRSA announcement, "Congress enacted the NRSA, or National Research Service Act program in 1974 to help ensure that highly trained scientists will be available in adequate numbers and in appropriate research areas to carry out the nation's biomedical and behavioral research agenda."

It is under this congressional authority that NCCAM awards individual and institutional NRSA training grants. Through the NRSA awards, NCCAM is committed to

providing funds for high-quality, mentored research training experience for both pre-doctoral and post-doctoral students who are interested in pursuing a career in CAM research.

Funding through NRSA research training grants are available both to CAM practitioners who wish to gain knowledge and experience to conduct rigorous research in their field, and to conventional researchers and practitioners who wish to increase their knowledge and experience in specific CAM research areas.

To do high-quality research that will advance the CAM field and make a significant impact on the health care system, both CAM practitioners and more conventional investigators need the same rigorous research training. They need to acquire knowledge of CAM, but in combination with a strong grounding in those disciplines necessary to do high-quality, clinical, and basic research.

One useful paradigm for training students in CAM is to include CAM-trained practitioners and researchers as part of the training faculty, so they can bring their important, unique perspective, philosophy, and experience to the training.

During the first year of funding, which was Fiscal Year 1999, NCCAM spent 1.3 percent of its budget on training. Training is defined here as the combination of NRSA awards and career development awards. In Fiscal Year 2000, it increased that to 3.8 percent of the NCCAM budget. During this fiscal year, that is 2000, NCCAM funded seven NRSA individual pre-doctoral fellowships, two NRSA individual post-doctoral fellowships, and two NRSA institutional training grants.

These two NCCAM institutional training grants, which support a total of 12 trainees, combine broad-based research training, both in CAM and basic scientific methodologies, necessary to perform high-quality research in any scientific area. NCCAM also has committed funds to support fellows on five institutional training grants sponsored by other institutes and agencies, and these are called co-pays.

In addition to these official training mechanisms, research training also occurs in our funded research centers in RO-1 grants, as you heard in the last session.

While many of the NRSA awardees come from

conventional research and educational backgrounds, these NRSA training programs have begun to attract trainees with degrees, for example, in traditional Chinese medicine and chiropractic.

The research and investigations these students or fellows are pursuing are wide-ranging and cover many different CAM modalities. These range from research on herbal remedies to treating various disease conditions, to investigations of the social processes that lead to the use of alternative medicine therapies to treat HIV, to studies of the effect of static magnetic fields on fibromyalgia.

We anticipate that the NRSA training portfolio will continue to grow in 2001. This growth will include the awarding of two more NRSA institutional training grants and additional NRSA individual pre-doctoral and post-doctoral fellowship awards. NCCAM has also issued a request for applications and made available money to fund minority researchers.

In conclusion, we feel that by providing a wide range of training initiatives, we can encourage maturation of the whole field.

DR. GORDON: Thank you.

Neal West.

Presenter: Neal West, Ph.D.

DR. WEST: Good morning.

DR. GORDON: Good morning.

DR. WEST: The NCCAM Post-Doctoral Career Development, or K Awards, are designed to ensure that continued mentored research opportunities are available to help a select group of highly accomplished individuals to make the transition to independent investigator status.

The NCCAM is currently supporting 11 Career Development Awards at a total cost of $1.3 million in Fiscal Year 2000, and we expect to make several additional awards this year.

Three current awardees have the K-01, which is the Mentored Research Scientist Development Award. This generally is made to a Ph.D.-trained scientist seeking a mentored career development experience in a research area new to the individual.

Two of our current awardees have the K-08, which is the Mentored Clinical Scientist Development

Award. This supports the development of outstanding clinical research scientists.

Four of our NCCAM awardees have the K-23, which is the Mentored Patient-Oriented Research Career Development Award. This supports clinically trained professionals who have the potential to develop into scientifically productive clinical investigators, focusing on patient-oriented research.

Two of NCCAM's K Awards are through the K-24, which is the Mid-Career Investigator Award in Patient-Oriented Research. This program is intended to further both the research and the mentoring endeavors of outstanding patient-oriented investigators. Both of our current K-24 awardees hold both the M.D. and the Ph.D. degree. This award enables them to expand their potential for significant contributions to their fields and to act as mentors for beginning clinical researchers.

NCCAM Career Development awardees are conducting research across a broad range of scientific and medical topics, including botanical/drug interactions, studies of glucosamine and cartilage, homeostasis and degradation, yoga in pregnant asthmatics,

and a separate K, yoga as a treatment for insomnia, Ayurvedic herbal effects on lipids and atherosclerosis, the pharmacology of ephedrine/caffeine supplements, and in one K-23 award to a chiropractor, the psychosocial behavior and immune factors in back pain.

Since the CAM research community and CAM research needs are so diverse, the NCCAM has made available to potential applicants this full range of traditional NIH career development grant mechanisms. The resulting successful Career Development awardees will constitute an elite corps of CAM researchers who are further preparing themselves to succeed within the highly competitive CAM research and NIH grant environments.

DR. GORDON: Thank you.

Robert Blanks.

Presenter: Robert Blanks, Ph.D.

DR. BLANKS: Well, I would first like to thank the members of the panel for inviting me, and I certainly look forward to the discussions.

I have been the medical educator and researcher-scientist, for 23 years, at the University of California, Irvine. I have had a lot of background in

terms of chairing institutional animal review committee for animal and human subjects. I currently chair our IRB. I have had the privilege of being a researcher in what I would prefer to term holistic, vitalistic modalities, focusing primarily subluxation-based chiropractic, and one of its modalities, and a little bit on Oriental medicine.

Throughout this time, it became very clear that I was quite ill prepared to deal with the nuances of training. Although I went through traditional Ph.D. training. I had trained medical students, residents, and faculty in this for a many years, it became clear that I had just one world view, which was the view of the RCT, the randomized, clinical trial. This was the view I had. Until quite recently, I had the privilege -- I won't say recently, 10 years ago, I had the privilege of meeting a very talented man, who I believe was providing testimony previously. I will get back to that in a second.

I had the privilege of talking with the person who now had the benefit of having a holistic view of the world, a very broad way of looking at health, and said, basically, I don't want to deal with symptoms in dealing

with my modality. I don't want to deal with outcome measures which are not honoring that human domain. We need to come up with very valid measures of health, which could include quality of life, which measures the full dimension of health.

At that point, my colleague pointed out that there are many different models, and I was to go back to the table, redevelop myself, redesign myself. So I began to research the process. About that same time, we developed a center, the Southern California Center for Complementary Medicine at the University of California, Irvine, since renamed.

We came up with an interdisciplinary approach, which talks to the specifics of the details of the committee today, which is basically how we deal with design of research, how we move cultures of evidence forward, and particularly what we are doing with the mind-body construct in a holistic or vitalistic approach to health.

The first team member we added then was a medical sociologist. We brought in an anthropologist. We brought people doing psychoneuroimmunology. I was

physiologist-trained at that point, and also medical people that brought in other people who were trained in specific disciplines. Indeed, we developed a health, wellness, and quality-of-life outcome measure.

It is now an 87-item questionnaire, validated in three separate samples, including a nutritional co-therapy sample, giving us a way of looking at this process of health, defined not specifically as a disease-oriented modality, disease treatment modality, but certainly embracing the broader constructs of health.

Let's come back to this issue of the world view, and this is indeed what we call the biomedicine model. I think there is no question that this is the dominant culture. I think there is no question that randomization does help with the issue of bias and so forth, but let's think of the problem at hand in dealing with these health modalities, and particularly those which are very vitalistic. I think the issue there is how you merge this culture of evidence, particularly at the lower levels, merge it to the higher level, which might be the RCT.

One of the things that I preferred to do, is

when I trained medical students to deal with investigators, is deal with this issue of training, that various models are out there, and I will just name a few. I gave handouts here, and you will see that there is a summary of what I consider the dualism of the world views of research and research training. In general, the biomedicine model seeks to classify, diagnose and treat, largely, symptoms.

There are other models. The one that is transitional now is one we call a social epidemiological model, which looks at the disease entity within the context of the broader social domain, which is often that person's socioeconomic condition, socio-behavioral condition and so forth. We are dealing with many of the other issues that have come up here.

Here is the last one, which is on the right side of the column, for the benefit of the handout here, the one I just termed the "social science model," but it is one that is often referred to as the holistic or the contextual model, which looks at the person, their bio, mental, social, and spiritual domain within the context of the society, defined broadly.

Now, we believe that in the first search for the various outcome measures that might allow us to address these broad domains of health, that we first sought the quality-of-life survey, which was the patient's perception of health, or what we call "health belief."

In that quest, we largely found, and as most of you may know, there are many quality-of-life scales, but many of these are disease-oriented. There is a separate one for mental status, for Alzheimer's patients. There is a separate one for the diabetic patients, and so forth.

In each case, it focuses largely on the disease domain, which is the ceiling of this. Either you have the disease, or you don't have the disease. The cap is not the vital standard, which is the human potential, but often is the absence of disease.

Going back again, as a quick reminder, in 1958, the definition of health by the World Health Organization simply said, and it was really a brilliant discussion, that health was complete physical, mental and social well-being, and not merely the absence of disease or

infirmity.

We have picked up that definition. We have sculpted a large part of our research outcome measures in health, wellness and quality-of-life through surveys around that definition. Again, it keeps away from the symptom, or what we call the biomedical model.

So we what could be classed as the three models of the world view. I use this, too, because I like to think of the dualism, like you have the yin and yang in the Oriental medicine philosophy. Your best state of health in Oriental philosophy is the flow of energy between the two extremes.

I believe that we need the flow of energy between health outcome and research models, one being biomedicine as RCT, and the other being more the social science model, and a very broad base of literature looking at many characteristics, such as patterns, processes, the context with which you are evaluating health, dealing with tracking entire rivers of information, as opposed to collecting facts and so forth.

Well, as to specific ideas and how one could proceed in the training, I believe the first starting