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RESTRICTION CODES

Presidential Records Act - [44 U.S.C. 2204(a)]

Freedom of Information Act - [5 U.S.C. 552(b)]

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P2 Relating to the appointment to Federal office [(a)(2) of the PRA]
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b(9) Release would disclose geological or geophysical information concerning wells [(b)(9) of the FOIA]

Brief Biography**BRIAN M. BERMAN, M.D.**

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Dr. Berman is the founder and director of the Complementary Medicine Program at the University of Maryland School of Medicine and Professor of Family Medicine. Board certified in family medicine and pain management, Dr. Berman has trained extensively in acupuncture and homeopathy and has integrated these therapies into his clinical practice over the past 17 years. He holds a diploma in Traditional Chinese Medicine and, in addition to being a founding member of the American Academy of Medical Acupuncturists, he is a member of the Royal Society of Medicine and the Faculty of Homeopathy in Britain.

Dr. Berman is principal investigator of a National Institutes of Health (NIH) center grant for the study of alternative medicine in the treatment of arthritis and related disorders. He is principal or co-investigator of eight research studies in complementary medicine funded by the NIH, the Department of Defense and private foundations, including a large, multi-site randomized controlled trial of acupuncture in the treatment of osteoarthritis and studies of acupuncture for acute post-operative pain and nausea and vomiting. Interested in investigating the scientific foundation and efficacy of therapies currently outside the mainstream of medicine and evaluating their contribution in the treatment of chronic ailments such as pain, Dr. Berman established the first university-based center in the United States focusing on research, education and clinical care in complementary medicine. He has published widely in the field and was recently awarded the international Seirin award in recognition of his contributions to acupuncture research.

Dr. Berman has served as adviser to the NIH, chairing the first advisory panel to the National Institutes of Health Office of Alternative Medicine (NIH-OAM) and participating as a member of the NIH Alternative Medicine Program Advisory Council for six years. In addition, he chaired the NIH-OAM editorial board for its 350-page report, *Alternative Medicine: Expanding Medical Horizons*. Dr. Berman also serves as Field Coordinator for the Complementary Medicine Field of the international Cochrane Collaboration, an organization dedicated to evaluating all medical practices.

Brian M. Berman M.D.
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**PRESENTATION TO THE WHITE HOUSE COMMISSION ON
COMPLEMENTARY AND ALTERNATIVE MEDICINE POLICY**
May 15, 2001

Mr. Chairman and members of the Commission, I am extremely honored to be given the opportunity to speak with you today on the evaluation of complementary and alternative medicine (CAM) research literature and the role of the Cochrane Collaboration, as well as research training for CAM practitioners and the integration of CAM research into conventional academic health centers.

I am a board certified family practitioner and pain management specialist with extensive training and clinical experience in a variety of CAM modalities. I am also Director of the University of Maryland Complementary Medicine Program and Principal Investigator of a National Institutes of Health (NIH)-funded Specialized Center of Research in CAM as well as a PI & co-investigator on a number of NIH-funded clinical trials. As such, I am both a clinician and a scientist. As I speak to you today I will mainly be wearing my research hat. One of the main areas of focus of our center at the University of Maryland is the investigation of the safety, efficacy and mechanism of CAM therapies for pain-related problems. We design and conduct original, rigorous research trials, in addition to systematically distilling the best evidence available worldwide and communicating these results to the clinical, scientific and public communities. The first half of my presentation will address the importance of the work in systematically reviewing the CAM scientific literature.

**Evaluation of CAM Research Literature and the Role of the Cochrane
Collaboration**

The Cochrane Collaboration is an international organization founded in 1993 that prepares, maintains and disseminates systematic, up-to-date reviews of health care interventions. It was started in response to the challenge made by Archie Cochrane, an eminent British epidemiologist, that people who want to make informed decisions about healthcare do not have ready access to reliable reviews of the available evidence.

The aims of the Collaboration are to provide information that is:

- Evidence-based
- Easily accessible
- Internationally developed
- Quality controlled
- Clinically useful
- Periodically updated

Brian M. Berman, M.D.

The Collaboration is being built on nine principles:

- Collaboration
- Building on the enthusiasm of individuals
- Avoiding duplication
- Minimizing bias
- Keeping up to date
- Ensuring relevance
- Ensuring access
- Continually improving the quality of its work
- Continuity

The significance of the work of the Collaboration to medicine has been compared to that of the Human Genome Project. Not only does it provide an invaluable service in overcoming "the great collective ignorance about the effects of health care" (Archie Cochrane), it also provides invaluable information to guide future research efforts.

The Cochrane Library

One of the main outputs of the Collaboration is the Cochrane Library which includes several databases:

- *The Cochrane Database of Systematic Reviews* contains Cochrane systematic reviews.
- *The Cochrane Controlled Trials Register* is a bibliographic database of controlled trials.
- *The Database of Abstracts of Reviews of Effectiveness (DARE)* includes structured abstracts of systematic reviews which have been critically appraised by reviewers.
- *The Cochrane Review Methodology Database* is a bibliography of articles on the science of research synthesis.
- *Reviewers' Handbook* on the science of reviewing research.
- *Glossary* of methodological terms and Cochrane jargon; and contact details for review groups and other groupings in the Collaboration.

At present there are 1081 reviews and 307,872 trials in the Reviews Database and the Registry and 2793 abstracts in DARE, an amazing achievement for an organization that has not yet celebrated its 8th birthday! The Library is available electronically.

The Complementary Medicine Field

In 1996, through the interest of a number of researchers from countries around the globe and the encouragement of Wayne Jonas (Director at the time of the NIH- Office of Alternative Medicine), a Complementary Medicine Field was registered within the Collaboration. The purpose of the Field is to 1) ensure the priorities and perspectives of CAM are reflected in the work of collaborative review groups; 2) compile a database of CAM reviews; 3) compile a registry of trials in CAM for uploading to the central Cochrane Registry; 4) coordinate activities with relevant agencies outside the Collaboration; and 5) comment on systematic reviews relating to CAM. The Field is

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coordinated by our Center at the University of Maryland and we now also maintain the CAM Registry. The work of the Field has received support from NCCAM.

The Cochrane CM Field Trials Registry

The CAM Trials Registry has been a significant undertaking since it aims to be inclusive of all randomized controlled trials in CAM, published or unpublished, in any language. Many of the trials and tribulations of finding relevant studies are outlined in an article about the CM Field published in JAMA in 1998. Challenges have included 1) the difficulty of capturing all CAM studies through MEDLINE (and other electronic medical database) searches due to factors such as the limited scope of practices defined by MEDLINE as alternative medicine and the limited number of journals containing CAM literature that have been indexed by MEDLINE, 2) the need to identify and search electronic databases world-wide that may contain CAM literature, and 3) the need to hand-search journals that are published around the world. As part of our effort to increase accessibility of CAM literature, members of the Field have worked with the National Library of Medicine to make recommendations to improve the number of CAM journals indexed by MEDLINE and to make their Medical Subject Headings indexing system more sensitive and precise for searching on CAM. There are now over 5300 randomized controlled trials and controlled clinical trials in the Cochrane CM Trials Registry.

Criteria for Inclusion as CAM

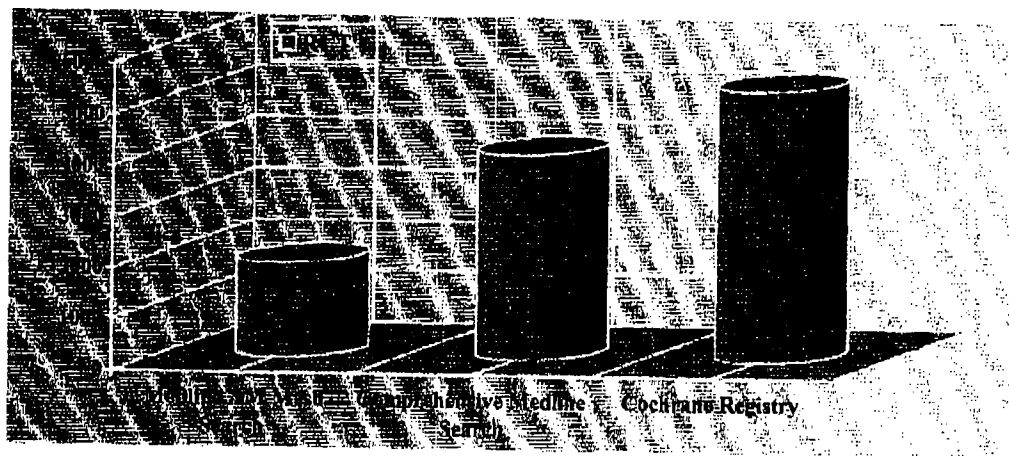
The criteria used in our selection process with regard to CAM topics is based on the definition of CAM developed at the April 1995 NIH, OAM Methodology Conference:

"CAM is a broad domain of healing resources that encompasses all health systems, modalities and practices and their accompanying theories and beliefs, other than those intrinsic to the politically dominant health system of a particular society or culture in a given historical period. CAM includes all such practices and ideas self-defined by their users as preventing or treating illness or promoting health and well-being. Boundaries within CAM and between the CAM domain and that of the dominant system are not always sharp or fixed."

However, since this definition does not necessarily guide decisions about whether an intervention falls under the rubric of CAM, we use the definition as an inclusion criteria and have developed three exclusion criteria. An intervention will be excluded from the Cochrane CAM registry if it meets two of the criteria:

1. Is the intervention, when practiced in this manner, at this dose, with these patients, almost exclusively practiced by those with "conventional medical qualifications"?
2. Is the intervention when practiced in this manner, at this dose, with these patients, a recommended treatment (i.e. a significant number of standard medical or paramedical references refer to use of the therapy as routine)?
3. Does the intervention fail to involve any theoretical divergence with mainstream medicine or science?

In Addendum 1 you will find the CAM search strategy that we have developed for MEDLINE, which also gives an overview of therapies that Cochrane considers to fall under the rubric of CAM. The value of this search strategy is demonstrated in the following graph, comparing the number of trials captured through three different search strategies. The left column reflects a search of MEDLINE using just the "Alternative Medicine" medical subject heading (MeSH) combined with "Randomized Controlled Trial" as a publication type. The middle column is a comprehensive MEDLINE search using the much broader Cochrane defined Complementary Medicine thesaurus and search strategy. The right column reflects a search using the Cochrane Complementary Medicine thesaurus and search strategy on multiple databases as well as conducting hand searches of non indexed journals, conference proceedings and abstracts



Systematic Reviews

Having identified all existing relevant literature, the next step is to conduct systematic reviews which will synthesize the results of these primary investigations. Systematic reviews are concise summaries of the best available evidence that address sharply defined clinical questions. The process of conducting a review is outlined in the following steps:

1. A well-formulated question is asked
2. A comprehensive search is conducted to identify all potentially relevant articles
3. Articles that meet explicit, reproducible criteria are selected
4. The study design and characteristics of each trial are critically appraised – there are 9 checklists and at least 25 different scales for assessing trial quality
5. The data are synthesized
6. The results are interpreted
7. A structured report is written
8. The review is updated periodically as new studies are identified

Looking specifically at steps 3 & 4, a clearly formulated question helps define the criteria that studies must meet to be included in the review. These inclusion criteria can be divided into five categories: 1) type of person (including disease, personal characteristics, population); 2) type of intervention; 3) type of control; 4) type of outcome; 5) type of

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study design. In evaluating the quality of the studies Cochrane uses scales, such as the Jadad and Oxman scales, with close attention paid to the recently revised Consort statement published in JAMA, April 18th, 2001. Of particular importance are the randomization process, allocation concealment, and masking (blinding) issues as well as whether there was adequate follow-up and attention to drop-outs. It is well recognized that poorly designed trials can exaggerate treatment outcomes and give misleading information on effectiveness. Likewise, poorly conducted reviews can be misleading, hence the emphasis on a systematic process to minimize error and bias.

There are now 208 systematic reviews in the Cochrane CM Field Reviews Registry. A list is attached (Addendum 2) but reviews range from topics such as acupuncture for low back pain, to echinacea for the prevention and treatment of the common cold.

What Use are Reviews to Us?

The value of a systematic review is that it helps keep us up to date. For consumers, systematic reviews can help cohere conflicting results of research. Policymakers can draw on systematic reviews when developing practice guidelines or conducting risks assessments and economic analyses. Practitioners (already overwhelmed at the number of journals published every year and the daunting task of synthesizing all this information so it is of use to them) can use reviews to answer specific clinical problems. Does this therapy work? Is it safe? Will it be safe and effective for my patient? Researchers can use reviews to define research agendas, summarize the existing data, refine their hypotheses and estimate sample sizes. What reviews cannot do is replace sound clinical reasoning. Knowledge, skills, values and research evidence need to be integrated into each patient clinical encounter. Reviews provide the quality evidence to this mix: evidence that is generated systematically, refined through a comments and criticisms process, and that is kept up to date on a regular basis.

The Value of Reviews – A Brief History in Time

As an example of the impact a systematic review can have there is an interesting short tale about the history of St. John's Wort in the U.S. St. John's Wort was until recently a little known herb in this country. In 1996, however, a founding member of the Cochrane CM Field, Klaus Linde, and some colleagues published a systematic review in the British Medical Journal showing the anti-depressant effects of St. John's Wort. Six months later the television show 20/20 used the review as the basis for a program. By 1997, St. John's Wort had gone from being well below the 20 best selling herbs to being one of the top 10. It reached the radar screen of the NIH and in 1998 they funded a multi-center Phase III clinical trial of St. John's Wort for severe depression. Had Linde never published his review the latter part of this story probably would still not have happened. Most of the literature showing the safety and effectiveness of this herb was published in non-English journals and no-one had ever gathered together this information to critically appraise it and draw out its clinical findings.

The Role of the Consumer in the Cochrane Collaboration

The Collaboration puts a high priority on consumer input throughout all levels of activity, from identifying important questions to commenting on drafts of reviews and helping disseminate results. As a whole, the Collaboration is a highly successful model of international cooperation and, especially in countries such as the United Kingdom, a model of participatory research among consumers, policymakers, investigators and clinicians.

Within the CM Field, our consumer representative, Claire Allen, has been very active in helping reviewers make their reviews more consumer friendly and composing lay summaries. These consumer related changes are timely – since 1999 all Cochrane abstracts of completed reviews appear in MEDLINE. Claire has also been involved with surveying consumers to identify obstacles to becoming involved with Cochrane.

Policy Recommendations Regarding the Evaluation of Research Literature in CAM

The work of the Cochrane CM field and CAM literature evaluation has only just begun. The effort in producing systematic reviews needs to continue and the scope of the work and its impact needs to be broadened. Specifically, I recommend that the infrastructure and collaborative work of the Cochrane CM Field be allocated on-going support allowing for continued maintenance of the registry, and coordination of the Field. With sufficient support the Field can increase its current work and significantly add to its value by:

1. Increasing the availability of reviews and their potential value by:
 - a. Making them available in the offices of policymakers, in public libraries and community health centers through on-line subscription to the Cochrane Library.
 - b. Developing executive summaries of systematic reviews that clearly and concisely state the results of the reviews.
 - c. Developing electronic, jargon-free versions of systematic reviews with hypertext links to allow readers with various backgrounds to access information at different levels of complexity
 - d. Expanding the current CM Field web-site (www.compmmed.ummhc.umaryland.edu) to include access to review summaries and to include consumer-friendly information.
2. Increasing participatory approaches to research in this country to ensure knowledge for action, in contrast to knowledge for understanding.
3. Identifying the public's needs through working with organizations such as the NCCAM Clearinghouse
4. Commissioning topics for reviews so that the questions addressed and the information developed are relevant to users of these treatments
5. Developing methodologies to evaluate non-randomized controlled trials, thus broadening the pool of information that can be drawn from.

With support in the region of \$500,000 a year the Field would be able to undertake an ambitious program of generating and disseminating high quality information to the public

Brian M. Berman, M.D.

The Challenge of Integrating CAM Research into Conventional Academic Institutions and the Training of CAM Practitioners as Research Investigators

The second half of my presentation is focused around issues relative to ensuring that research in CAM meets the highest scientific standards. A great deal of research is needed in this field and to accomplish this task we must tap into the resources of our country's academic institutions, for the infrastructure they provide as well as their intellectual wealth. At the same time, we need to ensure that those involved in CAM research are knowledgeable about the therapies they are investigating and cognizant of their unique paradigms.

Our center at the University of Maryland has been in existence now for 10 years so we are well aware of the challenges of bringing CAM research into an academic medical setting. I would like to emphasize, however, that taking an evidence-based approach to CAM has been the basis of our success in developing positive relationships within the institution. Through research collaborations with colleagues in Departments such as Epidemiology, Medicine and Pediatrics as well as the Schools of Dentistry, Pharmacy and Nursing, we have built a large clinical and pre-clinical trials program. Just as importantly, we have built up trust and respect and nurtured a common curiosity in finding out what works and what doesn't and how this translates to improving the care of our patients.

Challenge

Lack of knowledge and understanding of CAM among the conventional medical community is perhaps one of the first challenges facing any CAM initiative in a medical school or university. There is still a lot of bias against CAM and unwillingness to look at these therapies. Also, at times, if there is willingness, the interest can be driven more by chasing sources of funding. This latter scenario can lead to the unfortunate event of a highly experienced researcher designing and being funded for a study that is not sensitive to the manner in which a therapy is practiced. In addition, researchers may not have a good understanding of what are the key questions that need to be answered.

③ Another issue that relates to the above points is the importance of a clinical base in order to build a program of clinical research in CAM. At our own center we have a fully functioning out-patient clinic staffed by practitioners dual-trained in conventional medicine and CAM as well as highly qualified CAM practitioners. We have found the clinic to be vital as a nurturing-ground for research questions that are firmly based in clinical reality. However, establishing a clinic of this sort within an academic medical environment is not always welcomed or readily supported by the institution.

④ Complementary medicine research has suffered from the lack of CAM practitioners who are knowledgeable about research. The value of an academic-based center is the possibility of developing a team approach to designing and conducting rigorous CAM studies that draws on the expertise of methodologists, clinicians and CAM practitioners.

Nonetheless, the role of these centers should also be to train CAM practitioners to become skilled CAM researchers. These researchers, in turn, will ensure the future leadership of the field.

Even with the best team and with highly skilled CAM investigators, there are many practical issues, common to almost all research, in conducting well-designed studies. First there is the issue of limited funding resources for the type of large, multi-center trials that are needed. Some of the many challenges then of seeing the research trials through to their conclusion include: availability of adequate space to run the studies; the large amount of paperwork required by Institutional Review Boards and funding bodies; and the difficulty of keeping patients invested in the study especially if they are randomized into an arm of the study that does not include the CAM intervention.

Recommendations

Good science is the key component to evaluating the role CAM can and should play in the health care of Americans. In turn, education and training are key components in creating a community dedicated to rigorous evaluation of CAM. I have a number of recommendations for achieving these aims:

1. Fund a network of centers of excellence at academic institutions dedicated to the investigation of CAM. (Work of this sort has already been started by NCCAM and is creating the infrastructure necessary to support large and far-reaching research programs as well as educate and train a growing pool of investigators dedicated to the CAM field. The scope and number of these centers needs to grow)
2. Encourage collaboration between the CAM community, government, industry, philanthropy, and academic health centers through forged partnerships and joint funding.
3. Fund career development initiatives that would include:
 - (a) Research fellowships that include didactic teaching and hands-on training with appropriate mentoring aimed at creating skilled CAM clinical researchers.
 - (b) Master's of science degree in epidemiology with a CAM clinical research track, providing broad, rigorous training in research methods, closely mentored research experience and a specific focus on CAM interventions in a two year curriculum.
 - (c) Critical appraisals training focused on finding and assessing the scientific literature
 - (d) A national core curriculum in CAM for conventionally trained practitioners (including medical students, residents, pharmacists, nurses)
 - (e) CAM "tracks" at medical schools and in residency programs allowing interested individuals to focus on CAM. Ideally, both (d) and (e) would include experiential elements; history, philosophy and clinical uses of therapies; finding and assessing the evidence; self-care; and methodological issues in CAM research.

- f. The creation of a centralized database of curriculum topics and informational material to facilitate integration of CAM into existing courses
- 4. Encourage the NIH to continue funding and expand evaluation of CAM as well as research training initiatives.
- 3. Support of technology assessment workshops.

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Key Summary of Systematic Review
from Cochrane → NLM

And for Recommendation

Attitudinal Change → will find results

Don Lendberg Statement

CAM Information for Summer

ADDENDUM 1

Cochrane Collaboration MEDLINE Search Strategy for Complementary and Alternative Medicine

Therapies which are undeniably complementary medicine but which may not be clearly described as such in trial reports

1 ACUPUNCTURE

- 1.1 Insertion of an acupuncture needle
- 1.2 Stimulation by any modality of a recognised acupuncture point
- 1.3 Stimulation by any means other than manual pressure of a trigger point, defined as a locus in a muscle of increased tenderness.

2 HOMOEOPATHY

- 2.1 Administration of any remedy described as homoeopathic or produced by serial dilution and agitation

3 HERBAL MEDICINE (INCLUDES AROMATHERAPY)

- 3.1 Administration of any form product derived from plant or fungal material, including essential oils (aromatherapy).
- 3.2 Any product with fewer than 5 identified chemical constituents derived from plant sources will be excluded.

4. MANIPULATIVE THERAPIES: OSTEOPATHY AND CHIROPRACTIC

- 4.1 Any intervention brought about by the hands directly on the patient's body where the practitioner is identified as a chiropractor, osteopath or manual therapist
- 4.2 Manipulation or mobilisation of any bone
 - 4.2.1 Treatments of a break, fracture or dislocation will be excluded
 - 4.2.2 Concomitant use of general or local anaesthetic will be excluded
- 4.3 Sustained contact between the practitioners hands and the subject's cranium or sacrum.
- 4.4 Any technique described as cranial therapy / osteopathy, cranio-sacral therapy / osteopathy

5. MASSAGE

- 5.1 Any form of soft-tissue manipulation in which the intended effects are non-specific, that is, they are intended to bring about general improvements in health
- 5.2 Use of any of the following techniques: effleurage, gentle stroking, soft-tissue manipulation, myofascial release, sports massage, connective tissue massage, Bidegewebssmassage, caring touch, Hellerwork, Trager, Zero Balancing, Rolfing, Structural integration, Functional integration, Feldenkrais, Bowen therapy, neuromuscular technique, muscle energy techniques, proprioceptive neuromuscular facilitation, contract-relax / hold-relax, post-isometric contraction, strain counterstrain, shiatsu, acupressure, bioenergetics, manual stimulation of trigger points (see above), mechanical massage tools.
- 5.3 An intervention brought about by the hands directly on the patient's body where the practitioner is identified as a massage or body work therapist or a practitioner of any of the techniques mentioned in 5.2

6. HYPNOSIS

- 6.1 Induction of any mental state described as hypnotic by non-pharmacological means. The state can be induced by the subject him or herself.

6.2 Use of verbal suggestions by another whilst the subject is in a mental state thought to be receptive to suggestion, for example, in deep relaxation or under anaesthesia.

7. RELAXATION AND MEDITATION TECHNIQUES

7.1 Any method in which the subject undertakes mental exercises in order to reduce mental and / or physical arousal.

7.2 Any method in which the subject changes posture or breathing in order to reduce mental and / or physical arousal

7.3 Use of any of the following techniques: Jacobsen, sequential muscle relaxation, Mitchell method, autogenic training, visualisation, therapeutic imagery, tai chi, chi gong

8. HEALING AND THERAPEUTIC TOUCH

8.1 Attempts to bring about healing by an effort of will

8.2 Manipulation of an unspecified form of energy or aura for healing purposes by placing hands on or near the subject's body.

9. REFLEXOLOGY

9.1 Manual stimulation of points on the foot thought to correspond to the organs and structures of the body

10 IRIDOLOGY

10.1 Diagnosis of disease and dysfunction in organs other than the eye by analysis of characteristic markings of the iris.

11 ALEXANDER TECHNIQUE

11.1 Therapy designed to increase awareness and voluntary inhibition of personal habitual patterns of rigid musculoskeletal constriction

12 KINESIOLOGY

12.1 Diagnosis of non-musculoskeletal disease and dysfunction by looking for patterns of muscle weakness

13 ANIMAL EXTRACTS

13.1 Administration of any form of product derived from animal material

13.2 Any product with fewer than 5 identified chemical constituents derived from animal sources will be excluded

13.3 Any product used to provide specified compounds which are part of a necessary diet will be excluded

14. CANCER OR AIDS TREATMENT

14.1 Interventions offered by any institution self-defined as alternative or unconventional or which treats cancer or AIDS without drugs, surgery or radiotherapy

Therapies which can sometimes be described as complementary medicine

I. NUTRITION

I.I Any form of supplementation with vitamins, minerals or fatty acids to treat or prevent disease apart from:

I.I.I Treatment of deficiency disease (defined as any disease caused by levels of intake of a nutrient which are persistently lower than RDA)

I.I.II prevention of neural tube defects

I.I.III treatment of premature infants

I.I.IV treatment of cancer with b and d vitamin derivatives

I.I.V treatment and prevention of osteoporosis with calcium vitamin D

I.I.VI vitamin e or essential fatty acids to treat dermatological conditions

I.I.VII essential fatty acids to treat or prevent cardiovascular disease

I.I.VIII magnesium supplementation for cardiovascular disease

I.I.IX treatment and prevention of measles using vitamin A

I.I.X prevention of eye disease

- I.I.XI prevention of cancer in those not at increased risk
- I.I.XII treatment of insulin dependent diabetes mellitus
- I.I.XIII treatment of disease in developing countries
- I.I Elimination of any food from the diet other than when that food is not thought to cause disease by conventionally understood allergic mechanisms or by raising or reducing levels of an identifiable substance in the body apart from:
 - I.I.I Treatment or prevention of coeliac disease, ulcer
 - I.I.II Adherence to any of following diets: Hay, Dong, macrobiotic, high fibre for weight loss, Cambridge, vegetarian, vegan, "stone age", raw foods, essential fatty acid diet for multiple sclerosis

II PSYCHOLOGICAL INTERVENTIONS

- II.I Any form of talking therapy, counselling or social support other than:
 - II.I.I treatment of any form of mental health problem including problem behaviour (eg. obesity)
 - II.I.II peer support / self-help groups
 - II.I.III non-specific social support

III HYDROTHERAPY

- III.I Bathing in water in which salts or plant products have been added
- III.II Bathing in water chosen because of a high-concentration of salts
- III.III Bathing in natural springs and spas
- III.IV Bathing in alternatively warm and then cool water or hot air and cool water.
- III.V Any of the following: sitz baths, wraps, hydrogalvanic baths, carbon dioxide baths, underwater jet massage, mud packs, hyperthermia.

Complementary Medicine Field Search Strategy

Terms in italics are excluded

- | | |
|--|------------------------------------|
| 001 tai chi.tw. | 016 effleurage.tw. |
| 002 qigong.tw. | 017 soft tissue manipulation.tw. |
| 003 yoga.tw. | 018 myofascial release.tw. |
| 004 yoga/ | 019 aston patterning.tw. |
| | 020 connective tissue massage.tw. |
| 005 reflexology.tw. | 021 bidgewebsmassage.tw. |
| | 022 caring touch.tw. |
| 006 therapeutic touch.tw. | 023 hellerwork.tw. |
| 007 spiritual healing.tw. | 024 trager.tw. |
| 008 faith healing.tw. | 025 bowen therapy.tw. |
| | 026 bowen technique.tw. |
| "pnt" is short for "proprioceptive neuromuscular facilitation" a technique used by many manual therapists. However, it is also an abbreviation for a variety of phosphorylated compounds and for "primary nonfunction", a problem in transplantation | 027 neuromuscular therapy.tw. |
| 009 pnf.tw. | 028 bowen work.tw. |
| 010 <i>phosphorylated</i> .tw. | 029 muscle energy technique\$.tw. |
| 011 <i>primary nonfunction</i> .tw. | 030 neuromuscular facilitation.tw. |
| 012 <i>exp transplantation</i> / | 031 shiatsu.tw. |
| 013 10 or 11 or 12 | 032 zero balancing.tw. |
| 014 9 not 13 | 033 rolfing.tw. |
| | 034 structural integration.tw. |
| 015 proprioceptive neuromuscular facilitation.tw. | 035 functional integration.tw. |
| | 036 acupressure.tw. |
| | 037 trigger point\$.tw. |
| | 038 post isometric contract\$.tw. |
| | 039 contract relax.tw. |

040 hold relax.tw.

041 *relaxation/

042 *autogenic training/

043 exp *hypnosis/
suggestion

044 iris diagnosis.tw.

045 iridolog\$.tw.

046 shark cartilage.tw.

047 exp *tissue extracts/tu
actihaemyl
cell extracts
liver extracts
pancreatic extracts
pancreatin
placental extracts
thymus extracts

048 *bees/

bee venoms are conventionally used in
"immunotherapy".

049 exp *bee venoms/ad,tu

050 immunotherapy/

051 anaphylaxis/

052 desensitization, immunologic/

053 50 or 51 or 52

054 49 not 53

055 *honey/

056 alexander technique.tw.

057 hoxsey.tw.

058 gerson.tw.

059 qi gong.tw.

060 chi kung.tw.

061 chikung.tw.

062 doman delcato.tw.

patterning and conductive education are forms of
treatment for brain damaged children

063 patterning.tw.

064 exp *brain damage, chronic/

065 conductive education.tw.

066 (63 or 65) and 64

067 unani.tw.

068 flower remedy\$.tw.

069 vega test\$.tw.

Colonic irrigation is an alternative modality but is
used sometimes during surgery or for the treatment of
intestinal disease

070 colonic irrigation.tw.

071 exp surgery, operative/

072 exp intestinal diseases/

073 71 or 72

074 70 not 73

075 *sensory deprivation/

076 restricted environmental stimulation therapy.tw.

077 vitalism/

This bit was a mistake and is corrected nearer the end.

078 *terpenes/ad,tu

079 exp *vitamins/tu,ad

080 exp *retinoids/tu,ad

081 squalene/

082 exp *carotene/

083 exp *antioxidants/

084 or/79-83

085 75 not 84

Some physical therapy procedures are used in
complementary medicine

106 natural childbirth/

086 exp **physical therapy/*
 balneology
 amniotherapy
 baths
 baths, finnish
 mud therapy
 cryotherapy
 cryosurgery
 drainage, postural
 electric stimulation therapy/
 electroacupuncture
 transcutaneous electric nerve
stimulation
 exercise therapy
 motion therapy, continuous passive
 hydrotherapy
 hyperthermia, induced
 amniotherapy
 diathermy
 short-wave therapy
 ultrasonic therapy
 manipulation, orthopedic
 massage
 acupressure
 photochemotherapy
 hematoporphyrin photoradiation
 puva therapy
 photopheresis
 phototherapy
 color therapy
 heliotherapy
 ultraviolet therapy
 rewarming
 thalassootherapy

These are the ones we are removing

087 exp **rewarming/*
088 exp **photochemotherapy/*
089 exp **postural drainage/*
090 exp **cryotherapy/*
091 *motion therapy, continuous passive/*
092 *exercise therapy/*
093 exp *phototherapy/*
094 exp *hyperthermia, induced/*
095 **physical therapy/*

Take out orthopedic manipulation where associated
with treatment of fractures or dislocations

096 **manipulation, orthopedic/*
097 exp **fractures/*
098 exp **dislocations/*
099 97 or 98

Take out water birth

101 **baths/*
102 exp **delivery/*
103 exp **labor/*
104 102 or 103
105 101 and 104

107 exp alternative medicine/
 alternative medicine
 acupuncture
 acupuncture anesthesia
 acupuncture therapy
 acupuncture analgesia
 electroacupuncture
 meridians
 anthroposophy
 aromatherapy
 "biofeedback (psychology)"
 chiropractic
 color therapy
 diet fads
 eclecticism
 electric stimulation therapy
 electroacupuncture
 transcutaneous electric nerve
 stimulation
 homeopathy
 "imagery (psychotherapy)"
 kinesiology, applied
 massage
 acupressure
 medicine, traditional
 medicine, african traditional
 medicine, arabic
 medicine, unani
 medicine, ayurvedic
 medicine, herbal
 medicine, unani
 medicine, oriental traditional
 medicine, chinese traditional
 shamanism
 mental healing
 "mind-body relations (metaphysics)"
 moxibustion
 music therapy
 naturopathy
 organotherapy
 tissue therapy
 radlesthesis
 reflexotherapy
 rejuvenation
 relaxation techniques
 meditation
 therapeutic touch

108 osteopathic medicine/

109 oils, volatile/

110 exp plants, medicinal/

 aloe
 areca
 arnica
 artemisia
 belladonna
 cannabis
 capsicum
 cinchona
 coca
 colchicum
 digitalis

erythrina
 eucalyptus
 ferula
 garlic
 ginseng
 legumes
 acacia
 cassia
 glycyrrhiza
 mustard
 papaver
 plantago
 podophyllum
 rauwolfia
 rhamnus
 rhubarb
 stramonium
 valerian
 veratrum
 viscum

111 exp plant extracts/

 cascara
 curare
 drugs, chinese herbal
 guaiaac
 "ipecac (syrup)"
 podophyllin
 podophylotoxin
 etoposide
 psyllium
 senna
 tragacanth
 turpentine

112 exp plant oils/tu,ad

 castor oil
 corn oil
 cottonseed oil
 croton oil
 iodized oil
 ethiodized oil
 linseed oil
 safflower oil
 sesame oil
 soybean oil

Take out studies on chemistry, classification, genetics, ultrastructure or virology of edible plants. Take out studies on plants related to food industry. Take out immunotherapy (which may use plant extracts)

113 exp *plants, edible/ch,cl,ge,ul,vi

114 exp *food services/

115 *immunotherapy/

116 or/109-112

117 or/113-115

118 116 not 117

Take out cannabis and areca (betel nut) where this is the disease not the treatment

119 cannabis/

120 areca/

121 exp *substance use disorders/

122 (119 or 120) and 121

Take out carotid and ocular massage and treatment of pressure sores

- 123 *carotid body/
- 124 *intraocular pressure/
- 125 *glaucoma/
- 126 exp *carotid arteries/
- 127 *decubitus ulcer/
- 128 carotid.tw
- 129 or/123-128
- 130 massage.ti,ab,sh. and 129

Take out studies which are about bees, rather than their therapeutic use

- 131 *bees/ah,ch,cl,em,ge,gd,ph,re,ul,vi

Take out podophyllotoxins and pancreatin which are conventional drugs.

- 132 exp podophyllotoxin/
- 133 *pancreatin/

This bit does the physical therapy search

- 134 or/87-95,100,105
- 135 86 not 134

Take out a variety of other things

- 136 *dietary fiber/
- 137 electric stimulation therapy/
- 138 immunotherapy.tw
- 139 exp iodized oil/

These bits connect up the various bits of the search.
140 is what we do want, 141 what we don't.

- 140 or/1-8,14-48,54-62,66-69,74-77,85,106-108,118,135 83
- 141 or/122,130-133,136-139

Terpenes are substances derived from plants. Some, like certain vitamins, squalene, retinoids etc. are conventional drugs.

- 142 exp *terpenes/ad,tu
 - cannabinoids
 - cannabidiol
 - cannabinol
 - tetrahydrocannabinol
 - carotenoids
 - bacteriorhodopsin
 - carotene
 - beta carotene
 - canthaxanthin
 - xanthophyll
 - diterpenes
 - aphidicolin
 - dolichol
 - dolichol phosphates
 - forskolin
 - phorbols
 - phorbol esters
 - phytanic acid
 - phytol
 - retinoids

acitretin
etretinate
fenretinide
isotretinoin
retinaldehyde
tretinoin
vitamin a

eugenol
gefarnate
menthol
norbornanes
bornanes
camphor
mecamylamine
toxaphene
polyisoprenyl phosphates
dolichol phosphates
polyisoprenyl phosphate sugars
polyisoprenyl phosphate monosaccharides
dolichol monophosphate mannose
polyisoprenyl phosphate oligosaccharides
pyrethrins
allethrin
sesquiterpenes
farnesol
santonin
trichothecenes
t- toxin
trichodermin
thapsigargin
thymol
bromthymol blue
triterpenes
glycyrrhetic acid
carbenoxolone
gossypol
sapogenins
oleanolic acid
squalene

- 143 exp *vitamins/ad,tu
- 144 exp *retinoids/ad,tu
- 145 squalene/
- 146 exp *carotene/
- 147 exp *antioxidants/
- 148 or/143-147
- 149 142 not 148

- 150 exp *herbs/
- 151 140 or 149 or 150
- 152 151 not 141

152 is the total search for complementary medicine

All the following is the cochrane search for clinical trials

- 153 randomized controlled trial.pt
- 154 controlled clinical trial.pt
- 155 randomized controlled trials.sh
- 156 random allocation.sh
- 157 double blind method.sh

158 single blind method.sh.
 159 or/153-158
 160 (animal not human).sh.
 161 159 not 160
 162 clinical trial.pr.
 163 exp clinical trials/
 164 (clin\$ adj25 trial\$).ti,ab.
 165 ((singl\$ or doubl\$ or trebl\$ or tripl\$) adj25
 (blind\$ or mas
 166 placebos.sh.
 167 placebo\$.ti,ab.
 168 random\$.ti,ab.
 169 research design.sh.
 170 or/162-169
 171 170 not 160

172 171 not 161
 173 comparative study.sh.
 174 exp evaluation studies/
 175 follow up studies.sh.
 176 prospective studies.sh.
 177 (control\$ or prospectiv\$ or volunteer\$).ti,ab.
 178 or/173-177
 179 178 not 160
 180 178 not (161 or 172)
 181 161 or 172 or 180

Combine complementary medicine and cochrane search

182 152 and 181

Complementary Medicine and the Cochrane Collaboration

EVERY YEAR, millions of US consumers spend billions of dollars on alternative and complementary medical treatments.¹ A similar trend exists in the United Kingdom and Australia.^{2,4} As people increasingly use these treatments, questions arise from consumers, clinicians, payers, and policymakers as to the effectiveness of these interventions.

The Cochrane Complementary Medicine Field

To meet the increasing demand for evidence-based complementary medicine (CM), a CM Field, funded by the National Institutes of Health Office of Alternative Medicine, was established within the Cochrane Collaboration⁵ in 1996. The

goal of the Cochrane Collaboration is to produce, maintain, and disseminate systematic reviews on all topics in health care. The CM Field focuses on CM topics. Two major products of the Cochrane Collaboration are a database of systematic reviews and the Cochrane Controlled Trials Registry, the largest registry of its kind.⁶ Both databases are updated quarterly with information added regularly by the CM Field.

The systematic review is a method par excellence for synthesizing evidence on a given topic, and policy agencies are increasing use of it to summarize evidence.⁷ Cochrane reviews are more transparent than other reviews,⁸ so that conclusions are replicable and methods are explicit. Systematic reviews are valuable even when the results are inconclusive because reviews point out where knowledge gaps exist.

Search Strategies to Retrieve Randomized Trials of CM

Since the CM Field has been functioning, a great deal of effort has focused on laying the groundwork for reviews by con-

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structuring a database of randomized controlled trials (RCTs) on CM topics. Capturing all relevant trials in MEDLINE has yielded surprising challenges. The scope of practices defined as complementary within the CM Field is broader than those captured in a MEDLINE search of the term *alternative medicine*. For example, Chinese movement therapies such as Qigong and Tai Chi are considered complementary therapies by the Field's standards, but are not accessed by a hierarchical MEDLINE search of the term *alternative medicine*. Similarly, herbal remedies may be described by MEDLINE as plant extracts rather than by any alternative medicine term. To aid MEDLINE searching, a 250-line MEDLINE search strategy has been written and is available for public use.⁹

Assessments of MEDLINE sensitivity (the proportion of RCTs identified by a MEDLINE search relative to a "gold standard" of the known number of RCTs) have demonstrated that on average, MEDLINE searches yield only half of all known trials on a given topic, with CM topics usually scoring below average (eg, 17% for homeopathy, 31% for *Ginkgo biloba*, and 58% for acupuncture).¹⁰ The first reason for low MEDLINE sensitivity may be that articles are appearing in journals not indexed by MEDLINE. This is true for acupuncture¹¹ and vitamin C for the common cold.¹² Of approximately 16 000 serial medical journals worldwide, MEDLINE references about 3700 (23%).¹⁰ Of the 695 CM journals worldwide identified by the Office of Alternative Medicine and the National Library of Medicine, MEDLINE indexes 69 (10%). Collaborations between the National Library of Medicine, the CM Field, and the Office of Alternative Medicine should soon result in increasing the number of indexed CM journals and expanding the MEDLINE thesaurus to include more CM search terms.

To retrieve studies indexed in other databases, the CM Field is searching both standard medical databases and specialized CM databases. By mid-1998, the Cochrane CM Trials Registry contained more than 3500 RCTs, with only 33% identified by a MEDLINE search for RCTs in alternative medicine and 20% not found in MEDLINE. Periodically, the CM registry uploads its trials to the Cochrane Controlled Trials Registry, making these trials available to individuals with access to the Cochrane library. The CM Field maintains the CM registry, adds new trials, assists reviewers doing CM reviews, and proactively provides references to all 40 Cochrane Collaboration reviews and protocols that have a CM component. A second reason for low MEDLINE sensitivity is that articles exist in journals that are not indexed by any electronic database. Volunteers within the CM Field are now searching by hand approximately 40 indexed and nonindexed journals in English, German, Italian, Japanese, and Spanish and are reading every article published in these journals back to their first issues to locate every RCT.

Publication Bias

A third reason for low MEDLINE sensitivity is that studies exist that have never been fully published in any journal ("gray literature").¹⁰ Estimates from conventional medicine show that only about 50% of the RCTs that appear as conference proceedings ever materialize into published journal articles.¹⁰ Some observations¹³ estimate CM gray literature to be at least as plentiful. Complementary medicine gray literature includes expected sources, such as conference proceedings and dissertations, and unexpected sources such as US patents records.¹⁴

Beyond the hard-to-find trials in the gray literature lie the even harder to find studies that do not appear in print anywhere

and exist only in homeopathic company data files or researchers' file drawers.¹⁵ Gray literature plus unpublished data are collectively termed unpublished studies.¹⁶ Publication bias is "the tendency of investigators, reviewers, and editors to differentially submit or accept manuscripts for publication based on the direction or strength of the findings."¹⁷ To the extent that publication bias exists, systematic reviews that omit unpublished studies risk overestimating treatment effects. Bias has been demonstrated both in what investigators submit to journals¹⁶ and what conference abstracts editors accept.¹⁷ However, whether to include unpublished studies in reviews is still a source of debate.¹⁸ The influence of unpublished studies in CM systematic reviews is being analyzed by the CM Field as part of a review of 154 CM systematic reviews.⁹ Until the value of including CM unpublished studies can be answered more conclusively, the CM Field will continue to search for unpublished studies to help answer a frequently asked question: How much evidence exists in CM?

Examining how publication bias skews the CM evidence is important for the CM Field because some forms of publication bias may be unique to CM. One question is whether both positive and negative publication biases exist in CM. Asked another way, do CM journals tend to publish results favoring CM treatments and conventional medical journals publish results not favoring CM treatments?

Examining publication bias is not always straightforward. A study by the CM Field found that studies published in Russia and China had a disproportionately high number of statistically significant results (97% and 99%, respectively) when compared with England (75%).¹⁸ It is not yet evident whether these high proportions are due to extreme forms of publication bias or low study quality, which overestimated treatment effects.^{19,20} The CM Field is obtaining translations of these studies to examine study quality. The qualitative results will determine whether it is practical to devote efforts to the tedious task of identifying unpublished studies.

Language Bias

Moher and colleagues²¹ demonstrated that the quality of studies published in French, German, Spanish, and Italian is comparable with those published in English. The present research of the CM Field will extend methodological quality knowledge into studies from Russia and China. Egger and colleagues²² demonstrated that a language-related publication bias exists in which authors who publish in both German and English tend to report nonsignificant findings in German and significant findings in English. Preliminary observations suggest that an additional language bias may exist for CM. Regardless of whether results are significant, some CM topics are almost exclusively published initially in languages other than English. A systematic review on St John's wort for depression²³ noted that none of the trials had been originally published in English, although some were subsequently published in English. A similar experience has been reported for *Ginkgo biloba* for cerebral insufficiency,²⁴ which suggests that for certain topics in CM, there may be a language-related publication lag time—a trend not reported for conventional medicine. Trends such as this underscore the importance of the CM Field's effort to retrieve trials in languages other than English and to identify biases that may be unique to CM.

Quality Assessment of RCTs

Assessing study quality also may improve the validity of systematic reviews. The finding that low-quality studies have re-

Titles of Cochrane Systematic Reviews Pertaining to Complementary Medicine

Reviews completed

Acupuncture for asthma
 Acupuncture for nicotine addiction
 Balneotherapy (spa therapy) for arthritis
 Cabbage leaves to reduce breast engorgement in nursing mothers
 Garlic for lower-limb atherosclerosis
 Homeopathy for asthma
 Hypnosis for smoking cessation
 Massage for low-birth-weight infants
 St John's wort for depression
 Vitamin E for intermittent claudication
 Vitamin C for the common cold

Reviews in progress

Acupuncture for lower back pain
 Acupuncture for headache
 Acupuncture for osteoarthritis
 Alexander technique for asthma
 Echinacea for the common cold
 Evening Primrose Oil for premenstrual syndrome
 Ginkgo biloba for dementia
 Ginkgo biloba for intermittent claudication
 Manual therapy for neck pain
 Manual therapy for asthma
 Marine oil supplementation for type 2 diabetes mellitus
 Music therapy for dementia
 Padma 28 for intermittent claudication
 Pygeum africanum for benign prostatic hyperplasia
 Saeola cereale for benign prostatic hyperplasia
 Sarsaparilla for benign prostatic hyperplasia
 Spinal manipulation for low back pain
 Therapeutic Touch for wound healing
 Yoga for epilepsy

peatedly yielded exaggerated treatment effects has been documented for conventional medicine^{10,21} and acupuncture.²² Yet, methodological assessments are sometimes absent from non-Cochrane Collaboration CM systematic reviews. A summary of 29 meta-analyses of mind-body techniques, for example, demonstrated that only about half assessed study quality.²³ Although assessing study quality cannot compensate for fraudulent or inaccurate reporting, it can provide additional validity-related information to guide reviewers' conclusions. For CM, quality assessments will provide needed answers to another commonly asked question: How good is the quality of CM trials?

This quality question is usually raised as an implication that CM trials reflect lower methodological quality than conventional medicine trials. To examine this notion, Cochrane Collaboration methodologists are collaborating with members of the CM Field to compare the methodological quality of CM trials with conventional medicine trials on the same diseases. Low-quality meta-analyses for analgesic interventions have been found to be associated with more positive results than high-quality meta-analyses.²⁷ The analysis of CM reviews is to examine whether this can be replicated in low-quality vs high-quality CM reviews, and how conclusions of low-quality vs high-quality CM reviews on the same topic differ.

Reviews Completed by the CM Field

The CM Field has completed systematic reviews on acupuncture, massage, homeopathy, and herbal medicine. Nineteen reviews are in process (Table),²⁸ and the CM Field has commented on protocols of 12 planned and completed reviews.²⁹

Conclusions

Although there is no guarantee that systematic reviews will result in changing policy and practice, there is increasing evidence that policy organizations rely on systematic reviews more than they have in the past⁷ and that practitioners rely on reviews as a primary information source.²⁹ It has also been

suggested that consumers can use reviews to guide decision making.³⁰ Traditional literature reviews, however, have lacked explicit methods and have been susceptible to biases that generally tend to overestimate treatment effects.⁷ Therefore, at a time when the public is using CM treatments in record numbers and an explicit peer-reviewed and regularly updated systematic review method exists, it is imperative to apply this method to CM. The Cochrane Collaboration provides a forum of interdisciplinary cooperation in which to produce these reviews that we hope will result in improved patient care.

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Message From The Field Coordinator

The Complementary Medicine (CM) Field continues to grow in supporting the Cochrane Collaboration and in producing systematic reviews. As you will note, seven new reviews are complete and ten new reviews are in progress. These reviews are now available through our website.

The increased access to Cochrane reviews related to CM is thanks to the hard work of our Registry Coordinator Mac Beckner and web developer Ralph Reckly. That access as well as the indexing of Cochrane reviews on MEDLINE will go far to increase the awareness of the Cochrane Collaboration and to increase research related to CM. We still have a way to go, however. According to the World Health Organization, 70% of the world uses complementary and alternative therapies. In keeping with that, we continue to look for ways to increase international participation in the CM Field and to enhance the diversity of those involved. Language difficulties and cultural norms that can present challenges in conducting systematic reviews (see article on page 2) challenge us, in turn, to improve any language and cultural imbalances that exist in the Field. One suggestion offered to the Steering Group at its meeting in March 2000 was to add promoting inclusiveness to the list of Cochrane Collaboration principles.

I look forward to the continued growth of the CM Field and certainly welcome your suggestions on how we might improve and expand the Field.

Brian Berman, Field Coordinator

Conducting a Cochrane Review

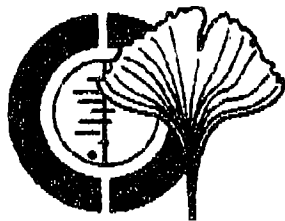
Who can do a Cochrane systematic review? In general, there are no exclusion criteria for who can undertake a review. There are some definite requirements, though: access to a computer, time, enthusiasm, and a sense of adventure! All Cochrane reviewers are volunteers and while we do not commission reviews on particular topics, we do recognize that volunteers are more likely to be able to review a question that they themselves want answered.

You'll find that Cochrane has resources available to help in the review process. RevMan is the Cochrane Collaboration's software for preparing and maintaining reviews in the appropriate format. Using RevMan, the reviewer can create protocols and reviews with text, study characteristics, comparisons, and study data and

then perform a meta-analysis, if appropriate. There are also training and support resources available, both self-paced exercises and more formal workshops. For details, visit www.cochrane.org/cochrane/.

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The Complementary Medicine Field Registry of Randomized Controlled Trials now contains approximately 5300 RCT's and CCT's, and another 5400 possible RCT's with nearly 1900 hard copy reports in the article archive. In June the updated registry was sent to the New England Cochrane Center (NECC) and it will be available on Issue 4 of the Cochrane Library by searching the keyword "compmed". Additionally, there are now 49 CM systematic reviews including 7 new reviews (see page 7) and 53 CM protocols registered on the Cochrane Library, with the total number of identified reviews in CM now over 200 (Linde).

We are continuing to execute database specific search strategies on all major bibliographic databases including the Cochrane library, as well as continuing to conduct hand searches of high priority CM journals. Additionally, in an effort to make the CM field registry more accessible to consumers, researchers and healthcare providers, we have mounted the registry so that it can be searched on the University of Maryland Complementary Medicine Program (CMP) website [<http://www.compmed.ummc.umaryland.edu>] Additional CM field information on the CMP website includes the CM field progress report and CM field advisory board members along with hyperlinks to Cochrane resources. In planning for the future, we are now evaluating Meerkat software as a means for managing the CM registry.

Individuals wishing to obtain a copy of the registry should contact the Registry Coordinator.

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The Colloquium theme will highlight key methodological, logistical, and social challenges that need to be addressed by the Collaboration in order to further its goals. The Colloquium includes plenary sessions, workshops, poster presentations and social events, providing Collaboration members with an opportunity to discuss their work and to look at the achievements of the Collaboration. This is the first Colloquium to be held in a developing country and it is hoped this will focus attention on recruiting participants from the developing world and making the work of the Collaboration more universally accessible.

8th INTERNATIONAL
 COCHRANE COLLOQUIUM
 25-29 October, 2000

Plenary 20: A Day
 Challenge for the
 Collaboration in the
 21st Century

Guests: Prof. David F. Cella
 Prof. David F. Cella

Consumer Update

Can Complementary Medicine be Intergrated into the National Health Service in the United Kingdom?

In June I attended the above Drug and Therapeutics Bulletin seminar. It was an interesting afternoon with presentations on different aspects of complementary medicine. A number of different complementary medicine practitioners attended, the majority from the UK, and the afternoon generated a great deal of discussion.

The afternoon started with David Pelter giving the Cochrane Collaboration's definition of complementary medicine: 'Complementary and alternative medicine (CAM) is a broad domain of healing resources that encompass all health systems, modalities and practices and their accompanying theories and beliefs, other than those intrinsic to the politically dominant health system of a particular society or culture in a given historical period. CAM also includes all such practices and ideas self-defined by their users as preventing or treating illness or promoting health and well-being. Boundaries within CAM and the CAM domain and that of the dominant system are not always sharp or fixed.' This definition became a theme throughout the afternoon. However it became apparent that complementary medicine (CM) has different meanings for different people.

It became clear that doctors' attitudes are changing, from CM being at the fringe of modern medicine to it becoming increasingly available on the NHS. It was reported also that adverse effects are rare, but that more primary research should be and is being carried out (there are 49 systematic reviews of CM in Issue 3, 2000 of *The Cochrane Library*¹). Most of the main complementary therapies are now covered by university degree courses apart from 'touch' based therapies. However, there seemed to be a general lack of confidence among general practitioners to learn complementary therapies and everyone agreed that better education and communication needs to take place between general and complementary practitioners.

The second presentation by George Lewith, Senior Research Fellow, Centre for the Study of Complementary Therapies, University of Southampton, confirmed the view that consumers want to make an informed decision about effectiveness and side effects of CM (or, in fact, conventional medicine). There was general consensus that CM is under-funded and under-resourced in the UK and that, if used more commonly, it could provide cost savings to the NHS. Again, it was emphasized that more research is needed before CM becomes part of the NHS provision.

Sarah Cant, Senior Lecturer from the University of Surrey, spoke at length about why consumers find CM attractive.

She suggested that consumers believe CM is more natural than conventional medicine and they have fewer concerns about side effects. Usually they have experienced failure from conventional practitioners and longer consultations with complementary providers give them a feeling of empowerment in their health care decisions. Because complementary practitioners treat consumers on an individual as well as holistic basis, consumers begin to have a greater understanding of their body and its reaction to the medical condition.

Consumers want to make
an informed decision
about effectiveness and
side effects of CM

Tina Raphael, a Lecturer in health care law and ethics, outlined the legal obligations of practitioners noting that although some CM practitioners are regulated, there is voluntary self-regulation for others. She also questioned how, in the absence of evidence, a complementary practitioner can inform the consumer of all the possible risks and benefits. She discussed obstacles to integrating CM into the NHS, the need to establish efficacy and safety, adequate training of practitioners, and the need for negotiation. It seems that CM will only be integrated if it is shown to be cost effective, if practitioners want it and if more research is undertaken.

Last, Michael Fox, Chief Executive of the Foundation for Integrated Medicine, reviewed the current position of the NHS in terms of complementary medicine. He reported that £0.80 in every £100 was spent on research in CM and this needs to be increased. He stated that the current position on regulation is unsatisfactory; there are over 150 different regulatory bodies for CM practitioners. One in five consumers is using CM in the UK with the most popular therapies being Herbal medicine (34%), Aromatherapy (21%), Acupuncture (20%), Homeopathy (17%), Massage (6%), Reflexology (6%), and Osteopathy (4%). Approximately 49,000 CM practitioners provide a huge variety of therapies at a cost of £1.6 billion, most of which is spent outside the NHS.

Claire Allen
Consumer Representative

¹Information on obtaining the Cochrane Library is found on page 5.

Find synopses of Cochrane reviews written for consumers at the Consumer Network web site: <http://hiru.mcmaster.ca/cochrane/cochrane/consumer.htm>

Include Dissertations in Systematic Reviews or Not?

One of the principles for systematic review is that all unpublished data should be included, if appropriate, but there is little information about doing so. Locating such data takes considerable time, effort, and expense, particularly if the author has not published the study and is no longer at the host institution. To what extent does the inclusion of dissertation research alter the findings or conclusions of a review?

In reviewing massage therapy for infants, we identified 17 dissertations. Almost all (13 studies) were excluded from the review, 11 because of no or improper randomization. Another three studies were subsequently published as a journal paper. That left one original dissertation that was included in our review although that one study made no difference to our review.

We also checked the Cochrane library and we found that 24 of the 878 reviews claimed to search for dissertations. However, only five reviews appeared to have identified at least one dissertation: three as an included study and two as an excluded study. In only one review did incorporating dissertation data affect the conclusion.

So what do we recommend? Allocate time and resources to the identification, retrieval and analysis of dissertations but be prepared that dissertations may not change the findings or conclusions of the review.

Andrew J. Vickers and Claire Smith

Lessons Learned while Doing a Systematic Review

Although I fully support Cochrane guidelines for conducting systematic reviews, there are a number of challenges that may be encountered due to the different scientific cultures and reporting conventions encountered in some countries. As an example, after I presented preliminary data on low energy laser irradiation (LELI) interventions in Russia at the Rome Colloquium in 1999, I was invited by the Infectious Diseases group to review LELI as adjuvant treatment for tuberculosis. While searching for publications, obtaining copies, writing letters to authors, and analysing the contents, I learned some lessons although some questions remain unanswered.

Of the 18 publications of controlled studies — all in Russian — only one stated that there was randomization. Not one author offered explanations in reply to my detailed letters, although one did send a letter of refusal. Analysis of the published texts revealed that only three publications could be considered for my review. Others were duplicates or suspected to be duplicates. For example, in a second publication from the same group of researchers using similar research methods, the number of patients was almost duplicated and some outcomes were the same. Without explanations from the authors about the design, the only option available to me was to analyse the phrases used to describe the origin of the control group. All studies showed a significant positive

effect of LELI, almost duplicating the outcomes (pulmonary cavities closed, perifocal infiltration reduced, no bacterial discharge).

All these authors believe that they not only conduct research, but that they save lives with LELI while evaluating it. However, in one study two physicians described the experimental application of LELI through rigid bronchoscope to children 1 to 4 years of age, under narcosis, using up to 12 procedures during one hospitalization.

Given that the quality of reporting for many of the studies was low, researchers did not use randomization, and authors did not reply to requests for further explanations, I am left to wonder: Can I believe that the one study where randomisation was mentioned really used this procedure? And, if not, how much reliance can we place upon systematic reviews based upon studies such as these?

Vasiliv Vlassov

At the 8th International Cochrane Colloquium meeting in Cape Town, South Africa, October 25-29, 2000, Dr. Vlassov will present a paper entitled "Low energy lasers for treatment of tuberculosis."

FOR

YOUR

INFORMATION

MEDLINE Listing

Cochrane Reviews are now listed in MEDLINE. The source is listed as the Cochrane Database of Systematic Reviews with the citation "(Cochrane Review)" appended to the title. This makes it difficult to identify cochrane reviews by searching for titles, but discussion is underway with the National Library of Medicine to amend the entries. If you have questions or comments about the MEDLINE indexing, contact Mark Starr, e-mail: mstarr@update.co.uk.

Introduction for Chinese Editors

The First National Exploratory Meeting on "Introduction to the Cochrane Collaboration and Evidence-Based Medicine" for the chief editors of leading Chinese medical journals was held in Chengdu in April 2000.

Cochrane News, Issue 18, June 2000.

Alternative Medicine Foundation, Inc.

The HerbMed® project continues to grow and gain recognition. HerbMed® is a non-affiliated evidence-based herbal database, providing independent scientific information on the use of herbs for health. Researchers find it a useful first point for tracking down RCTs for systematic reviews.

HerbMed® was chosen as Hot Pick in Science Magazine in June 2000 and Hot Site in USA Today in July 2000. The Western Journal of Medicine has featured the database and the foundation continues to receive testimonials and a record number of visitors.

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Jackie Wootton, M.Ed.

Tel: 301-581-0116; Fax: 301-581-0119

E-mail: jcw@amfoundation.org

Symposium on Systematic Reviews

For information about the 4th Symposium on Systematic Reviews: Beyond the Basics, contact Rochelle Seifas, Centre for Statistics in Medicine, Institute of Health Sciences, Old Road, Oxford, OX3 7LF, UK (e-mail: r.seifas@icrf.icnet.uk).

White House Commission Appointment

Dr. Wayne Jonas, CM Field Board Member, has been appointed to serve as a member of the White House Commission on Complementary and Alternative Medicine Policy.

How to Obtain the Cochrane Library

The Cochrane Library is published and distributed by Update Software. It is updated quarterly and is available in CD-ROM for Windows or 3-1/2 inch disk for Windows. Subscriptions are for one year and include current issue plus four quarterly updates. The Library contains the following information:

- ◆ The Cochrane Database of Systematic Reviews (CDSR)
- ◆ The York Database of Abstracts of Reviews of Effectiveness (DARE)
- ◆ The Cochrane Controlled Trials Register (CCTR)
- ◆ The Cochrane Review Methodology Database (CRMD)

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Fax: 1 760 734 4351
e-mail: info@updateusa.com

United Kingdom
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Middle Way
Oxford OX2 7LG UK
Tel: 44 1865 513 902
Fax: 44 1865 516 918
e-mail: update@cochrane.co.uk

News From The CM Field Board

Publications

Berman BM, Hartnoll S, Bausell B. 2000. CAM evaluation comes into the mainstream: NIH Specialized Centers of research and the University of Maryland Center for Alternative Medicine Research in Arthritis. *Complementary Therapies in Medicine* 8:119-122.

Berman BM, Bausell RM. 2000. The use of non-pharmacological therapies by pain specialists. *PAIN* 85:313-315.

Berman BM, Swyers JP, Ezzo J. 2000. The evidence for acupuncture as a treatment for rheumatologic conditions. In R. Panush (Ed.) *Rheumatic Disease Clinics of North America*. W.B. Saunders, Philadelphia, PA.

Berman BM, Swyers, JP, Singh B, Hartnoll S. 2000. The debate on alternative medicine: Finding a middle ground. *Alternative Therapies in Health and Medicine* 6(1): 98-101.

Ezzo JE, Berman BM, Hadhazy VA, Jadad AR, Lao L, Singh B. 2000 Is acupuncture effective for the treatment of chronic pain? A systematic review. *PAIN* 86:217-225.

Hondras MA, Linde K, Jones AP. Manual therapy for asthma (Cochrane Review). In: The Cochrane Library, Issue 3, 2000. Oxford: Update Software.

Jacobs J, Jiménez M, Malthouse MD, Chapman E, Crothers D, Masuk M, Jonas WB. Homeopathic treatment of acute childhood diarrhea: Results from a clinical trial in Nepal. *Journal of Alternative and Complementary Medicine*. 2000; 6:131-139

Jonas WB, Dillner DK. Protection of mice from tularemia infection with ultra-low, serial agitated dilutions prepared from *E. tularensis*-infected tissue. *Journal of Scientific Exploration*. 2000; 14: 35-52.

Jonas WB, Linde, K., Ramirez, G. Homeopathy and Arthritis. In: *Rheumatic Disease Clinics of North America*. Panush, R. S., (ed.) Philadelphia: W.B. Saunders Co., 2000; 26(1): 117-123.

Moerman D, Jonas WB. Toward a research agenda on placebo. *Advances*. 2000; 16: 33-46.

Richardson MA, Sanders T, Palmer JL, Greisinger A, Singletary SE. Complementary/alternative medicine use in a comprehensive cancer center and the implications for oncology. *J Clin Oncol*. 2000; 18(13):2505-14.

Sparber A, Jonas W, White J, Derenzo E, Johnson E, Bergerson S. Cancer clinical trials and subject use of natural herbal products. *Cancer Investigation*. 2000; 18(5), 436-439.

Tsutani K, Tsuruoka K, (trans). Soho iryo to Kokuran kyodo keikaku. *Orutanataribu Medisun* (Alternative Medicine) 2000; 4(3): 64-7. [Japanese translation of Ezzo J, Berman BM, Vickers AI, Linde K. Complementary Medicine and the Cochrane Collaboration. *JAMA* 1998; 280: 1628-30.

Presentations

Berman B.

"The University of Maryland Complementary and Alternative Medicine Program." Harvard State of the Science Symposium. Boston, MA (March 2000).

"Overview of Complementary Medicine." Supportive Care in Cancer. Washington DC (March 2000).

"Integration of Conventional and Complementary Medicine: The University of Maryland Experience." Association of American Medical Colleges Council of Deans. Puerto Rico (April 2000).

Jonas WB.

"Balancing Belief and Evidence in Alternative Medicine Decisions" (Workshop) 31st Annual Meeting of the Association of Applied Psychophysiology and Biofeedback. Denver, CO (April 2000).

"Applying Evidence-based Medicine Principles to Complementary Medicine." 48th Annual Clinical Meeting of the American College of Obstetrics and Gynecology. San Francisco, CA (May 2000).

"Complementary and Alternative Medicine: Actions and Interactions." 48th Annual Clinical Meeting of the American College of Obstetrics and Gynecology. San Francisco, CA (May 2000).

Jonas WB, Linde K.

"Homeopathy: State of the Science". International Conference Evidence-based Complementary Medicine. University of Munich, Munich, Germany (April 2000).

Romoli M.

"Changes and Limits in Evidence Based Research in Acupuncture." Conference sponsored by the Italian and Chinese Ministry of Health, Rome, Italy (September 2000).

Other

Dr. Mary Ann Richardson, M.P.H., Dr.P.H., CM Field Board Member, has been appointed program officer for extramural research at the National Center for Complementary and Alternative Medicine (NCCAM), National Institutes of Health. Dr. Richardson will direct NCCAM's oncology initiatives and manage the growing portfolio of oncology projects. She was previously Director of the University of Texas Center for Alternative Medicine Research in Cancer.

Dr. Kiichiro Tustani is handsearching two more acupuncture journals in Japanese for the Cochrane Registry: *Nihon Shinkyu Chiryō Gakkai Shi* (*The Journal of the Japan Acupuncture and Moxibustion Society*) 1951-1980 and *Ido no Nippon* (*The Journal of Japanese Acupuncture and Moxibustion*) 1948-2000.

- Dietary marine fatty acids (fish oil) for asthma
- Feverfew for preventing migraine
- Low level laser therapy for OA
- Low level laser therapy for RA
- Manual therapy for asthma
- Nutritional supplementation in stable chronic obstructive pulmonary disease
- Psychological therapies for sickle cell disease and pain

Low Level Laser Therapy (LLLT) in the Treatment of RA (Brosseau L, Welch V et al., 2000)

Objective: To assess the effectiveness of LLLT in the treatment of RA.

Selection criteria: Randomized controlled trials of LLLT for the treatment of patients with a clinical diagnosis of RA.

Main Results: Five placebo-controlled trials with a total of 204 patients. LLLT reduced pain by 70%, reduced morning stiffness duration by 27.5 minutes, and increased tip to palm flexibility by 1.3 cm relative to placebo. Functional assessment, range of motion and local swelling did not differ between groups.

Feverfew for preventing migraine

(Pitler MH, Vogler BK, Ernst E, 2000)

Objective: To systematically review evidence for or against the efficacy of feverfew versus placebo for the prevention of migraine.

Selection Criteria: Randomized, placebo-controlled, double-blind trials assessing the efficacy of feverfew for preventing migraine.

Main results: Four trials met inclusion criteria and majority suggested beneficial effects of feverfew compared with placebo. Highest quality trial, however, found no significant difference.

Conclusions: The efficacy of feverfew for the prevention of migraine has not been established.

LLT (continued)

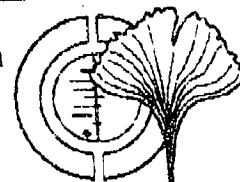
Conclusions: LLLT could be considered for short-term relief of pain and morning stiffness for RA patients. There is a need for RCTs that investigate the effects of wavelength, treatment duration of LLLT, dosage and site of application over nerves instead of joints on LLLT effectiveness.

REVIEWS in Progress

- Acupuncture for chemotherapy-induced nausea or vomiting among cancer patients *
- Acupuncture for lateral elbow pain in adults
- Acupuncture for osteoarthritis *
- Aerobic exercise interventions for people with HIV/AIDS
- Alexander Technique for chronic asthma
- Anti-oxidant foods or supplements for preventing cardiovascular disease in patients with and without ischemic heart disease
- Asthmatic exacerbations and magnesium sulphate
- Behavioral treatment of chronic low back pain
- Behavioural and cognitive interventions for faecal incontinence in children *
- Behavioural interventions for primary and secondary dysmenorrhoea *
- Breathing exercises in asthma
- Calcium and phosphate supplementation of human milk for promoting growth in preterm infants
- Cernilton for Benign Prostatic Hyperplasia
- Chinese herbal medicine for atopic eczema *
- Chinese medicinal herbs for chronic hepatitis B *
- Cognitive behaviour therapy for depressed carers of people with Alzheimer's disease and related disorders
- Complementary therapies for acne
- Cow's milk and childhood asthma
- Dietary marine fatty acids in asthma control
- Electrical stimulation for pressure sores
- Evening primrose oil or other essential fatty acids for premenstrual syndrome
- Food or supplements rich in omega-3 fatty acids for prevention of cardiovascular disease in patients with ischaemic heart disease
- Galantamine for Alzheimer's disease
- Ginkgo biloba in dementia and cognitive impairment
- Ginkgo biloba in intermittent claudication
- Manual therapy for mechanical neck disorders
- Marine oil supplementation in NIDDM
- Massage and aromatherapy for symptom relief in patients with cancer *
- Massage for low back pain *
- Mind/Body Therapy for Fibromyalgia
- Noninvasive physical treatments for chronic headache
- Omega-3 fatty acids supplementation for rheumatoid arthritis
- Omega-3 fatty acids for cystic fibrosis
- PFMT and/or biofeedback for faecal incontinence
- Phytoestrogens for menopausal symptoms
- PMS: Evening primrose oil
- Psychological interventions for non-ulcer dyspepsia *
- Pygeum africanum for Benign Prostatic Hyperplasia
- S-adenosyl-L-methionine for alcoholic liver diseases *
- Spinal manipulation for low back pain
- Tartrazine exclusion and asthma
- Therapeutic touch in wound healing
- Vitamin A for measles in children
- Vitamin B6 and placebo in premenstrual syndrome

* New for this issue

**Would You Like To Participate In The Cochrane Collaboration
Complementary Medicine Field?**



Name: _____ Country: _____

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Phone: _____ Fax: _____ E-mail: _____

Experience: _____

Please use this form to contact us:
 You may post or fax to:

Lowry, S. and R. A. D. (1988) The effects of the 1987/88 El Niño on the marine biota of the south-eastern Indian Ocean. *Journal of Marine Research*, **46**, 111–129.

Support Work of Collaborative Review Groups (CRGs)

- ___ Prepare and maintain Cochrane Complementary Medicine reviews
List topics of interest below
- ___ Liaison between CM Field and a CRG
- ___ Identify and prioritize needed Cochrane Reviews
- ___ Train and/or recruit reviewers
- ___ Other

How I Will Contribute to the Field

Identify Trials

- | | |
|----------------------|--------------------|
| Hand search journals | Translate articles |
| Language(s) | Language(s) |
| Other | |

Dissemination

- ☐ Promote The Cochrane Library
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ADDENDUM 2

Cochrane Collaboration Complementary Medicine Field Systematic Reviews and Protocols

LCM Field Completed Reviews

	1) Linde, K. Jobst, K. Panton, J.	Acupuncture for chronic asthma	1996, <i>Issue 3</i>
New	2) Melchart, D. Linde, K. Fischer, P. Berman, B. White, A. Vickers, A. Allais, G.	Acupuncture for Idiopathic headache	2001, <i>Issue 1</i>
New	3) Smith, CA. Crowther, CA	Acupuncture for induction of labour	2001, <i>Issue 1</i>
	4) Tulder MW, van, Cherkin, DC. Berman, B. Lao, L. Koes, BW	Acupuncture for low back pain	1999, <i>Issue 1</i>
	5) White, AR. Rampes, H. Ernst, E.	Acupuncture for smoking cessation	1997 <i>Issue 1</i>
	6) Dennis, J.	Alexander Technique for chronic asthma	2000, <i>Issue 2</i>
	7) Evans, JR. Henshaw, K.	Antioxidant vitamin and mineral supplements for preventing age-related macular degeneration.	1999, <i>Issue 4</i>
	8) Evans, JR.	Antioxidant vitamin and mineral supplements for age related macular degeneration.	1998, <i>Issue 1</i>
	9) Nixon, S. O'Brien, K. Glazier, RH. Wilkins, AL.	Aerobic exercise interventions for people with HIV/AIDS	2001, <i>Issue 1</i>
	10) McIntosh, HM. Oliaro, P.	Artemisinin derivative for treating uncomplicated malaria	1998, <i>Issue 2</i>
	11) McIntosh, HM. Oliaro, P.	Artemisinin derivatives for treating severe malaria	1998, <i>Issue 3</i>
	12) Verhagen, AP. De Vet, HCW. de Bie, RA. Kessels, AGH. Boers, M. Knipschild, PG.	Balneoherapy for rheumatoid arthritis and osteoarthritis	1999, <i>Issue 3</i>
	13) Norton, C. Hosker, G. Biazzelli, M.	Biofeedback and/or sphincter exercises for the treatment of faecal incontinence in adults.	2000, <i>Issue 2</i>
	14) Wilt, T. Ishani, A. Mac Donald, R. Stark, G. Mulrow, C. Lau, J.	Beta-sitosterols for benign prostatic hyperplasia	2000, <i>Issue 2</i>

	15)	Karjalainen, K. Malnivaara, A. van Tulder, M. Roine, R. Jaubainen, M. Hurri, H. Koes, B	Biopsychosocial rehabilitation for upper limb repetitive strain injuries	2000, <i>Issue 3</i>
	16)	Holloway, E. Ram, FSF	Breathing exercises for asthma	1998, <i>Issue 4</i>
New	17)	Kelly, AJ Kavanagh, J Thomas, J	Castor oil, bath and/or enema for cervical priming and induction of labor	2001, <i>Issue 2</i>
	18)	Wilt, T. Mac Donald, R. Ishani, A. Rutks, I. Stark, G.	Cernilton for benign prostatic hyperplasia	1998, <i>Issue 2</i>
New	19)	Liu, JP McIntosh, H. Lin, H	Chinese medicinal herbs for asymptomatic carriers of hepatitis B.	2001, <i>Issue 2</i>
New	20)	Liu, JP. McIntosh, H. Lin, H.	Chinese medicinal herbs for chronic hepatitis B	2001, <i>Issue 1</i>
	21)	Renfrew, MJ. Lang, S. Martin, L. Woolridge, MW	Treatments to relieve breast engorgement (Previous review title: Cabbage leaves for breast engorgement this review has been withdrawn see protocol 14)	1999, <i>Issue 4</i>
	22)	Price, JR. Couper, J.	Cognitive behavior therapy for chronic fatigue syndrome in adults	1998, <i>Issue 3</i>
	23)	Jones, C. Cormac, I. Mota, J. Campbell, C	Cognitive behavior therapy for schizophrenia	1999, <i>Issue 1</i>
	24)	Jepson, RG. Mihaljevic, L. Craig, J.	Cranberries for the prevention of urinary tract infections	1998, <i>Issue 4</i>
	25)	Jepson, RG. Mihaljevic, L. Craig, J.	Cranberries for the treatment of urinary tract infections	1998, <i>Issue 4</i>
	26)	Woods, RK. Thien, FCK. Abramson, MJ.	Dietary marine fatty acids (fish oil) for asthma.	2000, <i>Issue 3</i>
	27)	Van den Ende, CHM. Vliet Vlieland, TPM. Munneke, M. Hazes, JMW.	Dynamic exercise therapy for rheumatoid arthritis	2000, <i>Issue 3</i>
	28)	Melchart, D. Linde, K. Fischer, P. Kaesmayr, J.	Echinacea for the prevention and treatment of the common cold	1999, <i>Issue 1</i>
	29)	Ram, FSF. Robinson, SM. Black, PN.	Physical training for asthma.	1999, <i>Issue 1</i>
New	30)	Flemming, K. Cullum, N.	Electromagnetic therapy for the treatment of pressure sores	2001, <i>Issue 1</i>
New	31)	Flemming, K. Cullum, N.	Electromagnetic therapy for the treatment of venous leg ulcers	2001, <i>Issue 1</i>
	32)	Pittler, MH.	Feverfew for preventing migraine	2000, <i>Issue 3</i>

	Vogler, BK. Ernst, E.		
New	33) Olin, J. Schneider, L.	Galantamine for Alzheimer's disease	2001, <i>Issue 1</i>
	34) Jepson, RG. Kleijnen, J. Leng, GC.	Garlic for peripheral arterial occlusive disease	1997, <i>Issue 3</i>
New	35) Towheed, TE. Anastassiades, TP. Shea, B. Houpt, J. Welch, V. Hochberg, MC.	Glucosamine therapy for osteoarthritis	2001, <i>Issue 1</i>
	36) Evans, JR.	Ginkgo biloba extract for age related macular degeneration	1999, <i>Issue 3</i>
New	37) Little, CV. Parsons, T.	Herbal therapy for treating osteoarthritis	2001, <i>Issue 1</i>
New	38) Little, C. Parsons, T.	Herbal therapy for treating rheumatoid arthritis	2001, <i>Issue 1</i>
	39) Linde, K. Jobst K, A.	Homeopathy for chronic asthma	1998, <i>Issue 3</i>
	40) Vickers, AJ. Smith, C.	Homoeopathic Oscilloccinum for preventing and treating influenza and influenza like syndromes.	1999, <i>Issue 4</i>
	41) Abbot, NC. Stead, LF. White, AR. Barnes, J. Ernst, E.	Hypnotherapy for smoking cessation	1998, <i>Issue 2</i>
	42) Roberts, L. Ahmed, I. Hall, S.	Intercessory prayer for the alleviation of ill health	1999, <i>Issue 1</i>
	43) Jewell, D. Young, G.	Interventions for nausea and vomiting in early pregnancy	1996, <i>Issue 4</i>
New	44) Campbell, K. Waters, E. O'Meara, S. Summerbell, C.	Interventions for treating obesity in children	2001, <i>Issue 1</i>
	45) Flemming, K. Cullum, N.	Laser therapy for venous leg ulcers	1998, <i>Issue 4</i>
New	46) Higgins, JPT. Flicker, L.	Lecithin for dementia and cognitive impairment.	2000, <i>Issue 2</i>
	47) Brosseau, L. Welch, V. Wells, G. deBie, R. Gam, A. Harman, K. Morin, M. Shea, B. Tugwell, P.	Low level laser therapy for OA	2000, <i>Issue 4</i>
	48) Brosseau, L. Welch, V. Wells, G. deBie, R. Gam, A. Harman, K. Morin, M. Shea, B. Tugwell, P.	Low level laser therapy for RA	2000, <i>Issue 4</i>
	49) Hondras, MA. Linde, K. Jones, AP	Manual therapy for asthma.	2000, <i>Issue 3</i>

	50) Furlan, AD. Brosseau, L. Welch, V. Wong, J.	Massage for low back pain	2000, <i>Issue 4</i>
	51) Vickers, A. Ohlsson, A. Lacy, JB. Horsley, A	Massage to promote development in preterm and/or low birth weight infants	1998, <i>Issue 3</i>
New	52) Herxheimer, A. Petrie, KJ.	Melatonin for preventing and treating jet lag	2001, <i>Issue 1</i>
New	53) Koger, SM. Brotons, M	Music therapy in dementia	2001, <i>Issue 1</i>
	54) Ferreira, IM. Brooks, D. Lacasse, Y. Goldstein, RS	Nutritional supplementation in stable chronic obstructive pulmonary disease	2000, <i>Issue 2</i>
	55) Wilkinson, EAJ. Hawke, CI.	Oral zinc for arterial and venous leg ulcers	1998, <i>Issue 3</i>
	56) Joy, CB. Mumby-Croft, R. Joy, LA.	Polyunsaturated fatty acid supplementation (fish or evening primrose oil) for schizophrenia	2000, <i>Issue 1</i>
	57) Anie, KA, Green, J	Psychological therapies for sickle cell disease and pain	2000, <i>Issue 3</i>
	58) Wilt, T. Ishani, A. Stark, G. Mac Donald, R. Mulrow, C. Lau, J.	Serenoa repens (saw palmetto) for benign prostatic hyperplasia	1998, <i>Issue 4</i>
New	59) Suresh, GK; Davis, JM; Soll, RF	<i>Superoxide dismutase for preventing chronic lung disease in mechanically ventilated preterm infants</i>	2001, <i>Issue 1</i>
	60) Beamon, S. Falkenbach, A. Fainburg, G. Linde, K	Speleotherapy for the treatment of asthma	2000, <i>Issue 1</i>
	61) Linde, K. Mulrow, CD	St. John's Wort for depression	1998, <i>Issue 2</i>
	62) Douglas, RM. Chalker, EB. Treacy, B	Vitamin C for preventing and treating the common cold	1998, <i>Issue 1</i>
	63) Kleijnen, J. Mackerras, D	Vitamin E for intermittent claudication	1996 <i>Issue 2</i>
	64) Soares, KVS. McGrath, JJ	Vitamin E for neuroleptic induced tardive dyskinesia	2000, <i>Issue 3</i>
	65) Tabet, N. Birke, J. Grimley Evans, J. Ortel, M. Spector, A	Vitamin E in Alzheimer's disease	2000, <i>Issue 4</i>
	66) Ramaratnam, S. Sridharan, K	Yoga in the treatment of epilepsy	1999, <i>Issue 3</i>
	67) Marshall, I	Zinc in the treatment of the common cold	1999, <i>Issue 2</i>
	68) Mahomed, K	Zinc supplementation in pregnancy	1997, <i>Issue 3</i>

II. CM Field Protocols

of 160			
New	1) He, L. Zhou, D. Wu, B. Li, N.	Acupuncture for bell's palsy	2001, <i>Issue 1</i>
	2) Richardson, MA. Allen, C. Ezzo, J. Lao, L. Ramirez, G. Ramirez, T. Zhang, G.	Acupuncture for chemotherapy-induced nausea or vomiting among cancer patients	2000, <i>Issue 1</i>
	3) Green, S. Buchbinder, R. Hall, S. Barnsley, L. Forbes, A. Smidt, N. Assendelft, W.	Acupuncture for lateral elbow pain in adults	1999, <i>Issue 1</i>
	4) Ezzo, J. Hadhazy, V. Berman, B. Birch, S. Kaplan, G. Hochberg, M.	Acupuncture for osteoarthritis	1998, <i>Issue 3</i>
	5) Correia, M. Veloso, M. Correia, C.	Antioxidants for acute stroke	1998, <i>Issue 3</i>
	6) Correia, M. Silva, C. Veloso, M.	Antioxidants for secondary prevention after stroke or transient ischaemic attack.	1999, <i>Issue 3</i>
New	7) Orrell, RW. Lane, RJM. Ross, M.	Antioxidant treatment for amyotrophic lateral sclerosis / motor neuron disease	2001, <i>Issue 1</i>
	8) Hooper, L. Capps, N. Clements, G. Davy Smith, G. Ebrahim, S. Higgins, J. Ness, A. Riemersma, RA. Summerbell, CD.	Anti-oxidant foods or supplements for preventing cardiovascular disease	1999, <i>Issue 2</i>
	9) Brazzelli, M. Griffiths, P.	Behavioural and cognitive interventions for faecal incontinence in children	2000, <i>Issue 2</i>
	10) Wilson, ML. Murphy, PA. Partison, HM. Farquhar, CM.	Behavioural interventions for primary and secondary dysmenorrhoea	2000, <i>Issue 3</i>
	11) Snowden, HM. Renfrew, MJ. Woolridge, MW	Treatments to relieve breast engorgement during lactation	2000, <i>Issue 2</i>
	12) Hoare, C. Leonard, T. Williams, HC.	Chinese herbal medicine for atopic eczema	2000, <i>Issue 2</i>
	13) Charlesworth, G. Riordan, J. Shepstone, L.	Cognitive behavior therapy for depressed carers of people with Alzheimer's disease and related disorders	1999, <i>Issue 4</i>
	14) Coates, P. Eady A, E. Cove J, H.	Complementary therapies for acne	1999, <i>Issue 2</i>
	15) Caraballoso, M. Bonfill, X. Serra, C	Drugs for preventing lung cancer	2000, <i>Issue 1</i>
	16) Flemming, K.	Electrotherapy for chronic wounds	2000, <i>Issue 3</i>

	Cullum, N.		
	17) Flemming, K. Cullum, N.	Electrotherapy for pressure sores	2000, <i>Issue 3</i>
	18) Flemming, K. Cullum, N.	Electrotherapy for diabetic ulcers	2000, <i>Issue 3</i>
	19) Ruether, A; Bueschel, G; Leipner, J; Linde, K; Rostock, M; Horneber, M	Enzyme therapy in oncology	2000, <i>Issue 4</i>
	20) Strid, J. Jepson, R. Moore, V. Kleijnen, J. Iasco, SM	Evening primrose oil or other essential fatty acids for premenstrual syndrome	1998, <i>Issue 2</i>
	21) Kleijnen, J.	Ginkgo biloba for intermittent claudication	1996, <i>Issue 2</i>
New	22) Birks J, Grimley Evans J, Dongen M	Ginkgo biloba for dementia and impairment	2001 <i>Issue 2</i>
	23) Novak, F. Avenell, A. Heyland, DK. Croal, BL. Drover, JW. Jain, M. Noble, D. Su, X.	Glutamine supplementation for critically ill adults	2000, <i>Issue 3</i>
	24) Wilson, ML. Murphy, PA. Farquhar, CM	Herbal and dietary therapies for primary and secondary dysmenorrhoea	1999, <i>Issue 2</i>
New	25) Bennett M, Heard R	Hypertonic oxygen therapy for multiple sclerosis	2001, <i>Issue 2</i>
	26) Beamon, S. Falkenbach, A. Jobst, K.	Hydrotherapy for asthma	1999, <i>Issue 4</i>
	27) Blackhall K, Appleton S	Ionisers for chronic asthma	2000 <i>Issue 3</i>
	28) Bent, S. Tsourinas, C. Romoli, M. Linde, K.	Kava for Anxiety Disorder	1999, <i>Issue 3</i>
	29) Beamon, S. Falkenbach, A. Jobst, K.	Hydrotherapy for asthma	1999, <i>Issue 4</i>
	30) Shaw, K. Turner, J. Spinks, A. Del Mar, C	Management of Depression with Tryptophan and 5- Hydroxytryptophan	1999, <i>Issue 3</i>
	31) Gross, AR. Hondras, MA. Aker, PD. Peloso. P. Goldsmith, CH.	Manual therapy for mechanical neck disorders	1997, <i>Issue 3</i>

	32) Lockhart-Wood, K. Gambles, M. Wilkinson, S	Massage and aromatherapy for symptom relief in patients with cancer	2000, <i>Issue 3</i>
New	33) Urrutia, G Bonfill, X Del, 34) Pozo, P Fernandez A	Neuroreflexology for low back pain	2001 <i>Issue 2</i>
	35) Hadhazy, V. Ezzo, JM. Berman, BM. Creamer, P. Bausell, B	Mind/Body Therapy for Fibromyalgia	2000, <i>Issue 3</i>
	36) Greener, J. Enderby, P. Whurr, R.	Pharmacological treatment for aphasia following stroke	1998, <i>Issue 2</i>
	37) Bronfort, G. Nilsson, N. Assendelft, WJJ. Bouter, LM. Goldsmith, C. Evans, R. Haas, M.	Noninvasive physical treatments for chronic headache.	1999, <i>Issue 3</i>
	38) Salinas, A. Berchuk, M. Welch, V. Fortin, P. Shea, B.	Omega 3 fatty acids supplementation for rheumatoid arthritis.	1997, <i>Issue 3</i>
	39) Farmer, A. Dineen, S	Omega 3 fatty acids on glycaemic control of plasma lipids in type II diabetes mellitus	1997, <i>Issue 3</i>
	40) Juni, P. Fux, C. Hertog, MGL. Egger, M. Ernst, E	Padma 28 (a Tibetan herbal preparation) for intermittent claudication.	1997, <i>Issue 4</i>
	41) Beckles Willson, N. Elliott, TM. Everard, ML	Omega-3 fatty acids for cystic fibrosis	2000, <i>Issue 3</i>
	42) Lethaby, AE. Kronenberg, F. Roberts, H. Eden, J	Phytoestrogens for menopausal symptoms	1998, <i>Issue 4</i>
	43) Soo, S. Moayyedi, P. Deeks, J. Delaney, B. Forman, D.	Psychotherapy for non-ulcer dyspepsia	1999, <i>Issue 3</i>
	44) Wilt, T. Ishani, A. Mac Donald, R. Rutks, I. Stark, G	Pygeum africanum for Benign Prostatic Hyperplasia	2000, <i>Issue 2</i>
New	45) Gambles, MA. Lockhart-Wood, K. Wilkinson, SM	Reflexology for symptom relief in patients with cancer	2001, <i>Issue 1</i>
	46) Rambaldi, A. Ghuud, C.	S-adenosyl-L-methionine for alcoholic liver diseases	1999, <i>Issue 3</i>

	47) Wilson, ML. Murphy, PA. Johnson, TC. Farquhar, CM	Spinal manipulation for primary and secondary dysmenorrhoea	1999, <i>Issue 3</i>
	48) Assendelft, WJJ. Shekelle, PG.	Spinal manipulation for low back pain	1996, <i>Issue 1</i>
New	49) Rees, K. Bennett, P. Vedhara, K. West, R. Davey Smith, G. Ebrahim, S	Stress management for coronary heart disease	2001, <i>Issue 1</i>
New	50) Szatmari, Sz Whitehouse, PJ	Vinpocetine for cognitive impairment and dementia	2001 <i>Issue 2</i>
	51) O'Mathuna, D.	Therapeutic touch in wound healing	1998, <i>Issue 3</i>
	52) Iasco, SM. Castro, AA. Atallah, AN	Vitamin B6 and placebo in premenstrual syndrome	1998, <i>Issue 4</i>
	53) Kaur, B.	Vitamin C supplementation for asthma	1997, <i>Issue 3</i>

III. CM Field Newly Registered Titles

2001	Li, Zi	Chinese herbal medicine for chronic renal failure	March, 2001
2001	Xiong, Dylan	Compound red sage root (radix salviae miltiorrhizae) versus nitrate for angina	March, 2001
2001	Zeng, Xianrong	Ginkgo biloba extract for acute ischaemic stroke	March, 2001

Compiled by:
University of Maryland
Complementary Medicine Program
Cochrane Collaboration
Complementary Medicine Field

CAM evaluation comes into the mainstream: NIH Specialized Centers of research and the University of Maryland Center for Alternative Medicine Research in arthritis

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SUMMARY. In September of 1999 the National Institutes of Health (NIH) announced the funding of five Specialized Centers of Research in complementary and alternative medicine (CAM), bringing the total number of centers being supported to nine. The NIH center grant model provides a tremendous boost to the scientific investigation of CAM, nurturing an emerging field through the support of a step-wise research program of clinical and pre-clinical trials and developmental and feasibility studies; the building of infrastructure; and the training of a new cadre of scientific investigators in the field. This article explains the overall objectives of the NIH Specialized Centers program and focuses on one of the oldest CAM research centers in the USA, exploring some of the challenges faced in conducting CAM research while developing a center, and some of the goals and activities of the center. © 2000 Harcourt Publishers Ltd

In September 1999 the National Institutes of Health (NIH) announced the funding of five Specialized Centers of Research in complementary and alternative medicine (CAM), bringing the total number of centers being supported to nine. These grants are an encouraging jump-start into the new millennium and a fittingly symbolic ending to the last decade of the old millennium—a decade in which CAM research in the USA has experienced a changing of the tides and a slow, but steady, rise in its acceptability as a target for federal support. Each of the centers will be receiving approximately \$7.5 million in funding over the next 5 years and is expected to conduct clinical

and pre-clinical research; encourage developmental and feasibility studies; and educate and train a new cadre of scientific investigators in the field. The nine centers are located around the country and each will have a disease or therapy area of focus (Table 1). Two of the centers funded last year (Columbia University and University of Maryland) were previously funded by the NIH and will be building on the initiatives started over the past 4 years.

The NIH center grant model draws from the experience of more mature disciplines and is designed to nurture an emerging field through a carefully staged research process. This process

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Area of Focus	Institution	Principal Investigator
Addiction	Minneapolis Medical Research Foundation	Thomas Kiresuk, PhD
Arthritis and Related Disorders	University of Maryland	Brian Berman, MD
Cardiovascular Diseases	University of Michigan	Steven Bolling MD
Cardiovascular Diseases and Aging in African-Americans	Maharshi University	Robert Schneider, MD
Chiropractic	Palmer Center for Chiropractic Research	William Meeker, DC, MPH
Craniofacial Disorders	Kaiser Foundation Hospital, Oregon	Alexander White, DDS
Neurological Disorders	Oregon Health Sciences University	Barry Olsen, MD
Pediatrics	University of Arizona	Fayez Ghishan, MD
Women's Health & Aging	Columbia University	Fredi Kronenberg, PhD

includes generating information on the effectiveness of a therapy through a range of methodological designs, the phasing of studies leading up to large randomized, controlled trials, and the building of infrastructure through support of core resources (such as data management, statistical analysis, and administration) and the training of new investigators. Hence, a minimum of three studies are supported under each center grant and are expected to lead on to large, randomized, controlled clinical trials. At the same time, innovative preliminary projects will be funded (subject to rigorous peer review) by the centers' development and feasibility programs. Junior faculty and post-doctoral fellows will be provided education and training in CAM and research, thus growing a new generation of investigators who are sensitive to the issues and challenges particular to CAM.

The University of Maryland Center

The Center for Alternative Medicine Evaluation and Research in Arthritis is housed within the University of Maryland's Complementary Medicine Program. This center grant is a competitive renewal of one of the initial 10 center grants awarded by the NIH in 1995 and builds upon a research program that is focused around pain related conditions. While each of the CAM centers undoubtedly has its own valuable stories to share, the University of Maryland program, as one of the oldest centers in this country, will be the focus of this article. We will explore some of the challenges we have faced in conducting CAM research while developing a center, and outline the goals for our center.

Edging into the academic arena

Everyone involved in the scientific investigation of CAM as well as its clinical practice is aware of the many obstacles that have confronted this field in its struggle for legitimacy in the medical and research arenas. At the time that the University of Maryland CAM program was established in 1991, one of the

most often voiced criticisms of CAM was the lack of scientific data on its effectiveness and safety. However, at the same time, the CAM field lacked the infrastructure and research capacity with which to support and foster the sorely needed studies and trials. Most CAM practitioners themselves had little training in research, nor were there sources for the funding of research. Our program was fortunate to receive core funding from a private foundation and to find an academic institution open to embracing CAM evaluation at a time when the prevalent attitude to CAM in academic medical circles was characterized by hostility or distrust. With these resources at our disposal we were able to begin pilot studies which could generate crucial preliminary data allowing us to be competitive in applications to funding institutions such as the NIH.

Embarking on a research program

Before starting any studies and in order to assure ultimate usage of our limited means as well as identify the most needy and/or promising areas of investigation, we drew up a strategic plan for the center and set a research agenda. Our research agenda was based on surveys of CAM therapy usage rates, conditions identified as major public health problems, and review of the existing CAM literature.¹ As a result of this process we chose to focus on pain-related conditions and to initially examine therapies where there was the greatest body of evidence suggesting their usefulness, as well as evidence of their use by consumers.

Multiple preliminary studies based upon strong theory and the empirical work of previous investigators is always necessary before a definitive study is mounted. In our experience, following a step-wise progression of studies (somewhat mirroring the Federal Drug Administration guidelines for phasing of studies) has allowed for consideration of methodological issues, such as appropriate control groups, and other therapy-specific issues, such as appropriate dosage and safety, before embarking on full-blown, Phase 3, randomized controlled trials (RCT).

As an example of our approach, our group used the Phase 1 pilot studies to test suitable outcomes measurements and determine standardized acupuncture treatment protocols in studies of acupuncture for postoperative dental pain and for osteoarthritis. On the basis of this work we were able to successfully compete for some of the initial developmental grants funded by the newly-created NIH Office of Alternative Medicine. We then followed this work with two Phase 2 studies: one small trial ($n = 39$) comparing acupuncture to a mock acupuncture control (which involved no needle insertion) for acute pain; one larger study ($n = 73$) comparing acupuncture plus standard care to standard care alone with osteoarthritis patients.^{2,3} These studies allowed us to: 1) test our hypothesis on a small, cost-effective scale; 2) conduct a power calculation for a larger trial; 3) assess the feasibility of the research setting; and 4) resolve unforeseen problems and thus design a solid study protocol for the RCT. Both studies are now funded by the NIH at the Phase 3 stage and, with large sample sizes and multi-site location, will be more definitive efficacy studies. The osteoarthritis study is a three arm parallel design ($n = 570$) comparing real versus sham acupuncture versus an education control group; while the dental trial is a two experiment, two site study that combines elements of both Phase 2 and 3 trials.

Finding and evaluating the existing evidence

One stumbling block we encountered early in our investigation of CAM was establishing what is known already. Without a thorough knowledge of the literature it is impossible to set a research agenda, know the pertinent questions to be asked, the study designs that are needed, or the methodological issues to be confronted. Much of the literature on CAM had not been published in mainstream medical journals, was published in languages other than English, and was not available through traditional medical literature databases and libraries. In our search for the literature on pain we confronted this problem and were able, as part of our first NIH center grant funding, to compile a database of the literature in CAM and pain (CAMPAIN). We drew from electronic sources worldwide as well as carrying out extensive hand-searching of journals and conference proceedings. A review we conducted of acupuncture treatment for chronic pain problems serves as an example of the hurdle of finding the literature in CAM.⁴ In this study, a search of our CAMPAIN database yielded 58% more citations than a similar search of the National Library of Medicine's (NLM) Medline database. The CAMPAIN database (available on our website: www.compmed.ummc.umaryland.edu) currently contains 12 000 citations, testimony to the fact that there is existing evidence on CAM, although it has

just been more difficult to access than other medical literature. Our reviews to-date, however, suggest that the quality of the science is generally poor and there are many gaps in our knowledge.⁴⁻⁶

At the international level, efforts to collect and evaluate the CAM literature have been substantially improved through the establishment in 1996 of a complementary medicine (CM) field within the Cochrane Collaboration.⁷ The field is coordinated through our center and we maintain a comprehensive registry of RCTs in CAM which is uploaded to the central Cochrane library (which contains all known RCTs for all of medicine). The registry lays the groundwork for collaborators worldwide to conduct systematic reviews which will summarize existing evidence while minimizing bias. Furthermore, the CM field has also been working with the NLM to identify journals and to refine their thesaurus of CAM subject headings for Medline.

Evaluating CAM in a clinical setting

Some of the greatest challenges our center has faced has been in our clinical program. At the program's out-patient clinic, based at one of the University of Maryland hospitals, we have been assessing the value of integrating CAM therapies with conventional medicine in the treatment of patients with pain related conditions. However, generating truly useful data from outcomes research is extremely difficult due to the hectic, uncontrolled nature of clinical practice. On the whole, any data generated is generally less controlled than even our crudest pilot studies. For example, it is difficult to employ prospective exclusion/inclusion criteria for clinical patients and to administer outcomes measures specific to a particular diagnosis in a clinical setting. Although the clinic continues to be popular among patients and our data shows high satisfaction levels, developing meaningful outcomes data will continue to be a challenge for our center and the CAM community in general.

On a more practical level, obstacles we have faced in our clinical program have included distrust and unfamiliarity with CAM amongst many of the University's faculty and clinicians who have been opposed to CAM therapies being offered under the University's umbrella. However, we have sought to build confidence among our colleagues by offering only those CAM therapies for which there is some body of evidence to support their clinical usefulness and safety. Over time, the clinic has offered an excellent opportunity to build bridges through shared patient care, and has generated ideas for collaborative research endeavors. We have also had some interesting instances where some of our most skeptical research collaborators have resorted to acupuncture for relief of their own pain conditions. Personal experience of relief has often done more to change attitudes than objective research data!

Other hurdle we have faced have include staffing and reimbursement. The CAM therapists involved with our clinic have had extensive training in their respective fields and have been credentialed, however, with little standardized credentialing in most CAM professions to-date, finding suitable practitioners has not always been straightforward. Furthermore, lack of experience with or training in CAM has meant that there have been few physicians who can work at the clinic and coordinate integrated programs of care. Insurance coverage of CAM has only recently begun to improve and, while this obviously creates problems in making the clinic financially viable, it has also created problems in tracking long-term costs of CAM care.

Looking to the future

It will be exciting to observe how each Specialized Center confronts the issues and challenges of CAM evaluation. The NIH center grant mechanism, with its emphasis on rigorous scientific process, a structured progression of research, innovation, as well as training, provides the structure for CAM investigation to make huge advances in the new millennium. Our center will continue with efficacy trials (e.g. one study funded by our center grant will evaluate mind/body therapies for fibromyalgia), as well as studies of basic mechanism involved in CAM therapies (e.g. another program of research involves identifying the antagonist receptor system as well as the descending modulating pain pathway in the brain stem involved in electro-acupuncture using an animal model that we have pioneered in our basic science laboratory). We will also explore the long-term outcomes; patterns of health services utilization and costs of patients who are treated by acupuncture in the osteoarthritis RCT that is currently underway; as well as begin the investigation of the use of various herbs in the treatment of inflammation and immune mediated arthritis. In addition to our own primary research, we will continue to synthesize the results of CAM trials in order to make summary judgments regarding effective-

3. Equally exciting, the Special Center mechanism has provided a budget of approximately three quarters of a million dollars to fund projects involving promising investigators outside our program to continue the process that we have been involved with for the past decade. In this manner we hope to add to the scientific body of information on CAM and broaden the spectrum of evidence based treatments for chronic pain problems.

ACKNOWLEDGEMENTS

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Complementary medicine and medical education

Teaching complementary medicine offers a way of making teaching more holistic

Education and debate
p 154

Complementary and alternative medicine is no longer an obscure issue in medicine. Our patients are using alternative therapies in addition to conventional care¹ and sometimes do not share this information with us. But even if they did would we know how best to advise them about safety issues or about the effectiveness of a particular therapy for their problem? Surveys indicate that doctors and medical students are increasingly interested in complementary and alternative therapy,²⁻⁵ yet lack of knowledge is one of the greatest barriers to its appropriate use. Although many medical schools and training programmes now include teaching on complementary and alternative therapies, the approaches are variable and often superficial.

In this issue Owen et al ask provocative questions about our attitudes and behaviour towards complementary and alternative therapy (p 154),⁶ and point out that few of us encountered such therapy as medical students or during later training. Nevertheless, there are signs of change, and Owen et al describe initiatives to include complementary and alternative therapy in medical education in the United Kingdom. Similar changes are occurring in the United States. In 1995 a national conference on complementary and alternative therapy

education involving the National Institutes of Health recommended that complementary and alternative therapy should be included in nursing and medical education. Two years later a survey of all 125 US medical schools found that 75 of them offered some form of education on complementary and alternative therapy.⁷

Teaching includes elective modules, core curriculum lectures, and inclusion in problem based learning at undergraduate and residency level. Institutions such as Harvard and Stanford offer continuing postgraduate education courses, and the universities of Maryland and Arizona offer research and clinical fellowships. In addition, special interest groups in complementary and alternative therapy have been formed in professional organisations such as the Association of American Medical Colleges, and the Society for Teachers of Family Medicine has issued guidelines on including complementary and alternative therapy in the curriculum for residents.⁸ The NIH-National Center for Complementary and Alternative Medicine recently issued funding initiatives to support the development of teaching on complementary and alternative therapy in medical, dental, and nursing education. The centre also supports career development and training programmes at several of its research centres around the country.

BMJ 2001;322:121-2

Editorials

When in 1992 we developed a complementary and alternative therapy curriculum at the University of Maryland we thought it was important to present the therapies in the context of their own philosophies and models of health and illness. Students and residents have the opportunity to experience the clinical practice of these therapies both in the community and in our own integrated medical clinic. We also teach students how to find and evaluate the evidence for the safety and efficacy of complementary and alternative therapies. Our goal is to encourage the additional skills of openness, sensitivity to cultural influences and beliefs, communication, and critical appraisal of the literature of complementary and alternative therapy treatments.

Nevertheless, great heterogeneity exists in the content, format, and requirements of complementary and alternative therapy courses for medical students and physicians in training. Typically, courses give an overview of the main complementary and alternative therapies and their uses and possible effects, but they do not teach skills to a clinical level of competence. Decisions about which complementary and alternative therapies to include in teaching will necessarily be dictated by usage patterns and resources in one's locality. However, guidance about the main complementary and alternative therapy categories can be obtained from sources such as the National Center for Complementary and Alternative Medicine (<http://nccam.nih.gov>). In addition, however, some general consensus needs to be reached on the essentials of a core curriculum. This should aim to improve doctors' knowledge of complementary and alternative therapy practices and their place in patient care; their ability to advise and guide patients about these therapies; their ability to refer patients to practitioners of complementary and alternative therapy; and their knowledge of the practicalities, such as credentials and legal and reimbursement issues.

Most medical schools have a packed curriculum, so complementary and alternative therapy options tend to be electives with only a smattering of core curriculum lectures. Given the shift towards problem based and case based learning, it is a realistic goal to have complementary and alternative therapy treatment options integrated into existing teaching at all levels. This highlights the need for faculty development. Academics who are not experts in complementary and alternative therapy

but accept its legitimacy at some level must gain knowledge of the subject in order for students to receive this exposure. Complementary and alternative therapy educators will need clearly to define their objectives and goals and be rigorous in evaluating whether their aims are being met. Nevertheless, until qualification requirements include components on complementary and alternative therapy it may seem an indulgence to curriculum committees and students to dedicate time to complementary and alternative therapy.

We know from research that people are drawn to complementary and alternative therapy mostly out of a desire for a more humanistic, "holistic" approach.^{9,10} Medical education should re-examine the emphasis it places on the importance of the integration of mind, body, and spirit and acknowledge the role of social, cultural, and environmental influences and the power of self care and healing. Healthcare professionals, patients, and our healthcare system can only benefit if medical education bridges the gap with complementary and alternative therapy.

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Concerns About CAM

Divider Title: _____

Questions for the Panel on Concerns about CAM and CAM Research Panel:

What are your major concerns about CAM practices and products and about CAM research?

When addressing the need to find research methods and approaches to establish the safety and effectiveness of CAM practices and products, in addition to data collection and clinical trial methodology, consider how we can study the complex questions inherent in CAM such as multiple interventions; complex systems and complex compounds; mind-body interactions; individualization; the placebo effect; qualitative research; energy medicine; provider/patient interaction; multiple populations including culture/race, gender, age; and so forth?

What policy recommendations can you offer regarding research on CAM practices and procedures for the Commission's consideration as it develops its report to the President and Congress?

William M. London

William M. London, EdD, MPH is the president of The National Council Against Health Fraud, Inc. He is an associate professor of health care management and the director of the Graduate Program in Health Care Management, College of St. Elizabeth in Morristown, New Jersey. He also has an appointment as a specialized faculty mentor in the Master of Science in Public Health program of Walden University. Dr. London is a contributing editor to *The Scientific Review of Alternative Medicine and Aberrant Medical Practices*. He is a co-author of sixth edition of the college textbook *Consumer Health: A Guide to Intelligent Decisions* and a co-author of the seventh edition of the textbook, which is scheduled for publication in July 2001.

Statement of William M. London

**A Call to Oppose Health Fraud and Quackery Promoted as "Complementary" and
"Alternative" Medicine**

Statement to the White House Commission on Complementary and Alternative Medicine

May 15, 2001

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2. WHCCAM should promote opportunities for research to increase knowledge about quackery/health fraud as a public-health problem associated with the “complementary” and “alternative” medicine marketplace.⁸
3. WHCCAM should declare that it is misleading to use the terms “complementary” and “alternative” to refer to questionable, unproven, and disproved methods. Reliable and useful information must be grounded in principles of consumer protection and science.
4. WHCCAM should recommend that appropriate access and delivery of healthcare be based on principles of consumer protection and science.

¹ Eisenberg DM et al. Unconventional medicine in the United States: Prevalence, costs, and patterns of use. *N Engl J Med*. 328:246-252;1993.

² Gorski T. Do the Eisenberg data hold up? *Scientific Review of Alternative Medicine* 3(2):62-69;1999.

³ Angell M, Kassirer J. Alternative medicine—the risks of untested and unregulated remedies. *New Engl J Med* 339:839-841;1998.

⁴ London W. Alternative health (letter). *The Plain Dealer Magazine*. November 19, 1989, pp. 14, 32.

⁵ Green S. A critique of the rationale for cancer treatment with coffee enemas and diet. *JAMA* 268:3224-3227;1992.

⁶ Jury calls the ‘hair test’ a scam. *PROBE* 8(10 & 11):9;2000.

⁷ Garner BA. *A Dictionary of Modern American Usage*. New York: Oxford University Press, 1998, p. 34.

⁸ Jarvis WT. Quackery: The National Council Against Health Fraud Perspective. *Rheumatic Disease Clinics of North America* 25:805-814;1999.

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Quackery: "Promoting health products, services, or practices of questionable safety, effectiveness, or validity for an intended purpose." [NCAHF, 1986]

Health fraud/quacks: "Health fraud is the promotion, for financial gain, of fraudulent or unproven devices, treatments, services, plans or products (including, but not limited to, diets and nutritional supplements) that alter or claim to alter the human condition. Those who promote such medical remedies that do not work or have not been proven to work are called 'quacks.'" [The Assembly Republican Task Force on Health Fraud and the Elderly, New York State Assembly, June 1986]

Health fraud: "The deceptive promotion, advertisement, distribution or sale of articles, intended for human or animal use, that are represented as being effective to diagnose, prevent, cure, treat, or mitigate disease (or other conditions), or provide a beneficial effect on health, but which have not been scientifically proven safe and effective for such purposes. Such practices may be deliberate, or done without adequate knowledge or understanding of the article." [Compliance Policy Council of the U.S. Food and Drug Administration. Announced in a letter from M. L. Frazier, Director, State Information Branch, June 18, 1993.]

Recommendations

1. The education and training of health care practitioners must address principles of consumer protection and science. Health care practitioners must learn to recognize quackery/health fraud associated with "complementary" and "alternative" medicine.

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- Providing a center for communication between individuals and organizations concerned about health misinformation, fraud, and quackery.
- Supporting sound consumer health laws.
- Opposing legislation that undermines consumer rights.
- Encouraging and aiding legal actions against those who violate consumer protection laws.
- Sponsoring a free, weekly e-mail newsletter.

NCAHF's publications rely on the following definitions:

Fraud: "An intentional perversion of truth for the purpose of inducing another in reliance upon it to part with some valuable thing. . . . a false representation of a matter of fact, whether by words or by conduct, by false or misleading allegations, or by concealment of that which should have been disclosed, which deceives or is intended to deceive another so that he shall act upon it." [Black's Legal Dictionary, 4th Edition, 1968]

Misinformation: "Untrue or misleading information." [Webster's Seventh New Collegiate Dictionary, 1972]

Promote: "To contribute to the growth or prosperity of, to present for public acceptance through advertising and publicity." [Webster's New Collegiate Dictionary, 1975]

Quack: "Anyone who promotes medical schemes or remedies known to be false, or which are unproven, for a profit." [United States House of Representatives, Select Committee on Aging, Subcommittee on Health and Long-term Care. Quackery: A \$10 Billion Scandal. Washington, DC, 1984, US Government Printing Office.]

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- Professionals in the health sciences, academia, law and business as well as government agencies share a responsibility to help consumers protect themselves from deception and exploitation in health-related matters.
- The scientific process is essential for discovering truths and validating health claims and information.
- Health products and services should be:
 - proved safe and effective before marketing with proponents bearing the burden of such proof.
 - accurately labeled or fully described.
 - truthfully advertised.
- As noted in the Consumer Bill of Rights, consumers have:
 - The right to free and informed choice.
 - The right to accurate information.
 - The right to safety.
 - The right to be heard.
 - The right to consumer education.

Activities and Purposes

NCAHF's activities and purposes include:

- Investigating and evaluating claims made for health products and services.
- Educating consumers, professionals, business people, legislators, law enforcement personnel, organizations and agencies about health fraud, misinformation, and quackery.

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motto of The National Council against Health Fraud is: "Enhancing freedom of choice through reliable information."

About The National Council Against Health Fraud, Inc.

The National Council Against Health Fraud is a nonprofit, tax-exempt voluntary health agency that focuses its attention upon health fraud, misinformation, and quackery as public health problems. It is private, nonpartisan, and nonsectarian. Its members are health professionals, educators, researchers, attorneys, and other concerned citizens. Its officers and board members serve without compensation.

Background History

The Council originated in 1977 as the Southern California Council Against Health Fraud, Inc. and became the California Council Against Health Fraud in 1978. The Council became national in 1984. It is now incorporated in California and has members in all 50 states, the District of Columbia, and several foreign countries. Nearly all of our funding comes from membership dues and individual contributions.

Basic Principles

NCAHF bases its claim to be a consumer organization on its founding principles derived from consumer protection law and the scientific process. Included are the beliefs that:

- "Consumer" is not a special class but a role played by all; everyone in a free enterprise society has a stake in maintaining high standards for health products and services.

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According to a usage dictionary, "First, *alternative* may suggest adequacy for some purpose...; and second, it may suggest compulsion to choose."⁷ Questionable and dubious methods are not adequate for their intended purposes. And consumers should not feel compelled to choose them.

It is unavoidable for legitimate practitioners to use unproven methods. Medicine will never have all the answers. Clinical judgment and innovation will always be important to the art of delivering healthcare. However, responsible healthcare professionals do not promote unproven methods. The promotion of unproven methods through such methods as advertising and publicity is objectionable because it is deceptive. It violates the ethical principles of veracity and non-maleficence.

Everyone wants alternatives, but they want genuine alternatives. Many promoters of "alternative" medicine exploit this by calling for "freedom of choice" for consumers. What these promoters really want is freedom from accountability to consumers. They support the concept of caveat emptor, "let the buyer beware," but they have a problem with the concept of caveat vendor, "let the seller beware." Caveat vendor provides a rationale for consumer protection laws to compensate for the disadvantageous bargaining position consumers have in the health marketplace. It is difficult to evaluate claims for health products and services. We are vulnerable to mistaken perception and deception especially when we feel threats to our well-being and when we are desperate for answers. It is important to protect consumers from both intentional and unintentional deception. And it is also important to preserve true freedom of choice. Thus, the

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Genuine alternatives or genuinely complementary methods tend not to require the justification of labels like “alternative” or “complementary” in marketing.

Experimental methods are unproven, but are studied responsibly with extra care given to seeking informed consent from study participants and protecting them from exploitation. It is reasonable for taxpayers to expect that their financial support will be used to study promising rather than implausible methods. But many taxpayers don’t realize that alternativists do not espouse such values. Alternativists have no problem with taxpayers supporting the study of implausible methods.

Remarkably, NCCAM is currently funding a study of an “alternative” protocol involving enzyme supplements and coffee enemas. The protocol is implausible.⁵ had been used on a Hodgkin’s lymphoma patient who died. Last year a jury found that the patient was 51% responsible for her harm. The jury said that the patient was “negligent” in letting the physician treat her and for foregoing the standard care her original doctors had recommended.⁶

Questionable methods are those for which scientific evidence is insufficient to support the claims made by proponents. The most implausible questionable methods are legitimately described as dubious. (Perhaps I should add a fourth category of plausible alternatives with clear benefits and clear risks when used for an intended purpose, but for which it is unclear whether proven benefits outweigh the risks. Estrogen replacement therapy for postmenopausal women might belong in this fourth category.)

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hunches, clinical impressions, subjectivity, anecdotes, reports of best cases, legends, and so-called “other ways of knowing,” as sufficient “proof” to justify their promotional efforts. They tend not to value efforts to identify sources of clinical illusions and to reduce the problems of systematic and nonsystematic errors leading to faulty conclusions.

Alternativists also value different credentials and standards of practice than most consumers expect. “Alternative” credentials and standards of practice tend to be different in that they don’t espouse the need for professional accountability. I believe the WHCCAM should note that this poses a problem for consumers.

“Alternative” medicine methods generally do not allow or necessitate a choice between two or more things, as suggested by dictionary definition number 1 above for “alternative.” Drs. Marcia Angell and Jerome P. Kassirer, former editors of *The New England Journal of Medicine* have pointed out: “There cannot be two kinds of medicine—conventional and alternative. There is only medicine that has been adequately tested and medicine that has not, medicine that works and medicine that may or may not work.”³

I have proposed that alternatives be classified into three categories: genuine, experimental, and questionable.⁴

Genuine alternatives are backed by sufficient scientific evidence showing that the potential for benefit exceeds the potential for harm to specific populations for specific intended purposes.

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methods. Traditionalists and true-believers cling to unsafe and ineffective methods as a matter of faith.

I am unaware of any efforts by OAM and later by NCCAM to identify methods promoted as “complementary” or “alternative” that should be discarded. In order to provide reliable and useful information about complementary and alternative medicine, it is necessary to identify methods that should be discarded. I ask that the WHCCAM to make recommendations to accomplish this based on principles of consumer protection and science discussed later in this paper.

Much has been written about the established institutions and systems of delivering medical care. I think it is fair to note the existence of the “alternative” medical establishment which is composed of prominent promoters, practitioners, organizations, foundations, retail businesses, wholesale businesses, politicians, the NCCAM, the WHCCAM, and other institutions. The “alternative” medical establishment has even extended its reach into medical schools, other professional schools, colleges and universities, hospitals, and insurance plans. In so doing, alternativists have increased their power and, in effect, invalidated the NCCAM definition of complementary and alternative medicine.

“Alternative” medicine *is* alternative in the sense of espousing or reflecting values that are different from those of the establishment (definition 2a above), if by establishment we mean people who insist that health products and services be proved safe and effective—with proponents bearing the burden of such proof—before promoting them. Alternativists often value

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complements anything else in providing benefit to health. The claim that a particular method is complementary to anything else is misleading unless the claim can be supported by evidence. If a method doesn't add to the outcome then it isn't complementary; it just adds to the cost. Few, if any, methods, marketed as "complementary" medicine have been shown to complement anything else.

What Would Make "Alternative" Medicine Alternative?

The American Heritage Dictionary of the English Language, Third Edition defines alternative, when used as an adjective, as: "1. Allowing or necessitating a choice between two or more things. 2.a Existing outside traditional or established institutions or systems : *an alternative lifestyle*. b. Espousing or reflecting values that are different from those of the establishment..." (p. 55.)

The NCCAM definition suggests that "alternative" medicine is "alternative" in the sense of dictionary definition 2a. To some extent this is a fair characterization. However, "alternative" medicine is largely "traditional" itself and it has become its own "establishment." Promoters of "alternative" medicine often promote traditional systems for alleged healing. Strong reliance on tradition is one of "alternative" medicine's biggest problems. Tradition-bound systems resist change. Their proponents selectively seek affirming evidence while rejecting disconfirming evidence and criticism. Proponents adhere to orthodoxy.

On the other hand, science/evidence-based medicine is iconoclastic. Medical practice changes over time because scientifically-based practitioners learn to discard unsafe and ineffective

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“unconventional.”) The study reported on a national telephone survey of the use by adults of methods such as relaxation techniques, massage, exercise, prayer, self-help groups such as Alcoholics Anonymous, imagery, biofeedback, and hypnosis. Many of the methods discussed in the survey are either methods of self-care or, in contradiction to the definition used for “unconventional medicine” in the study, are methods with established medical uses.² The study showed that few survey respondents used commercially promoted methods such as acupuncture, homeopathy, energy healing, megavitamin therapy, and herbal medicine. Strangely, 30% of respondents who reported use of chiropractic didn’t actually see a provider of chiropractic services.

The NCCAM definition has little to do with what the words “complementary” and “alternative” actually mean. To refer to “complementary” and “alternative” methods is to imply that such methods actually complement other methods or serve as alternatives to other methods. The “complementary” and “alternative” medicine marketplace is dominated by products, services, and regimens that have not been shown to complement or serve as a genuine alternative to any other method for significant intended purposes.

What Would Make “Complementary” Medicine Complementary?

The *American Heritage Dictionary of the English Language, Third Edition* defines complementary as: “1. Forming or serving as a complement; completing. 2. Supplying mutual needs or offsetting mutual lacks.” (p. 386). Thus, to refer to something as “complementary medicine” implies that it completes what some other medicine does not do on its own. However, just because someone refers to a method as complementary does not mean it actually

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Problems with Terminology

According to Executive Order 13147, the White House Commission on Complementary and Alternative and Medicine shall provide a report on recommendations addressing: “(a) the education and training of health care practitioners in complementary and alternative medicine; (b) coordinated research to increase knowledge about complementary and alternative medicine practices and products; (c) the provision to health care professionals of reliable and useful information about complementary and alternative medicine that can be made readily accessible and understandable to the general public; and (d) guidance for appropriate access to and delivery of complementary and alternative medicine.”

In order to make these recommendations, I recommend that the Committee acknowledge that the term “complementary and alternative medicine” implies much more than what is in the definition of complementary and alternative medicine used by the National Center for Complementary and Alternative Medicine (NCCAM). According NCCAM: “Complementary and alternative medicine (CAM) covers a broad range of healing philosophies, approaches, and therapies. Generally , it is defined as those treatments and healthcare practices not taught widely in medical schools, not generally used in hospitals, and not usually reimbursed by medical insurance companies.”

The NCCAM definition is similar to the definition used for “unconventional medicine” in a paper by Eisenberg et al,¹ which is often misrepresented as providing evidence that Americans are so interested in “complementary and alternative medicine” that NIH funding of CAM research is needed. (“Complementary” and “alternative” have far more promotional value than

Simeon Margolis, M.D., Ph.D.

Dr. Margolis received his M.D. and Ph.D. degrees at the Johns Hopkins University School of Medicine. He was appointed to the Hopkins faculty upon completion of his residency on the medical service at Johns Hopkins Hospital in 1965. He is presently a Professor of Medicine and Biological Chemistry. He was the Director of the Division of Endocrinology and Metabolism in the Department of Medicine from 1968 to 1981 and from 1985 to 1990. He served as the Associate Dean for Academic Affairs from 1984 to 1990 and subsequently was Associate Dean Administration and to the National Institutes of Health as a member of the Metabolism Study Section, the General Clinical Research Centers Committee, and the Committee on Specialized Centers for Atherosclerosis Research. Dr. Margolis' laboratory research had focused on the factors that regulate the synthesis and breakdown of cholesterol in isolated liver cells. His clinical research has involved studies on the effects of diet and drugs on the levels of serum lipids and lipoproteins. He was an active participant in the Lipid Research Clinics Coronary Primary Prevention Trial which showed that lowering cholesterol levels led to a significant reduction in the complications of coronary heart disease.

Dr. Margolis' practice has been directed to the prevention of premature coronary heart disease, mainly by proper management of abnormalities of serum lipids and lipoproteins. He has been very active in teaching the principles of diagnosis and treatment of these disorders to both medical students and practicing physicians and has written many articles and book chapters on this subject. Over the last decade he has written and edited a number of books and other publications directed at the lay public, including the monthly Johns Hopkins newsletter Health After 50.

Dr. Simeon Margolis: Summary of Remarks

Let me preface my remarks by stating that I would enthusiastically welcome any alternative and complementary product or practice that is proven to be effective.

As you have heard or will hear from other members of the panel, the major problems with CAM are well recognized:

Most CAM products and practices are either untested or based on unreliable research.

Nonetheless, they are aggressively promoted, usually with guarantees of success. Yet any experienced physician knows that no treatment or procedure is always effective.

These promotions and promises mean that patients may waste money on unproven measures, and at the same time fail to seek medical attention and obtain medications or procedures with proven effectiveness for illnesses that may have serious consequences.

People are urged to use CAM products because they are "natural", apparently forgetting that poison ivy, floods, hurricanes and tornadoes prove that natural isn't necessarily good.

And finally, because CAM products are unregulated, patients can be subjected to serious risks.

I will take one example - chelation therapy - and have included an article I have written on the subject as a reference.

Chelation involves a course of 2 to 3 weekly, 2-hour long intravenous infusions of EDTA for a total of 30 treatments. Based on a number of uncontrolled studies, chelation therapy is reputed to improve the activity-related pain of coronary artery disease and peripheral vascular disease by binding calcium and heavy metals that may cause damage by enhancing the oxidation of tissues and blood proteins. With the exception of one small, short study, all of the CAM-based studies of chelation had no control group. Two earlier randomized, blinded studies, done in Scandinavia and New Zealand on patients with claudication, injected either EDTA or saline alone in a control group. After treatment, there were no differences between the EDTA group and the control group in how long they could walk on a treadmill before developing leg pain. A recent study from Canada of 80 angina patients, reported this March at a meeting of the American College of Cardiology, found no differences between the EDTA and control groups in how long they could walk on a treadmill before developing ischemic changes on an ECG. BUT in all three studies patients in both the EDTA and control groups had modest improvements in how long they could walk before developing leg pain or angina. These findings emphasize the importance of a control group in studies of chelation, or any other CAM product or procedure.

In the Canadian study, patients in both groups reported on questionnaires that they had less angina and better quality of life after the treatments. Chelation patients often feel they were improved by the treatment; but I suspect that anyone in this audience would tell their doctors they were better, and indeed believe they were improved, after they underwent 30 intravenous infusions and spent about \$5000 out-of-pocket.

Most distressing to me is the statement made in response to the Canadian study by Dr. Michael Janson, past president of the American College for Advancement in Medicine, who is quoted as saying

"I've been doing it for 18 years and have seen some dramatic differences. I've been really impressed with it". He also said that 75% of his patients respond and are able to walk farther and have less chest pain. His reaction raises the concern that CAM practitioners will not accept the negative results of scientifically valid studies and alter their practices accordingly.. If that is true, properly conducted research by either CAM investigators or NIH-supported investigators at academic institutions will be nothing more than a waste of time and money.

A second question we were asked to address is how valid research can study the complex issues inherent in CAM research.

I submit that the problems associated with CAM research are inherently no different than those faced in other areas of clinical research. What is needed is some ingenuity, the design of carefully controlled studies, and the willingness of investigators to roll up their sleeves and do the work.

My recommendations to the Commission are:

1. CAM research requires large well-controlled studies which provides scientific evidence that either supports or rejects the value of all CAM products, such as herbs and vitamins, as well as procedures, like chelation and therapeutic touch. Such studies on safety and efficacy must be done before marketing and promotion of products because it would ^{be} exorbitantly expensive for government agencies to fund such studies on every herbal product, for example, reputed to be beneficial. The failure to carry out such studies means that the public will lose out on two scores:

First, the public will continue to waste money using ineffective and possibly risky CAM products.

Secondly, they will not have widespread access to CAM products and practices that really are effective.

2. The Commission should urge Congress to revise the "dietary supplement " act of 1994 so that the FDA has some control over CAM products and procedures.

3. Finally, the Commission and CAM practitioners must accept and act appropriately if the results of sound studies prove that a CAM product or practice is ineffective or dangerous.

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EDTA CHELATION THERAPY SHOULD BE MORE COMMONLY USED IN THE TREATMENT OF VASCULAR DISEASE

L. Terry Chappell, MD

L. Terry Chappell is in private practice in Bluffton, Ohio. He is assistant professor of family practice at Wright State School of Medicine and is president-elect of the American College for Advancement in Medicine.

EDTA chelation therapy is safe, effective, and more economical than commonly used surgical treatments for vascular disease. This article includes evidence of effectiveness, mechanisms of action of EDTA, a discussion of studies that have been done regarding the therapy, and some brief case reports. The conclusion is that EDTA chelation therapy should be a therapeutic option for vascular disease, either by itself or in conjunction with standard protocols. (Alternative Therapies in Health and Medicine. 1995;1(2):53-57)

Standard treatments of coronary, cerebral, and peripheral vascular disease are expensive and have high complication rates and significant mortality. The integration of ethylenediaminetetraacetic acid (EDTA) chelation therapy with these treatments would make them safer and more cost-effective and would often result in better clinical outcomes.

The following facts are supported by the literature:

- The mortality rate of coronary bypass is 4% to 10%,¹ and is even higher in elderly patients.² Common complications are restenosis within 7 years³ and significant cerebral dysfunction after the procedure.⁴
- Only a limited number of vessels can be treated by angioplasty, and restenosis rates are as high as 40% within 6 months.⁵
- A cardiac bypass procedure costs about \$50,000⁶; EDTA

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CHELATION THERAPY IS INEFFECTIVE FOR THE TREATMENT OF PERIPHERAL VASCULAR DISEASE

Simeon Margolis, MD, PhD

Simeon Margolis is a professor of medicine and biological chemistry at Johns Hopkins School of Medicine in Baltimore, Md.

The case against chelation therapy for cardiovascular disease (CVD) can be summarized in one sentence: Although advocates of chelation therapy have reported favorable results based on uncontrolled, usually retrospective "studies," two double-blind, randomized, placebo-controlled, prospective trials have shown that infusions of ethylenediaminetetraacetic acid (EDTA) are no more effective in improving the manifestations of peripheral vascular disease (PVD) than are infusions of a placebo.

Proponents have claimed that chelation therapy improves liver function, memory, and vision; lowers cholesterol; relieves symptoms of arthritis, Parkinson's disease, and multiple sclerosis; and reduces the incidence of cancer. The major use of chelation therapy, however, has been to treat CVD. In at least 50 published papers, chelation therapists have reported remarkable improvements in symptoms and objective findings following a course of chelation treatment. Unfortunately, these reports provide no acceptable scientific evidence for the benefits of chelation therapy because none of them included a control group.

In a meta-analysis Chappell and Stahl¹ selected 19 of 40 articles describing the effects of chelation treatment on CVD. They concluded that 87% of the patients included in their analysis "demonstrated clinical improvement by objective testing." A letter by Jonas² points out that this meta-analysis is fatally flawed despite a reasonable statistical approach. The absence of a control group in all but one of the studies is sufficient to reject the validity of the analysis. As shown in controlled studies described below, chelation therapy does provide some objective, short-term improvement in patients with PVD, but similar improvement occurred in the control patients. In addition to the other weaknesses cited by Jonas, 94% of the subjects included in the meta-analysis (21,629 of 22,765 subjects) were from two

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chelation therapy costs about one tenth that amount.

In the last 20 years, mortality due to cardiovascular disease has declined somewhat.⁷ This improvement is probably due more to lifestyle changes than to new therapeutic interventions.⁸

Good, clean, precise, double-blind controlled trials on cardiovascular therapies are desirable, but because of the number of variables, such studies are very difficult to conduct with high accuracy, and they often conflict. None have been performed for bypass, angioplasty, or EDTA chelation.

A preponderance of evidence shows that EDTA and other chelating agents are effective in treating vascular disease and are dramatically effective in certain patients. When given according to the published protocol, EDTA is safe, with a mortality rate that approaches zero and very low morbidity.⁹

EVIDENCE OF EDTA EFFECTIVENESS

Chappell and Stahl¹⁰ did a meta-analysis to determine whether correlation between treatment with EDTA and improvement in vascular disease was significant. Meta-analysis is a technique that is particularly well-suited for determining the net effect of multiple studies with somewhat different designs, and for evaluating controversial therapies.^{11,12} Of the 41 studies we found in a literature search, 19 that were published or submitted for publication met our criteria that objective data be listed on individual patients with vascular disease. A total of 22,765 patients had been enrolled in these studies; 87% of them had measurable improvement with treatment, and the correlation coefficient was highly positive at .88. To ensure that there was no type I publication bias by excluding unpublished data, a follow-up study¹³ on 1241 patients from 32 investigators was done. That meta-analysis also showed a correlation coefficient of .88, and 88% of the patients improved. Our conclusion was that EDTA was indeed effective in treating vascular disease. Using the square of the correlation coefficient as an estimate of the variability, it was estimated that 77% of the variability in improvement was due to EDTA and the rest to unknown factors. The improvement rate of 87% is comparable to that in the primary trials of pentoxifylline¹⁴ for the treatment of peripheral vascular disease (84%).

Several clinical studies merit special mention. Olszewer and Carter¹⁵ published a study of 2870 patients with various chronic degenerative diseases, primarily vascular. Almost 90% of them showed good to excellent outcomes. They also completed a small double-blind, crossover, controlled study¹⁶ on cardiovascular patients that was strongly positive. Van der Schaar¹⁷ demonstrated that by using the double and triple product on treadmill testing, almost all patients improved with EDTA treatment. Rudolph et al¹⁸ documented consistent improvement on Doppler ultrasound readings for patients with carotid artery obstruction and recently published a case study¹⁹ with retinal photographs showing improvement in macular degeneration. Brittenham and associates²⁰ used the iron chelator deferoxamine to prevent vascular

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studies.²⁴ The size of these two studies so dominates the outcome of the meta-analysis that the other 17 studies don't affect the results.

Are these two large studies examples of careful clinical investigation? Judge for yourself. In the larger study, with 19,147 subjects, which was unpublished at the time of the meta-analysis, investigators apparently used only thermography to measure improvement. Although a survey⁶ showed that the majority of authors and half the responding editors felt that it was acceptable to include unpublished data in a meta-analysis, the scientific rigor and validity of this large study, which accounts for the vast bulk of the patients included in this meta-analysis, are impossible to evaluate. Both of these studies were retrospective, included no controls, and involved a mixture of patients with PVD, coronary artery disease (CAD), and cerebrovascular disease. The lack of validity in lumping these three aspects of CVD together in a meta-analysis is evident from another publication by the authors of the smaller of these two studies,⁶ in which marked improvement in 91% of patients with PVD, 77% with CAD, and only 24% with "cerebral diseases" was reported. No improvement was seen in the 88 patients who had suffered a stroke at least 6 months before the initiation of treatment.

A placebo-controlled study of chelation therapy was started in 10 patients with PVD by Olszewer and coworkers,⁷ but after 10 infusions they noted that "some patients were improving substantially but others were not." When the code was broken, these investigators found that the five subjects who had not improved were receiving the placebo infusions. Accordingly, all subjects were then treated with 10 infusions of EDTA, and those initially in the control group improved nearly as much as those receiving the full 20 infusions. Incidentally, this raises the question of whether 30, 20, 10, or even fewer treatments with EDTA are needed to achieve the improvements claimed for chelation therapy. This issue has never been carefully evaluated.

To date, three reports have described the results of two randomized, double-blind, placebo-controlled studies of EDTA chelation for treatment of PVD. The first⁴ reported results from a subset (30 patients) of 153 Danish patients with claudication treated with 20 infusions of either sodium EDTA or saline. They found no differences between the 15 treated with EDTA and the 15 control patients in angiograms, ankle-brachial indices, transcutaneous oxygen tension, walking distance, or subjective improvement measured before, during, and after the infusions. This paper was soundly criticized in an unsigned editorial⁵ as a "harsh critique" revealing "political bias" rather than welcoming it as the first careful, controlled study of the issue. The editorial suggested that the 30 patients selected for inclusion in the study might not be representative of the whole group of 153 subjects and that "the authors may conveniently forget to publish the entire data." The absence of a bibliography was deemed "unusual."

The results from all 153 subjects were published,¹⁰ along

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complications in patients with iron overload. Casdorph^{21,22} used technetium-99 isotope techniques that demonstrated improvement in coronary and carotid disease.

Researchers in two studies (published in three journals^{23,24}) have claimed the studies to be randomized, well-controlled, double-blind clinical trials; they supposedly did not confirm the effectiveness of EDTA chelation treatment. Subjects in both groups were primarily smokers who had severe disease and were given minimal treatment (20 sessions, instead of the 30 or 40 suggested for such patients by physicians experienced with chelation). The fact that so many were smokers greatly limits the usefulness of the studies. But despite the limitations, 50% to 60% of the treated patients improved in both studies. Sloth-Nielson and colleagues did not follow the protocol for EDTA use established by the American College for Advancement in Medicine, although they claimed to have done so. The study was criticized in at least four journals^{25,26} and also by the Danish Council on Scientific Dishonesty.³⁰ The trial by Van Rij and colleagues²⁶ actually compared two chelating solutions, one with EDTA and the other without. Intermittent claudication patients treated with both solutions showed significant improvement, the former (60%) slightly more than the latter (59%). Since this improvement is much higher than expected in similar patients treated with placebo,³¹ the study actually confirms the therapeutic effect of chelating solutions.

Of 65 patients who were on a waiting list for cardiac bypass surgery, 58 were able to cancel their surgery after chelation therapy by Hancke and Flytlie.³² Similarly, 24 of 27 patients awaiting amputation were able to cancel their surgery after EDTA chelation treatment. Chappell³³ applied these figures to such cases in the United States and speculated that if chelation therapy had been used as a primary treatment in 1992, 363,000 of 407,000 bypasses might have been avoided and 102,000 limbs might have been saved. The estimated direct cost savings in that year alone would have been close to \$8 billion.

MECHANISMS OF ACTION

Multiple mechanisms of action have been documented for EDTA therapy: it decreases plaque formation and has a positive influence on cell membrane function. Kaman and associates³⁴ demonstrated the removal of metastatic calcium from rabbit aortas. Kindness and Frackelton³⁵ showed a dramatic inhibition of platelet aggregation and prolongation of partial thromboplastin time. Gutteridge³⁶ identified increased effectiveness of hydroxyl-radical scavengers in the presence of EDTA. Rudolph et al³⁷ showed a reduction of iron with chelation treatment. Further effects include improved lipid levels³⁸ and the restoration of electromagnetic potential across cell membranes.³⁹ Several detailed reviews of these mechanisms have been published.^{34,42}

Free radicals have been shown to cause ischemic cardioplegia after bypass.⁴³ Grech and associates⁴⁴ recently demonstrated a marked increase in free-radical activity after primary coronary

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with 21 references. When examined 3 and 6 months after the two courses of treatment, identical numbers of subjects in both groups reported that their symptoms were unchanged or improved; and there were no differences between the two groups in objective measurement of distance the subjects could walk before developing leg pains. The above-mentioned editorial made the following criticisms of this study: the use of sodium EDTA instead of magnesium EDTA would cause local pain and unblind the study; mineral and vitamin supplementation was not provided; the load of 8.4 g of sodium with the EDTA was detrimental; and two thirds of the patients continued to smoke.

The authors of the Danish paper mentioned in their Discussion section that the incidence of local pain and phlebitis was the same in those treated either with EDTA or saline alone. Others have reported the same beneficial effects from sodium and magnesium EDTA. A daily oral supplement of vitamins and minerals was given throughout the study. The amount of sodium added with the EDTA is trivial compared with the amount of sodium in the saline used for both sets of infusions, and it is not clear why chelation would be ineffective in smokers. The major benefits of chelation are now attributed to their antioxidant effect; and a recent epidemiological study⁴⁵ showed that intake of the antioxidant β -carotene reduced CAD in current and former male smokers, but not in men who had never smoked.

The latest double-blind, randomized, placebo-controlled trial of chelation therapy for PVD was carried out in New Zealand.⁴⁶ The 32 subjects received 20 saline infusions each, oral and intravenous vitamins, and sodium EDTA plus magnesium in the treatment group of 15 patients. Subjects were not permitted to smoke. No clinically significant differences were detected between the two groups up to 3 months after treatment in subjective and measured walking distance, ankle/brachial pulse indices, mood state, activities of daily living, or quality of life factors. It is particularly instructive to note that an improvement in walking distance was reported in 60% of the chelation group and 59% of the control group. Similar results were obtained in the Danish study; 50% of the placebo patients and 48% of those treated with EDTA reported mild to great improvement in their symptoms. These findings once more demonstrate the strong placebo effect of many treatments and the questionable validity of claims for benefits from any therapeutic approach unless a comparison is made with some type of placebo treatment.

One wonders what kind of criticism of this study will emerge from the advocates of chelation treatment. Perhaps the answer is best predicted by quoting the last paragraph from the editorial supporting chelation therapy.⁴⁷ "Our obligation as physicians and scientists is to prove by well-planned studies that this technique which we use constantly in our practices is beneficial to the long-suffering chronically sick people who are our patients. Thus, and only by such measures, do we remove the ugly bias which stalks the subject of EDTA chelation. This is, indeed, why ACAM [American College of Advancement in

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angioplasty in acute myocardial infarction. Since chelating agents can often control free-radical activity, they appear to be ideal agents for improving outcomes in patients with coronary artery disease.⁴³⁻⁴⁷

Certainly, well-designed, randomized studies on the use of EDTA for vascular disease should be completed. But the above evidence is sufficient at this time for the off-label use of chelating agents with informed consent.

DRAMATIC CASES

Physicians who offer chelation therapy often have successfully treated patients who had had multiple surgical procedures and been told that nothing remained to be done except to go home and die. I have had two patients who were previously on the heart transplant waiting list. After EDTA treatment, both were removed from the list by their cardiologists and both lead active lives. Another patient, a 59-year-old man, had spent 120 days per year in the hospital for 3 years. He had a history of five myocardial infarctions, seven angioplasty procedures, and one bypass. He required a meperidine injection to walk a block without chest pain. In the 2 years since EDTA treatment was begun, he has been in the hospital for only 2 days (for noncardiac pain). He takes no oral medication whatsoever and he bowls and plays golf for the first time in years. His insurance company paid approximately \$600,000 for functionally ineffective hospital care (although it may have kept him alive) and reimbursed none of the \$5000 he spent on the highly successful EDTA treatment.

INTEGRATION OF EDTA CHELATION THERAPY INTO CURRENT PROTOCOLS

EDTA treatment is not a "magic bullet." Physicians who use it must be well-trained.⁹ The American Board of Chelation Therapy has a rigorous certification process to identify specialists in the field. The therapy is only part of a comprehensive program that includes lifestyle changes and a continuation of medications that appear beneficial. Overall, 87% of patients who use the treatment demonstrate improvement with objective testing. Many are able to reduce medications and significantly improve function. The therapy is perhaps most important for those who are able to avoid the risks of surgery and for those who have responded poorly to standard protocols and improve dramatically with EDTA. Many of the latter patients would be disabled or perhaps dead without the benefits of EDTA treatment. A few patients require bypass surgery, angioplasty, or other interventions despite receiving chelation therapy.

Modern protocols should include EDTA therapy as an option for all types and degrees of vascular disease. This therapy should be encouraged before bypass or amputation (unless a life-threatening situation exists) in an attempt to avoid surgery and improve outcome. Chelation therapy should be used in nonsurgical candidates who are doing poorly. Some will show dramatic improvement. Furthermore, EDTA should be studied as a postbypass

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Medicine] founded its Journal, to be used as a proper instrument for reporting appropriate clinical and scientific studies which support what we are doing" (my emphasis). This last sentence does not seem to reflect a desire to learn the truth about chelation therapy, and now well planned studies, not an ugly bias, have shown that chelation therapy has no place in the treatment of PVD.

The bias frequently referred to by the advocates of chelation therapy suggests that their "opponents" fear the potential financial loss associated with the cure of CVD by chelation therapy. My guess is that others, like myself, have no fear that conventional treatments will be replaced by chelation therapy. Rather, we are concerned that a multitude of sufferers will continue to spend about \$5000 each out of pocket (since insurers do not cover the costs of chelation) for a treatment proven to be ineffective. Never mentioned is the potential bias of the chelation practitioners, who face significant financial loss if patients are finally convinced that chelation treatment is a waste of money.

The ball is now in the court of the proponents of chelation therapy. This treatment does appear to provide short-term improvement, although it is probably a placebo effect. The real question, however, is whether chelation treatments give long-term benefits for patients with PVD or other CVD. None of the studies has yet addressed this issue. If those carrying out chelation therapy wish to justify the practice, their obligation is to prove by well-planned studies that this technique provides long-term benefits to the sick people who are their patients.

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and/or angioplasty treatment to prevent restenosis and also as a prevention technique for type I cardiac patients, especially those with high risk factors for cardiovascular disease and stroke.

EDTA treatment is not a substitute for the judicious use of surgery or the appropriate use of pharmaceuticals, nor does its use preclude the appropriate use of either when indicated. When conscientiously applied by a trained physician in a comprehensive program that includes lifestyle modification and rational pharmacotherapy, EDTA chelation is scientifically sound, clinically effective, exceptionally safe, and comparatively inexpensive. And it is compatible with other treatment modalities. What more can be asked from a medical therapy?

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Arthur P. Grollman, M.D. – Biographical Sketch

Dr. Arthur Grollman is currently the Evelyn Glick Professor of Experimental Medicine, Professor of Pharmacological Sciences at the State University of New York at Stony Brook (SUNY-SB) and Director of the Zickler Laboratory of Chemical Biology. He received a B.A. in chemistry from the University of California at Berkeley and an M.D. from the Johns Hopkins School of Medicine. Following a residency in internal medicine at Johns Hopkins, he conducted research from 1961-1963 at the National Institutes of Health and served on the faculty of the Albert Einstein College of Medicine from 1964-1974. In 1974, he became the founding Chairman of the Department of Pharmacological Sciences at SUNY-SB and continued in this role until 2000, when he relinquished his administrative responsibilities to devote full time to research. From 1970-1972 and again from 1994-1996, he served concurrently as Associate Dean for Scientific Affairs.

Dr. Grollman is internationally known for work in cancer research which currently focus on molecular and environmental carcinogenesis. He serves as Principal Investigator for two NIH-supported Program-Projects: "Exocyclic DNA Adducts and Oxidative DNA Damage" and "Molecular Toxicology of DNA Adducts", and holds a MERIT Award for "Molecular Pharmacology of Tumor and Virus Inhibitors". Under Dr. Grollman's leadership, Pharmacological Sciences at SUNY-SB consistently ranked among the top five Departments of Pharmacology in the U.S. Dr. Grollman also played a central role in establishing a Center for Structural Biology and initiated a pharmacology major in the College of Arts and Sciences—one of only two such undergraduate programs in the country.

Dr. Grollman has published more than 150 papers in the field of molecular pharmacology and toxicology, including studies on active principles derived from botanical products. He served as Attending Physician at hospitals associated with Albert Einstein and Stony Brook and as Visiting Professor at Stanford, Johns Hopkins, and the Weizmann Institute. He has served on many national scientific advisory boards and recently organized a symposium sponsored by the American Association of Medical Colleges entitled "Alternative Medicine—The Importance of Evidence in Medicine and in Medical Education".

Herbal Medicines: Danger and Opportunity (危機)^{1,2}

Since the advent of the era of modern medicine, the majority of Americans have relied heavily on prescription drugs and/or over the counter medications for relief from symptomatic illness. The first effort by the federal government to protect consumers of drugs took place in 1906 with the passage of the Pure Food and Drug Act, which was prompted by journalistic exposure of false and misleading advertisements for patent medicines. The first legislation designed to ensure safety of drugs, introduced in 1938, was an amendment to this Act, following the deaths of children treated with sulfanilamide, an early antimicrobial, which had been formulated as a toxic elixir. In 1962, human tragedy again resulted in new regulations when women in Europe, given thalidomide as a sleeping medicine during the first trimester of pregnancy, subsequently gave birth to infants with phocomelia, a rare birth defect. Legislation requiring premarketing testing of new drugs for carcinogenicity and teratogenicity was promptly enacted. The responsibility for monitoring safety and efficacy of drugs has been placed on the Food and Drug Administration with funding and oversight provided by Congress (1).

Most Americans take effective FDA surveillance for granted. Relatively few are aware that a major change has occurred with respect to the regulation of what are now called dietary supplements, including herbal medicine. This category comprises products taken by more than 100 million Americans.

¹ 危機 = Chinese characters for danger and opportunity which together translate as "crisis".

² Statement to be presented to WHCCAM on May 15, 2001

The Dietary Supplement Health and Education Act of 1994 (DSHEA) now allows botanical products to be marketed without prior testing for safety. Omission of such protection is considered by pharmacologists, pharmacists, physicians, consumer health advocates, regulators, and some leaders in the botanical industry to be, in the words of one eminent pharmacologist, “an accident waiting to happen” (2).

Five centuries ago, Paracelsus wrote that “all drugs are poisons—it is a question only of the dose”. This wisdom from the father of modern pharmacology is applicable to this discussion of herbal medicine. Some proponents of complementary and alternative medicine (CAM) have been quoted as saying that herbs, being “nature’s chemicals,” are intrinsically non-toxic. Nothing could be further from the truth! Some of the world’s most toxic substances, including strychnine, hemlock, poison mushrooms, and tobacco, are derived from plants. The handful of plant products whose therapeutic effectiveness is unquestioned (digoxin, morphine, quinine, etc.), exhibit exceedingly narrow therapeutic windows. In permitting botanicals to be marked as dietary supplements rather than as drugs, Congress regrettably has released manufacturers from the burden of providing “proof of safety” prior to exposing a large and potentially vulnerable population to serious adverse effects (3). In contrast, before a new drug can be marketed or even administered to patients in clinical trials, studies on experimental animals, followed by limited Phase I tests in human volunteers, are required. Phase I studies explore the potential of a new drug to produce adverse effects, including drug interactions.

Three current situations epitomize the problems inherent in permitting herbal products to be classified as dietary supplements and to circumvent the premarket safety

testing required for drugs. The dangers associated with the herb *Aristolochia fanchi* will be discussed first but the story is not unique. Many other herbs are toxic (4) as reflected in numerous reports to Poison Control Centers throughout the U.S. (5).

Aristolochia—The herb *Aristolochia fanchi* (also known as birthwort) has been used since ancient times and is a component of traditional Chinese medicine. *Aristolochia* is available in capsule form in the U.S. (6). This herb was reported to be nephrotoxic as long ago as 1964; shortly thereafter, it was shown to cause cancer in experimental animals. In 1992 in Belgium, more than 100 cases of renal failure, requiring chronic dialysis and/or kidney transplantation, were reported (7). An epidemiological investigation revealed that the victims, most of them young women, had been given *Aristolochia fangchi* in the same weight reduction clinic. More than half of these women went on to develop urothelial cancer (8). Despite this report—and the banning of this herb in many European countries—*Aristolochia* remained on sale in the United States. In April, 2001, nine years after the first clinical report, the FDA belatedly wrote letters to physicians, pharmacists, consumers, and manufacturers, alerting them to the serious danger to health associated with use of this herb (8). It is instructive to contrast this sequence of events—where the ability of the FDA to take preventive action against a toxic and demonstrably carcinogenic dietary supplement is constrained by the provisions of DSHEA—with those associated with thalidomide—where the FDA acted on European reports before the drug was released in the United States, protecting the American public against exposure to a drug associated with irreversible birth deformities.

Ephedra—Many dietary supplements contain ephedra alkaloids, the active principle of a popular herb known as ma huang. Ephedra is heavily promoted for use in weight reduction programs and for energy enhancement—a so called “thermogenic” product or “pep pill”. The safety and efficacy of products containing ephedra have not been established and reports of their adverse effects—including permanent injury and death—have appeared with increasing frequency since passage of DSHEA (10). Between 1993 and 2000, the FDA received over 1,100 such reports including notices of heart attacks, cardiac arrhythmias, hypertension, acute psychoses, seizures, and in a few cases, death (11). More than half of these events occurred in persons less than 40 years of age. An independent study revealed that FDA records less than 1% of the total number of adverse events resulting from dietary supplements; thus, more than 100,000 consumers may have suffered similar adverse effects over this period of time.

Why has regulatory action against ephedra not been taken? Because, under DSHEA, *there are no provisions for manufacturers to demonstrate proof of safety or effectiveness for any substance classified as a dietary supplement before it reaches the consumer!* In contrast to new drugs, manufacturers and distributors of dietary supplements are not legally required to record, investigate, or even forward to the FDA reports they may receive of injuries or illness related to the use of their products (3). Following release for public consumption, FDA assumes full responsibility for proving that a supplement is unsafe. Only then may it take action to restrict the product's use or to remove it from the marketplace. As documented in an important recent report from the Office of the Inspector General (5), Congress has failed to allocate sufficient resources to conduct necessary investigations. Making matters worse, in the case of

ephedra, FDA was blocked in 1997 from mandating labels warning of potential toxicity and setting dosage limits for reasonable use.

Phenylpropylamine—The pharmacological effects of phenylpropylamine (PPA) on the cardiovascular system are very similar to those of ephedra. It is instructive to compare the handling of these two products by the FDA. A controlled study describing hemorrhagic stroke in young women taking PPA appeared in the same issue of *The New England Journal of Medicine* as a detailed report from UCSF analyzing the adverse effects of ephedra (12). As a direct result of this study, PPA was banned by the FDA and OTC products containing the drug were voluntarily removed by pharmacies throughout the U.S. In contrast, the sale of ephedra herbs without appropriate labeling to warn consumers of their inherent risks continues unchecked.

I have cited only two examples of serious toxicities resulting from the failure to regulate dietary supplements. Toxic effects of many other herbs have been reported (4) and calls to Poison Control Centers to report adverse reactions to dietary supplements have increased sharply since 1997, reaching 17,000 last year (5).

Another important safety aspect of the marketing of herbal products relates to the lack of standardization (13). Even for commonly used herbal products the amount state on the label often differs substantially from the amount contained in the preparation (14). In addition, adulteration of herbal remedies with heavy metals and prescription drugs (including steroids) is widespread. A random analysis of herbal products sold in San Francisco, conducted by the California Department of Health, revealed that 40% of herbs tested contained these such toxic contaminants (15). To complicate matters, it is difficult and often impossible for an analytical chemist to determine whether a botanical

remedy contains the specific herb(s) named on the label. Good manufacturing processes have been promised by industry but are slow in coming as they are required by common sense but not by law. Unannounced inspections and strong penalties for violations are required to address this present threat to public health. An effective system for reporting adverse effects of dietary supplements as recommended by the OIG (5) is crucial and should promptly be put in place.

Drug Interactions—The failure to regulate herbal medicine is associated with a major risk of drug interactions. This problem can—and probably does—occur with many herbal preparations, as recently shown for St. John's Wort, a product used widely in the U.S. and in Europe for the treatment of depression. The administration of St. John's Wort concomitantly with a protease inhibitor used in the treatment of AIDS, was shown to result in a dramatic decline in the level of the inhibitor (16). This situation is life-threatening to the HIV-infected individual who requires protease inhibitors for continued viral suppression. Furthermore, patients with heart and kidney transplants receiving immunosuppressants showed signs of organ rejection after co-administration of St. John's Wort (17).

Follow-up investigations confirmed that a common family of P450 enzymes involved in metabolism of these and many other pharmaceuticals is induced by St. John's Wort. Other drugs metabolized by this pathway (designated CYP3A4) include many of those used by the millions of Americans being treated for hypertension, heart failure, asthma, certain infections, and other chronic diseases, conferring on this herbal remedy—innocuous when taken alone—the ability to inactivate life-saving drugs on which many elderly patients depend. Because the potential for drug interactions is

proportional to the number of chemical constituents present; herbals are much more likely than single drugs to be involved in drug interactions, due to the myriad of chemical principles they contain. *The scope of this problem could be significantly reduced by requiring premarketing safety testing.*

As the title of this presentation suggests, there is an “opportunity” to improve the safety of dietary supplements. Health professionals and consumers should be informed about the dangers of herbal medicines and the need for controlled studies to evaluate efficacy as well as safety. These issues recently have been addressed in editorials in leading medical journals (18-19) and in a symposium sponsored by the American Association of Medical Colleges (20). Journalists and consumer advocates have a special responsibility to convey messages regarding drug safety to the public.

RECOMMENDATIONS

What should the White House Commission on Alternative and Complementary Medicine recommend to the President to reduce the dangers associated with the use of herbal medicines? I suggest the following:

1. As a matter of the highest priority, Congress should amend DSHEA so that manufacturers of dietary supplements, including herbs and other botanicals, would be required to obtain pre-marketing approval by demonstrating to the FDA that the product does not present a significant or unreasonable risk of injury under conditions of uses recommended or suggested in the label. Additionally, manufacturers should be required to develop warning labels for consumers and to participate in good

manufacturing processes. Severe penalties would be imposed on manufacturers who avoid or neglect this public health responsibility.

2. All recommendations contained in the OIG report should be promptly implemented. These actions will ensure that the FDA receives necessary information regarding adverse reactions to herbs, botanicals, and other dietary supplements, facilitating early detection of toxicity and disclosure of this essential information to consumers. A modest (0.3%) increase in the FDA budget would be sufficient to effect the recommended changes.
3. NIH should conduct randomized double-blind, placebo-controlled clinical trials designed to test the efficacy of selected herbal medicines and, at the same time, quantify their adverse effects. This basic information has been recently obtained for St. John's Wort (21) and will help to establish the risk/benefit ratio.
4. Basic research should be conducted on the mechanism(s) of action and toxicity of commonly used herbal medicines. This approach may provide leads to new drugs and help to anticipate toxic effects.

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EXECUTIVE SUMMARY

PURPOSE

To assess the effectiveness of the Food and Drug Administration's (FDA) adverse event reporting system for dietary supplements in protecting the American consumer.

BACKGROUND

Dietary supplements are increasingly popular. Currently about 60 percent of Americans take some form of dietary supplement every day without any apparent problems. Supplements include substances such as vitamins, minerals, botanicals, and amino acids. Although many of these supplements can be beneficial, there are risks associated with some. For example, ginkgo biloba may lead to excessive bleeding, vitamin A in high dosages during pregnancy may lead to birth defects, and St. John's Wort may reduce the effectiveness of some antiviral drugs. Unlike new prescription and over-the-counter drugs, FDA does not have the authority to require supplements to undergo premarket approval for safety and efficacy. Instead, it relies mostly on its adverse event reporting system to identify safety problems.

FDA's Adverse Event Reporting System for Dietary Supplements

FDA's adverse event reporting system for dietary supplements includes (1) detecting adverse events, (2) generating signals of possible public health concerns, (3) assessing those signals, and (4) taking appropriate safety actions based on its assessment. An adverse event is an incident of illness or injury that *may* be associated with a product or ingredient. With further investigation, the association may or may not be confirmed. Reporting adverse events is entirely voluntary, and FDA receives reports from a variety of sources including consumers and health professionals.

When a signal of a possible health problem is generated from the adverse event reporting system, FDA assesses whether it is an actual public health problem warranting attention. FDA can assess these signals by reviewing scientific literature, consulting with experts, reviewing clinical data, conducting its own laboratory tests, and/or commissioning studies. If FDA confirms that a public health problem exists, it can take a range of safety actions, such as issuing warnings to consumers and health professionals, issuing import alerts, requesting product recalls, or seizing products.

This Inquiry

In this report, we evaluate how well FDA's adverse event reporting system for dietary supplements functions as a consumer protection tool. We analyzed data from FDA's database; reviewed FDA laws, regulations, policies, and procedures; reviewed several adverse event reports; reviewed relevant literature; and interviewed FDA officials, industry representatives, and scientific experts. We did not evaluate the internal

operating procedures of the system.

FINDINGS

FDA's adverse event reporting system detects relatively few adverse events.

Adverse event reporting system typically detect only a small proportion of the events that actually occur. This appears to be especially true of FDA's system for dietary supplements. A recent FDA-commissioned study estimated that FDA receives less than 1 percent of all adverse events associated with dietary supplements. Among the factors that may contribute to under-reporting are that many consumers presume supplements to be safe, use these products without the supervision of a healthcare professional, and may be unaware that FDA regulates them. FDA's limited outreach concerning this system contributes to this unawareness.

It has difficulty generating signals of possible public health concerns.

FDA lacks much of the information that is necessary to effectively analyze adverse event reports and to generate possible signals of concern. Below we document the lack of information by presenting FDA data between 1994-1999.

Limited medical information. FDA did not receive the medical records for 58 percent (464 of 801) of the reports for which it requested them. Only 20 percent (527 of 2,547) of adverse event reports received by FDA came from health professionals.

Limited product information. FDA was unable to determine the ingredients for 32 percent (1,153 of 3,574) of the products mentioned in adverse event reports. FDA does not have the product labels for 77 percent (2,752 of 3,574) of the products mentioned in reports. FDA does not have product samples for 69 percent (1,301 of 1,888) of the products for which it requested them. Product samples are especially helpful because dietary supplement ingredients are not standardized.

Limited manufacturer information. FDA reports that it has received fewer than 10 adverse event reports directly from manufacturers. FDA was unable to determine the manufacturer of dietary supplement products for 32 percent (1,153 of 3,574) of the products involved in reports. FDA was unable to determine the city and State for 71 percent (644 of 904) of the manufacturers.

Limited information on the dietary supplement consumer. FDA was unable to follow-up with 27 percent (214 of 801) of the reports it tagged for follow-up primarily because the reports lacked sufficient information to identify the alleged injured party.

Limited ability to analyze trends. FDA has difficulty analyzing trends of adverse event reports because it lacks an adequate computer database for routine analysis and receives relatively few reports.

FDA lacks vital information to adequately assess signals of possible public health concerns generated by the adverse event reporting system.

In order to assess such signals, FDA must draw upon key information external to the system. But FDA faces obstacles in obtaining such information. For a recent case study that documents these obstacles see appendix A.

Limited clinical information. There is some clinical information available on dietary supplements and more is becoming available every day. But, the current regulatory framework for dietary supplements permits manufacturers to market a supplement without premarket safety studies. For this and other reasons, FDA has relatively little clinical information on particular products. The law requires manufacturers of certain new dietary ingredients to notify FDA 75 days prior to market and include “relevant” safety information. However, very few dietary ingredients are subject to this requirement, and FDA has issued no guidance on the type of safety information that should be submitted.

Limited information on consumer use. FDA lacks a mechanism to track the number of consumers using a particular supplement. Such information can be helpful to determine the incidence of certain adverse events in the user population and thus, the extent of the public health problem that it poses.

As a result, FDA rarely takes safety actions related to the adverse event reporting system.

Safety actions can be of significant benefit to consumer safety. For example, based on FDA’s investigation of adverse event reports, it found products containing plantain were contaminated with *Digitalis lanata*, a plant that can cause heart attacks in certain individuals. FDA issued a consumer warning against certain products containing plantain and asked supplement manufacturers to voluntarily recall their products contaminated with *Digitalis lanata*.

But, between January 1994 and June 2000, we were able to document only 32 safety actions that FDA took based on the adverse event reporting system—a period when more than 100 million people were taking supplements. With limited information to draw upon to generate and assess signals, FDA rarely reaches the point of knowing whether taking a safety action is warranted.

Public disclosure of adverse event reports can also be considered a type of safety action. FDA uses its website as its main vehicle for disclosure. However, its website has significant limitations; for example, it provides no evaluation of the reports, contains misleading information, and is rarely updated.

RECOMMENDATIONS

Our evaluation of FDA’s dietary supplement adverse event reporting system leads us to conclude that without further development of the overall regulatory framework for

dietary supplements, the potential of the system to serve as a consumer safeguard is inherently limited. The program simply cannot serve as an adequate safety valve until other measures are taken that will allow FDA to generate and confirm signals of possible public health concerns.

Below we offer our recommendations as a blueprint for action that FDA can take over a reasonable period of time. It has already called for some of them in its strategic plan for dietary supplements. We recognize that some of our recommendations will call for legislative or regulatory changes. We also recognize that resources are limited and that some of our recommendations may require additional resources.

RECOMMENDATION 1: Facilitate greater detection of adverse events.

Require dietary supplement manufacturers to report serious adverse events to FDA for some products. FDA should examine what types of products or ingredients should fall under this requirement. FDA already requires pharmaceutical manufacturers to report adverse events for all prescription and some over-the-counter drugs.

Contract with Poison Control Centers to obtain their adverse event reports on dietary supplements. These centers hold information that may be useful to FDA. Reports from Poison Control Centers may provide additional data to help generate signals of possible public health concern.

Inform health professionals and consumers about the adverse event reporting system for dietary supplements. The main way FDA can accomplish this is by expanding its outreach to health professionals and including information about the safety actions it has taken. Other possibilities include requiring manufacturers to provide a toll-free number on their product labels or placing FDA's toll-free number on labels.

RECOMMENDATION 2: Obtain more information on adverse event reports in order to generate stronger signals of public health concerns.

Educate health professionals about the importance of including medical information in adverse event reports. Without medical information about the alleged injured parties, FDA lacks crucial information for determining the likelihood that an adverse event was related to the use of a dietary supplement. When FDA conducts outreach it should encourage health professionals to obtain permission from their patients to release their medical records when appropriate.

Require dietary supplement manufacturers to register their products with FDA. A complete product registry would allow FDA to instantly access a list of all of the ingredients in a particular product and determine the product manufacturer's name as soon as it receives an adverse event report.

Require dietary supplement manufacturers to register with FDA. A registry of manufacturers would enable FDA to quickly and easily contact a manufacturer whose product was associated with an adverse event to obtain additional information.

Notify manufacturers when FDA receives a serious adverse event report. Alerting manufacturers of adverse events in which their products have been mentioned would give FDA the opportunity to obtain more product information from the manufacturer. It would also allow manufacturers to reevaluate the safety profile of the product, including manufacturing procedures, in a timely manner.

Emphasize to health professionals and consumers the importance of providing a way to identify the alleged injured party. Without this information FDA may be unable to gather additional information excluded from the report.

Develop a new computer database to track and analyze adverse event reports. To help identify signals, FDA needs a database that allows for querying by ingredients as well as products and types of adverse events.

RECOMMENDATION 3: Obtain vital information to adequately assess signals generated by the adverse event reporting system.

Issue guidance on the type of safety information that manufacturers should include in the 75-day premarket notification requirement for some new dietary supplement ingredients. FDA should take full advantage of its existing authority to obtain as much safety information as possible prior to marketing.

Explore the possibility of a monograph system for dietary supplements that would contain safety information on particular ingredients. Monographs are point papers on particular ingredients that contain safety and efficacy information. Such a system would allow FDA to have in a systematic fashion safety information that it could rely upon to help make decisions.

Collaborate with the National Institutes of Health in setting a research agenda addressing safety issues. Another way that FDA can gain clinical information is by collaborating with the National Institutes of Health that funds and conducts research related to dietary supplements.

Assist industry and the United States Pharmacopeia in standardizing dietary supplement ingredients, particularly botanicals. Standardized ingredients would allow FDA to have the confidence that taking action against unsafe products or ingredients is addressing all the products posing a health risk.

Expedite the development and implementation of good manufacturing practices for dietary supplement manufacturers. Standardized ingredients must be complemented by FDA enforcing those standards through good manufacturing practices. These are essential for FDA to be assured of the precise contents of each batch of supplements that is manufactured.

RECOMMENDATION 4: Disclose more useful information to the public about dietary supplement adverse events.

FDA should provide more useful data on its website so that consumers can, to some extent, evaluate the likelihood that the adverse event was related to the supplement. FDA could update the information on its website more regularly. FDA could also accomplish this by providing summary data on the numbers and types of reports received by product types or ingredients. Over time, as resources become available it could consider indicating the likelihood the event was caused by a product.

COMMENTS

We received comments on our draft reports from the Food and Drug Administration. We also solicited and received comments from three trade associations (Consumer Healthcare Products Association, American Herbal Products Association, and the Council for Responsible Nutrition) and two public interest organizations (Public Citizen's Health Research Group and the Center for Science in the Public Interest.) See appendix C for the comments in their entirety.

On the basis of these comments we made several changes that are reflected in this final report. Some involved minor technical changes, and others involved brief elaboration to clarify and add context. In two instances we modified our recommendation to target them more effectively and to minimize regulatory burden. We limited the scope of mandatory reporting of adverse event reports to events that are both serious in nature and fall under a certain subset of products to be determined by FDA. Similarly, instead of calling for FDA to notify manufacturers of all adverse event reports it receives, we called for it to notify the manufacturers of serious reports only.

Food and Drug Administration

FDA reported that our findings were a fair assessment of the challenges it faces. It also agreed with the majority of our recommendations. As part of its comments, it categorized our recommendations into three areas: (1) tasks that it can currently accomplish, (2) tasks that require additional resources, and (3) tasks that require both legislative changes and additional resources. FDA documented the progress it has made in each of these categories. FDA indicated that the major difficulty it faces to improving the system is a lack of adequate resources.

FDA is making progress toward improving the system along the lines we call for in our report. Many of our recommendations are already included among FDA's top priorities for the year as well as in its 10-year strategic plan. We also encourage FDA to seek the authority it needs to require manufacturer and product registration and mandatory manufacturer reporting of adverse events.

Trade Associations

The three trade associations provided some support for our recommendations, but for the most part, they were highly critical of both our findings and recommendations. While we disagree with the thrust of their comments, they help sharpen the issues that need to be addressed as part of any reform.

One of their major critiques was that we chosen not to evaluate the internal operating procedures of FDA's adverse event reporting system, thereby leaving us with little basis for our broader recommendations. We agree that there could be value to a procedural review. FDA should be doing everything it can to make sure the current system operates as effectively as it possibly can. However, we offer strong evidence that the current system is fundamentally flawed and cannot provide an adequate consumer safeguard unless FDA is given more tools to do the job.

Another significant critique was that we failed to view dietary supplements in the context of a food-related system. This failure, they claim, led us to call for more extensive oversight, similar to that for prescription drugs. Our inquiry focused on how the current system was functioning and made us acutely aware of just how little information FDA has available to determine whether adverse events about dietary supplements (however characterized) present dangers that should be addressed. Without an improved capacity to obtain such information, FDA's adverse event reporting system will continue to fall short of its potential.

Still another critique was that our report reflects a negative view of dietary supplements and fails to recognize their role as self-care products that so many consumers value. We regret any implication of such a negative view. If the kind of recommendations we call for are enacted, we suggest that consumers would have more extensive and useful information available to them on these self-care products and could have more confidence that an adverse event reporting system was providing them with a valuable measure of protection.

Public Interest Organizations

The two public interest organizations strongly supported our report. Their main critique was that we did not go far enough. One called for legislative changes that, over time, would significantly enhance FDA authorities. The other called for FDA to support a systematic study of dietary supplements safety and efficacy. While our evidence did not allow us to go as far as these organizations would like, it did lead us to emphasize that a comprehensive set of changes must be carried out if the adverse event reporting system is to provide an adequate consumer safety valve.

Max Heirich is associate director of the University of Michigan Health Policy Forum and also serves on the Advisory Board for the University of Michigan Medical School's Complementary and Alternative Medicine Research Center. For the past twenty-five years he has been teaching courses on Asian medical systems, designing demonstration/evaluation research which incorporates CAM approaches into worksite wellness programs, and also doing research on health care policy. A professor emeritus and research scientist emeritus at the University, he currently serves as an adjunct lecturer in the University of Michigan's School of Medicine and directs the Worker Health Program at the University of Michigan's Institute of Labor and Industrial Relations. He has been a consultant on prevention to committees of the U.S. Senate and the Michigan State Senate, to Merck Pharmaceutical Company, the United Auto Workers, Ford and General Motors. Heirich has had research grants from the National Institutes of Health's Heart, Lung, and Blood Institute, the National Institute on Drug Abuse, and the Public Health system's Center for Substance Abuse Prevention, a part of SAMHSA. Heirich coauthored an NIH-sponsored manual, a research-based, step-by-step guide for doing worksite cardiovascular wellness programs, and later chaired a working group of nineteen national organizations that drew up recommended guidelines for worksite health promotion. He is the author of several books, including **RETHINKING HEALTH CARE: INNOVATION AND CHANGE IN AMERICA**, Westview Press, 1998, and numerous articles. His most recent work has focused on the development of strategies for getting more effective health care to those who now have only limited access to health care services.

for patients suffering from chronic disease and negotiating with managed care companies to reimburse these cost saving programs. The US Public Health Services estimates that 70% of the health care budget is spent on 20% of the population, that segment of the population which suffers from chronic diseases.

Testimony

The recommendations that follow are intended for healthcare as it exists today, for the urgent needs of patients without choice, providers without the right to make clinical decisions, and payers without answers.

The origin of CPT was created by the desire to obtain utilization data for conventional medicine techniques and procedures. The role of CPT in the eyes of the AMA was to categorize conventional medical services in effort to objectify services rendered in the physicians office. The license to use these codes is then purchased by the insurer and the CPT books are sold to physicians offices. This mass distribution of CPT resulted in the creation of a standard language used to submit information to insurance carriers. There are three main factors that have attributed to the demise of the clinical usage of CPT, the administrative paper war associated with CPT and the crash of managed care systems because of the misuse of CPT.

First, the clinical usage of CPT in the physicians office was severely misused and abused in the 70's and 80's. The crack down by Medicare's fraud investigation unit discovered huge abuses in the way services were reported and began to create guidelines around how long a physician could spend with a patient with a given disease and how that service needed to be coded in order to be paid. Once the commercial insurers caught on to this same kind of abuse, meetings began to take place with the large insurance companies in the country and Health Maintenance Organizations (HMO), and the advent of Managed Care resulted.

The **second** factor of the demise of the administrative side of health care was when the simple use of the CPT, used to track utilization and cost data, became the tool for measuring best practices in managed care. Actuarial firms all over the country purchased large quantities of CPT data from many sources, and from those data decided what were the best practices in medicine. Then, these firms sold the analyses of their data to managed care and insurance companies who started to create software that would "kick out" claims if the ICD 9 (diagnosis code) did not match the best practices analyses generated from the CPT data previously collected.

Picture this..... if every physician decided to treat terminal cancer patients by significantly changing their diet – given the way we make best practices decisions today – chemotherapy might cease to be considered best practice. Just because the data indicate a treatment is most widely used, it does not prove the efficacy of that treatment. CPT data should be used only as it was intended to be used – for utilization review and not the determination of best clinical practices. In making these data best practices guidelines, we have increased the cost of health

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care significantly by giving many patients the wrong treatments *for them* because it was the only thing the insurer would cover. Using CPT to provide best practices guidelines assumes we are all the same. That is an assumption that will continue to increase health care costs in this country until we stop and realize that the way we capture data must change.

Finally, we must record some objectified measurement of patient outcomes and/or progress at the encounter level to assist the payers with controlling overutilization. A potential example of how we might do is as follows:

- The provider submits a protocol with a estimated number of treatments and specific objective treatment goals
- For each subsequent claim, the patient indicates on a scale of 1-10 his/her perceived rating of the current status of the presenting problem and progress towards treatment goals
- The provider enters this patient rating on one of the “open” fields on the current HCFA 1500 form
- That we begin the coding of innovative treatments by starting with HCFA at the HCPCS level and then adopt codes into CPT as their meaning and utilization are studied. This gives the insurers time to update their systems and provide for education in the use of these new codes and speeds up the amount of time it will takes to get these new codes accepted by CPT/AMA.
- I believe we should not try to replace CPT but instead to enhance its use and provide a bridge for consumers to access therapies that cannot be coded legally today.

If no progress is being made or no improvement is shown (patient reported) then the patient would be switched to a new treatment plan. This approach allows **all of us to choose the kinds of treatment we want to receive, patients and providers to collaborate on treatment options, providers to responsibly innovate in the treatments they offer patients, and payers to control cost – all better than we are now.** Waste is minimized, and administrative costs are slashed because providers no longer must generate huge volumes of paperwork to convince payers to consider coverage for innovative treatments. Health services research at the patient encounter level provides a valuable realworld corroboration of the results of randomized controlled trials. It measures the appropriateness and the outcome of treatment plans to which both the patient and the provider have agreed, with which both can willingly comply, and which improve the odds of a positive outcome.

Best practices are only best for those patients who respond best to them. The rigidity with which we are now managing care puts physicians into ethical quandaries, and puts patients into the predicament where they are receiving the wrong treatment plan *for them* because that is what is covered by insurance.

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Research Methodology
Divider Title: _____

Questions for the Research Methodology Panel:

When addressing the need to find methods and approaches to establish the safety and effectiveness of CAM practices and products, in addition to data collection and clinical trial methodology, consider how we can study the complex questions inherent in CAM that require study such as multiple interventions; complex systems and complex compounds; mind-body interactions; individualization; qualitative research; the placebo effect; provider/patient interaction; multiple populations including culture/race, gender, age; and so forth?

How do current methodologies need to be modified to address questions concerning energy medicine?

How can good data on CAM procedures and products be developed?; accessed? What would a workable progression be from early anecdotal reports to the development of good data?

What can CAM practices and products contribute to investigations where there is overlap with conventional areas of research, e.g., wellness/health promotion and disease prevention/preventive medicine, nutrition, exercise, chronic conditions, pain management, self care, care for the terminally ill?

How can research collaborations between conventional and CAM institutions be facilitated?

How can communication between conventional investigators designing CAM protocols and CAM practitioners be improved?

When studying CAM products and procedures, how often are cost-benefit analyses included?

At what point is the knowledge base sufficient to move results to clinical practice?

What policy recommendations can you offer regarding research on CAM practices and procedures for the Commission's consideration as it develops its report to the President and Congress?

John Chabot, M.D.
Columbia University

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[001]

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7/1/95 - 6/30/98	Voting Member-Faculty Council of the Faculty of Medicine
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11/96 - Present	Vice Chairman, Department of Surgery
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1979	Sigma Xi, Scientific Research Society
1979	Alpha Omega Alpha, Dartmouth Medical School
1980	1985-87 Irvington House Institute Fellowship
1987	Upjohn Young Scientist Award
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1990	Blakemore Award for Surgical Research
1990	Ortho Foundation Award
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Professional Development:

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Committees:

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1990-Present	Annual Preceptor for Third Year Clinical Clerks-Surgery
	Monthly Teaching Seminar for Third Year Clinical Clerks on Pancreas
1997	Annual Lecture "Biliary Physiology", AIBB II Curriculum Teacher of the Year, P & S Graduating Class of "97"
9/8/00	Radiation Oncology: 2000 Intraoperative Radiation Therapy & Brachytherapy - Columbia University College of Physicians & Surgeons - Departments Radiation Oncology, Surgery and Gynecological Oncology held at The Roosevelt Hotel, New York City Presentation Entitled: Sarcomas and Pancreatic Cancer - Moderator

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John A Chabot, MD
Associate Professor of Clinical Surgery
Columbia University

I became involved with a specific alternative medicine protocol when the director of our comprehensive cancer center, Karen Antman, MD was asked to consider designing and running a clinical trial of its efficacy. Dr. Antman asked me to consider running the clinical trial because of my focus and expertise in pancreatic cancer. My initial reaction was highly skeptical, however I agreed to consider the trial. The therapy consists of high dose oral pancreatic enzyme supplements, a strict nutritional regimen with a focus on fresh fruits and vegetables as well as several cleansing and cathartic procedures.

I reviewed the treatment provided to eleven patients in a pilot study completed several years earlier by Nicholas Gonzalez, MD. This group of patients lived for a significantly longer period of time than I would expect. Patients with advanced pancreatic cancer are expected to live approximately six months (median survival 5.7 mo). The median survival in this group was 17 months. I validated the underlying disease and reviewed records to confirm that these were advanced cases. Although, I could not explain or understand the underlying mechanism of this protocol, I chose to become involved because of the dramatic results obtained in the pilot study.

After obtaining approval of our Cancer Committee and the Institutional Review Board we opened an NCI funded randomized clinical trial comparing the Gonzalez regimen with Gemcitabine (standard chemotherapy for advanced pancreatic cancer). Despite widespread publicity and a multitude of interested patients, we enrolled very few patients in the first year. The vast majority of patients who contacted us for information were either ineligible due to very narrow eligibility criteria or declined to participate when learning of the randomized nature of the trial. Those people who expressed interest in the regimen in most cases would not consider chemotherapy as a reasonable treatment for their disease. They wanted the Gonzalez regimen or nothing. It became clear to us that we would never enroll the 70 to 90 patients we required to draw a valid conclusion regarding the efficacy of this treatment. We therefore redesigned the trial to allow patients to choose which therapy they would receive. We will still compare the Gonzalez regimen to chemotherapy based treatment. We will carefully control the two critical variables that predict survival in advanced pancreatic cancer patients, extent of disease and ability to eat. Without a randomized design, however, we increase the risk that bias will enter the study and skew our results. We expect that

rigorous adherence to protocol criteria and careful analysis of results will allow us to draw conclusions.

Thus far, I have made three observations:

1. Among those people we have screened for this protocol, the bias toward alternative therapy is very strong.
2. Patients who express interest in this protocol are generally healthier than the overall population of patients with advanced pancreatic cancer. The patients who meet the eligibility criteria are clearly healthier than the general population of advanced pancreatic cancer patients.
3. The effects of psychosocial support and the availability of hope are not insignificant. In the absence of blinded, randomized trials, separating these effects from physiological or pharmacological effects represents a major challenge to clinical trial design.

*Problems in randomised controlled Clinical Trial
Pts want treatment not conventional tx*

MAY-10-2001 15:52 SURGICAL SPEC. 212 305 5992 P.15
From: "Pollen, Geraldine (NCCAM)" <polleng@od.nih.gov>
To: "jac4@columbia.edu" <jac4@columbia.edu>
Subject: White House Commission
Date: Fri, 20 Apr 2001 14:09:01 -0400
Status: O

Dear Dr. Chabot:

I hope by this time our contractor has contacted you about your travel and other logistics, and roster information.

I am sending you a draft agenda of the Commission's research meeting on May 15-16, and questions for the panel on research methodology on May 16. These questions are for guidance only and should not limit your remarks.

We ask that each panelist speak for 10 minutes and participate in a discussion with the Commissioners. The panel process does not allow for slide presentations.

We also ask that each panelist send us by May 7 a summary of his remarks and a brief personal biography. These materials are included in the Commissioners briefing books, which are sent to them prior to the meeting.

Please let me know if you have any questions.

We are looking forward to your participation in this meeting.

Questions for the Research Methodology Panel: (for guidance only)

When addressing the need to find methods and approaches to establish the safety and effectiveness of CAM practices and products, in addition to data collection and clinical trial methodology, consider how we can study the complex questions inherent in CAM that require study such as multiple interventions; complex systems and complex compounds; mind-body interactions; individualization; the placebo effect; provider/patient interaction; multiple populations including culture/race, gender, age; and so forth?

How do current methodologies need to be modified to address questions concerning energy medicine?

How can good data on CAM procedures and products be developed?; accessed? What would a workable progression be from early anecdotal reports to the development of good data?

What can CAM practices and products contribute to investigations where there is overlap with conventional areas of research, e.g., wellness/health promotion and disease prevention/preventive medicine, nutrition, exercise, chronic conditions, pain management, self care, care for the terminally ill?

How can research collaborations between conventional and CAM institutions be facilitated?

How can communication between conventional investigators designing CAM protocols and CAM practitioners be improved?

When studying CAM products and procedures, how often are cost-benefit analyses included?

At what point is the knowledge base sufficient to move results to clinical practice?

Qualitative Research

Printed for "John A. Chabot, M.D." <jac4@columbia.edu>

What policy recommendations can you offer regarding research on CAM practices and procedures for the Commission's consideration as it develops its report to the President and Congress?

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Biographical Sketch of Marcia Angell, M. D., F.A.C.P.

Marcia Angell, M. D., is Senior Lecturer in the Department of Social Medicine at Harvard Medical School. She stepped down as Editor-in-Chief of the *New England Journal of Medicine* on June 30, 2000. A graduate of Boston University School of Medicine, she trained in both internal medicine and anatomic pathology and is a board-certified pathologist. She joined the editorial staff of the *New England Journal of Medicine* in 1979, became Executive Editor in 1988, and Editor-in-Chief in 1999.

Dr. Angell writes frequently in professional journals and the popular media on a wide range of topics, particularly medical ethics, health policy, the nature of medical evidence, the interface of medicine and the law, and care at the end of life. Her critically acclaimed book, *Science on Trial: The Clash of Medical Evidence and the Law in the Breast Implant Case*, was published in June, 1996, by W. W. Norton & Company. In addition, Dr. Angell is co-author, with Dr. Stanley Robbins and, later, Dr. Vinay Kumar, of the first three editions of the textbook, *Basic Pathology*. She also wrote chapters in several books dealing with ethical issues.

Dr. Angell is a member of the Association of American Physicians, the Institute of Medicine of the National Academy of the Sciences, the Alpha Omega Alpha National Honor Medical Society, and is a Fellow of the American College of Physicians. In 1997, *Time* magazine named Marcia Angell one of the 25 most influential Americans.

Angell

RESEARCH METHODOLOGY IN CAM

by Marcia Angell, M. D.

CAM is an umbrella term for a large number of disparate practices based on different theories. These include, for example, homeopathy, therapeutic touch, naturopathy, chiropractic, acupuncture, herbal medicine, imagery, crystal healing, and chelation therapy. They 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.

Because CAM consists of such disparate practices, it makes no sense to imagine that we need to develop a single new research methodology for studying them all or that this differs from the methodology for studying standard medicine. A clinical trial of acupuncture, for example, presents different methodological problems from a trial of ginseng. The former would require careful attention to the selection of a comparison group or groups, whereas the latter would require attention to the purification and standardization of the product being tested. In fact, the problems in studying various CAM practices differ at least as much from one another as they do from the equally diverse problems in designing studies of standard practices. The problems in designing trials of new cocktails to treat leukemia are not all that different from the problems in studying herbal remedies. And the problems in studying fetal cell transplantation for Parkinson's disease are similar to those of studying acupuncture.

But none of the methodological problems are insoluble. For years, scientists have managed to devise valid ways to study potential new remedies, and there is nothing qualitatively different about CAM. We need to get on with the job, because millions of people are taking remedies for which there is little or no evidence. These remedies need to be put to the test. Tradition and testimonials are no substitute for scientific evidence. This has been demonstrated repeatedly in medical history. The spectacular advances in clinical medicine during the 20th century correlated with the acceptance of

Angell

the need to demonstrate effectiveness scientifically and objectively. What seems self-evidently true often proves false, and we have no choice but to rely on the scientific method to settle the matter.

Despite some differences in the details of research methodology, the overarching approach is the same for studying any potential new treatment -- whether considered as CAM or standard medicine. The scientific method includes formulating a hypothesis that can be tested, designing a study to test it, collecting data, and drawing those conclusions -- and only those conclusions -- that are supported by the data. It proved to be the only way to gain information about the natural world -- and our bodies are a part of that world. The scientific method was not a regional or cultural choice; it was forced on people all over the world, because it worked.

In summary, 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. In general, CAM falls into the second category. Standard medicine falls into both. Whether biologically implausible (or even impossible) remedies should be tested is arguable. I have come to believe that widely used remedies should be tested for safety and effectiveness, even when they are biologically implausible. If they are shown to be effective and reasonably safe, they should be incorporated into clinical practice, regardless of whether they originated as CAM. But there are no short-cuts, and there should be no free passes.

German Commission E Monographs
1978 380 monographs - No citation to research studies