THE RICHARD AND HINDA ROSENTHAL LECTURES

2001

Exploring Complementary and Alternative Medicine

INSTITUTE OF MEDICINE
OF THE NATIONAL ACADEMIES

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The serpent has been a symbol of long life, healing, and knowledge among almost all cultures and religions since the beginning of recorded history. The serpent adopted as a logotype by the Institute of Medicine is a relief carving from ancient Greece, now held by the Staatliche Museen in Berlin.

"Knowing is not enough; we must apply.
Willing is not enough; we must do."
—Goethe

INSTITUTE OF MEDICINE
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Shaping the Future for Health

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Foreword

In 1988, an exciting and important new program was launched at the Institute of Medicine. Through the generosity of the Richard and Hinda Rosenthal Foundation, a lecture series was established to bring to greater attention some of the critical health policy issues facing our nation today. Each year a subject of particular relevance is addressed through three lectures presented by experts in the field. The lectures are published at a later date for national dissemination.

The Rosenthal lectures have attracted an enthusiastic following among health policy researchers and decision makers, both in Washington, D.C., and across the country. Our speakers are the leading experts on the subjects under discussion and our audience includes many of the major policymakers charged with making the U.S. health care system more effective and humane. The lectures and associated remarks have engendered lively and productive dialogue. The Rosenthal lecture included in this volume explores the world of complementary medicine and its implications for medical research, clinical practice, and policy in the United States. There is much to learn from the informed and real-world perspectives provided by the contributors to this book.

I would like to give special thanks to Roger Bulger for moderating the November 2001 lecture. In addition, I would like to express my appreciation to Jennifer Otten, Bronwyn Schrecker, Hallie Wilfert, Jennifer Bitticks, and Curtis Taylor for ably handling the many details associated with the lecture programs and the publication. No introduction to this volume

would be complete, however, without a special expression of gratitude to the late Richard Rosenthal and to Hinda Rosenthal for making this valuable and important education effort possible and whose keen interest in the themes under discussion further enriches this valuable IOM activity.

Harvey V. Fineberg, M.D., Ph.D.
President
Institute of Medicine

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Complementary and Integrative Medical Therapies: Current Status and Future Trends

David Eisenberg

I. DEFINITIONS AND TERMINOLOGY

"Complementary," "Alternative," and "Integrative" Medical Approaches

Complementary and alternative medical (CAM) therapies encompass a broad spectrum of practices and beliefs (1). From an historical standpoint, they may be defined "... as practices that are not accepted as correct, proper, or appropriate or are not in conformity with the beliefs or standards of the dominant group of medical practitioners in a society" (2). From a functional standpoint, complementary (a.k.a."alternative") therapies may be defined as interventions neither taught widely in medical schools nor generally available in hospitals (3). Ernst et al. contend that "complementary" medical techniques "[complement] mainstream medicine by contributing to a common whole, by satisfying a demand not met by orthodoxy or by diversifying the conceptual frameworks of medicine" (4). The terminology currently in use to describe these practices remains controversial. Many commonly used labels (e.g., "alternative," "unconventional," "unproven") are judgmental and may inhibit the collaborative inquiry and discourse necessary to distinguish useful from useless techniques (5). Complementary and alternative medicine (CAM) is the language currently used by the National Institute of Health (NIH) and U.S. federal agencies to describe this field of inquiry**.** The NIH National Center for Complementary and Alternative Medicine (NCCAM) defines CAM as "healthcare practices outside the realm of conventional medicine, which

are yet to be validated using scientific methods." Two recent articles by Kaptchuk et al., explore the taxonomy of CAM therapies in the context of medical pluralism (6;7).

Integrative medicine refers to ongoing efforts to combine the best of conventional and evidence-based complementary therapies while emphasizing the primacy of the patient-provider relationship and the importance of patient participation in health promotion, disease prevention, and medical management. "It (integrative medicine) views patients as whole people with minds and spirits as well as bodies and includes these dimensions into diagnosis and treatment" (8). In the January 2001 *British Medical Journal* edition devoted entirely to integrated medicine, the *Journal*'s editor, Richard Smith, wrote: "It mightn't be too pretentious (although it might) to say that such a growth (of integrative medicine) might restore the soul to medicine—the soul being that part of us that is the most important but the least easy to delineate" (9). A variety of articles and editorials have wrestled with the challenges of properly labeling and describing this field of inquiry (8;10-16).

Dietary Supplements

The Dietary Supplement Health and Education Act (DSHEA) defines dietary supplements as products (other than tobacco) intended to supplement the diet that bear or contain one or more of the following dietary ingredients: a vitamin, mineral, amino acid, herb or other botanical; or a dietary substance for use to supplement the diet by increasing the total dietary intake; or a concentrate, metabolite, constituent, extract, or combination of any ingredient described above; and intended for ingestion in the form of a capsule, powder, soft gel, or gelcap, and not represented as a conventional food or as a sole item of a meal or the diet. The DSHEA legislation stipulates that botanicals and other dietary supplements are not "drugs" and, as such, are not held to the same regulatory requirements as drugs (i.e., prerequisite evidence of both safety and efficacy). Manufacturers of dietary supplements are not allowed to make "disease claims" but are permitted to make "structure/function" claims. This has resulted in a range of interpretations and has complicated both clinical decision making and efforts to perform scientific research involving botanicals (17;18).

II. EPIDEMIOLOGY

A. Prevalence, Costs, and Patterns of Use of CAM Therapies in the United States

Findings from a 1997 follow-up national survey of complementary and alternative medicine (CAM) prevalence, costs, and patterns of use (19) include the following:

Between 1990 and 1997:

- The prevalence of CAM use increased by 25 percent from 33.8 percent in 1990 to 42.1 percent in 1997.
- The prevalence of herbal remedy use increased by 380 percent.
- The prevalence of high-dose vitamin use increased by 130 percent.
- The total number of visits to CAM providers increased by 47 percent from 427 million in 1990 to 629 million in 1997.
- The total visits to CAM providers (629 million) exceeded total visits to all primary care physicians (386 million) in 1997.
- In 1997, adults made an estimated 33 million office visits to professionals for advice regarding the use of herbs and high-dose vitamins.
- Estimated expenditures for CAM professional services increased by 45 percent exclusive of inflation and in 1997 were estimated at $21.2 billion dollars.
- Out-of-pocket expenditures for herbal products and high-dose vitamins in 1997 were estimated at $8 billion.
- Out-of-pocket expenditures for CAM professional services in 1997 were estimated at $12.2 billion. This exceeded the out-of-pocket expenditures for all U.S. hospitalizations.
- Total out-of-pocket expenditures relating to CAM therapies were conservatively estimated at $27.0 billion. This is comparable to the projected out-of-pocket expenditures for all U.S. physician services.
- An estimated 15 million adults in 1997 took prescription medications concurrently with herbal remedies and/or high-dose vitamins. These individuals are therefore at risk for potential adverse drug-herb or drug-supplement interactions.
- Current use of CAM services is likely to under-represent utilization patterns if insurance coverage for CAM therapies increases in the future.
- Despite the dramatic increases in the use and expenditures associated with CAM services, the extent to which patients disclose their use of CAM therapies to their physicians remains low. Fewer than 40 percent of CAM therapies used were disclosed to a physician in both 1990 and 1997.

The authors concluded that CAM use and expenditures increased substantially between 1990 and 1997, attributable primarily to an increase in the proportion of the population seeking CAM therapies, rather than increased visits per patient.

Other nationally representative surveys of CAM prevalence and patterns of use have provided additional useful information. These include a study by Astin (20) which concluded that "…the majority of alternative medicine users appear to be doing so not so much as a result of being dissatisfied with conventional medicine, but largely because they find their health care alternatives to be more congruent with their own values, beliefs and philosophical orientation towards health and life." Druss and Rosenheck's national survey (21) found that practitioner-based CAM therapies appear to serve more as a complement than an alternative to conventional medicine; and, individuals in the top quartile of numbers of physician visits were more than twice as likely as those in the bottom quarter to have used CAM therapies during the prior year. Two recent analyses of national survey data provide additional information regarding CAM patterns of use in adults over age 65 (22) and adults with anxiety or depression (23).

A recent publication by Kessler et al. examines the long-term trends in the use of CAM in the United States (24). It found that 68 percent of adults had used at least one CAM therapy in their lifetime; and lifetime use steadily increased with age across age cohorts: approximately three in 10 respondents in the pre-baby boom cohort, five of 10 in the baby boom cohort, and seven to 10 in the post baby boom cohort reported using some type of CAM therapy by age 33. Moreover, a wide range of individual CAM therapies increased in use over time, and the growth was similar across all major sociodemographic sectors. The authors concluded, "Use of CAM therapies by a large proportion of the study sample is the result of a secular trend that began at least a half century ago. This trend suggests a continuing demand for CAM therapies that will offset health care delivery for the foreseeable future."

A recent publication by Eisenberg et al. examined perceptions about CAM therapies relative to conventional therapies among adults who used both. The authors found that the majority of CAM therapy users: (1) perceived the combination of CAM and conventional care to be superior to either alone (79 percent); (2) typically saw a medical doctor before or concurrent with their visits to a CAM provider (70 percent); (3) had a similar level of perceived confidence in both their CAM provider and MD; and (4) they did not disclose their CAM therapy to their medical doctor (63-72 percent). Principal reasons for nondisclosure were: "It wasn't important for the doctor to know" (61 percent); "The doctor never asked" (60 percent); "It was none of the doctor's business" (31 percent); and "The doctor

would not understand" (20 percent). Fewer respondents (14 percent) thought their doctor would disapprove of or discourage CAM use. The authors concluded that, "Adults who use both expect to value both and that to be less concerned about their doctor's disapproval than about their doctor's inability to understand or incorporate CAM therapy use within the context of their medical management." (25)

The above-mentioned surveys are all based on nationally representative random samples of adult Americans. In addition, there have been a number of convenience samples investigating CAM therapy use among individuals with a particular condition or disease. Examples include surveys involving CAM therapy use among individuals with: cancer (26-35); rheumatologic disorders (36-38); self-reported disability (39); HIV (40); inflammatory bowel disease (41); and rhinosinusitis (42); as well as surgical patients (43); and patients in an emergency department (44).

National surveys performed outside the United States suggest that CAM is popular throughout the industrialized world (45). The percentage of the population who used CAM therapies during the prior 12 months has been estimated to be 10 percent in Denmark (1987) (46), 33 percent in Finland (1982) (47), and 49 percent in Australia (1993) (48). Public opinion polls and consumers' association surveys suggest high prevalence rates throughout Europe and the United Kingdom (49-52). The percentage of the Canadian population who saw a CAM therapy practitioner during the previous 12 months has been estimated at 15 percent (1995) (53). The wide range of utilization rates can be explained, in part, by the disparity in definitions of CAM therapy and the selection of therapies assessed.

B. Prevalence and Patterns of Use of Herbal Products, Vitamins, and Non-Herbal Dietary Supplements in the United States

A recent *JAMA* publication by Kaufman et al. (54) describes patterns of medication use (for both prescription and non-prescription drugs) by the ambulatory adult population of the United States. Among their findings were the observations that: (1) 40 percent of the population routinely used one or more vitamin or mineral supplements; (2) herbals and supplements were taken by 14 percent of the population over the prior week; (3) among prescription drug users, 16 percent also took an herbal or supplement.

Attitudes Toward Dietary Supplement Regulation

A recent study by Blendon et al. (55), involving Americans' views on regulating dietary supplements, suggests that:

- Forty-four percent of users believe MDs know "little" or "not much at all" about these products.
- Seventy-two percent would continue use even if a government scientific study was negative.
- Eighty-one percent would require evidence of efficacy, safety, and FDA approval *prior* to allowing for the sale of the product.

TABLE 1 Ten Most Commonly Used Vitamins/Minerals and Herbals/Supplements

Ten Most Commonly Used Vitamins/Minerals*		Ten Most Commonly Used Herbals/Supplements*	
Vitamin/Mineral	% Use	Herbal/Supplement	% Use
Multivitamin	26	Ginseng	3.3
Vitamin E	10	Gingko	2.2
Vitamin C	9	Garlic	1.9
Calcium	9	Glucosamine	1.9
Magnesium	3	St. John's Wort	1.3
Zinc	2	Echinacea	1.3
Folic Acid	2	Lecithin	1.1
Vitamin B_{12}	2	Chondroitin	1.0
Vitamin D	2	Creatine	0.9
Vitamin A	2	Saw Palmetto	0.9
Any Vitamin/Mineral	40	Any Use	14

*Kaufman, et al. (54).

In light of these findings, the authors conclude that there is broad public support to increase governmental regulation to ensure that advertising claims about health benefits of dietary supplements are true.

III. EDUCATIONAL PROGRAMS

A survey of courses involving CAM at U.S. medical schools was published in the 1998 *JAMA* theme issue devoted to medical education (56). This article, by M. Wetzel et al., included the following results: 64 percent of the U.S. medical schools reported offering courses on CAM. Of the 123 courses reported, 68 percent were stand-alone electives and 31 percent were part of required courses. Common topics included chiropractic, acupuncture, homeopathy, herbal therapies, and mind-body techniques. The American Association of Medical Colleges has established a Special Inter-

TABLE 2

U.S. Vitamins and Mineral Sales

	$Millions
Multivitamins	839
Calcium	340
Vitamin C	230
Vitamin B-complex	90
Vitamin B	82
Iron	57
Vitamins A & D	34
Zinc	28
Potassium	14

(*Drug Store News*, May 2000)

Top Selling U.S. Herbal Supplements 2001 vs. 2000

	Retail Sales $ Millions	% Change From 2000 to 2001
Gingko	99	–32
Ginseng	63	–25
Garlic	61	–20
Echinacea	58	–20
St. John's Wort	56	–45
Saw Palmetto	44	–2.5
Soy	41	+116
Valerian	17	+71
Kava Kava	15	–16
Milk Thistle	9	+15
Green Tea	3	+39
Yohimbe	2	+13
Total Herbs	591	-15%

(*Herbal Gram; 51*, 2001)

TABLE 3

Non-Herbal Dietary Supplement Sales

	$Millions
Glucosamine / chondroitin	288
CoQ-10	41
Melatonin	31
Amino acids	21
Fish oil / omega fatty acid	14
DHEA	11
Acidophilus	11
Lecithin	10
Gelatin	8
Glucose	7
Shark cartilage	6

(*Drug Store News*, May 2000)

Top Herbs, U.S. vs. Europe

	United States†	Europe‡
1	Gingko Biloba	Gingko Biloba
2	St. John's Wort	St. John's Wort
3	Ginseng	Horse Chestnut
4	Garlic	Yeast
5	Echinacea	Hawthorn
6	Saw Palmetto	Myrtle
7	Kava Kava	Saw Palmetto
8	Soy	Stinging Nettle
9	Valerian	Ivy
10	Evening Primrose	Mistletoe

† *Drug Store News*, May 2000
‡ *German Commission E*, 1998

est Group devoted to CAM, and this topic continues to be discussed at the AAMC's annual meetings and by the AAMC Council of Deans.

An article by Caspi et al. questions "whether a true integration of conventional and unconventional therapies is even possible" and addresses educational options in this regard (57).

In recent years, the NIH NCCAM has awarded multiple educational training grants to a growing number of medical schools, universities, and CAM educational institutions. These grants include the following: Fellowship Training Program Grants; Faculty Development Awards; Curriculum Development Grants; and support for CAM-related educational conferences and meetings. Ten medical schools have received curriculum development grants (R-25) and will be meeting to discuss reproducible models of CAM-related curriculum reform. (See NCCAM website: www.nccam.nih.gov for additional information; see also the Macy Foundation proceedings relating to CAM education [58].) Currently, there is no standardized curriculum involving CAM medicine educational objectives at the undergraduate, post-graduate, or continuing medical educational levels.

IV. RESEARCH: BEST EVIDENCE

In 1992, the NIH established the Office of Alternative Medicine. In November of 1998, Congress established the National Center for Complementary and Alternative Medicine (NCCAM). Its mission is: "To prevent and alleviate human suffering through research on the safety and effectiveness of CAM modalities and through research, training, and information dissemination for healthcare providers and consumers." Currently, the NIH supports more than 200 studies involving complementary and alternative medicine therapies. (Additional information on NCCAM can be found at: http://www.nccam.nih.gov)

The NIH has also established the Office of Dietary Supplements (ODS). The scientific goals of the ODS include:

Goal 1: Evaluate the role of dietary supplements in the prevention of disease and reduction of risk factors associated with disease.

Goal 2: Evaluate the role of dietary supplements in physical and mental health and in performance.

Goal 3: Explore the biochemical and cellular effects of dietary supplements on biological systems and their physiological impact across the life cycle.

Goal 4: Improve scientific methodology as related to the study of dietary supplements.

Goal 5: Inform and educate scientists, healthcare providers, and the public about the benefits and risks of dietary supplements.

(Additional information on the ODS can be found at http://odp.od.nih.gov/ods/about/about.html)

Prior to 1990, relatively little was known about the relative safety, efficacy, cost-effectiveness, and mechanism of action of individual CAM therapies. Increasingly, however, the peer-reviewed medical literature has included consensus conferences, randomized controlled trials, systematic reviews, and meta-analyses involving CAM therapies. Noteworthy examples of recently published original trials and reviews include:

Selected Consensus Reports, Clinical Trials, and Reviews Suggesting That CAM Therapies May Be Effective and/or Warrant Further Clinical Investigation

1) *Chiropractic for Acute Low Back Pain (59;60)*
2) *Mind/Body Techniques for Pain, Insomnia (61)*
3) *Lifestyle Changes for Coronary Heat Disease (62;63)*
4) *Acupuncture for Nausea and Dental Pain (64)*
5) *Psychosocial Support Groups for Cancer (65)*
6) *Homeopathy as Distinct from Placebo (66)*
7) *St. John's Wort for the Treatment of Depression (67)*
8) *St. John's Wort vs. Imipramine vs. Placebo (68)*
9) *Gingko for the Treatment of Alzheimer's Type Dementia (69;70)*
10) *Chinese Herbs for the Treatment of Irritable Bowel Syndrome (71)*
11) *Saw Palmetto for the Treatment of Benign Prostatic Hyperplasia (72)*
12) *Garlic for Hypercholesterolemia (73-75)*
13) *Glucosamine and Chondroitin for Osteoarthritis (76;77)*
14) *Kava Kava for Anxiety (78)*
15) *Homeopathy for Vertigo (79)*
16) *Homeopathy for Allergic Rhinitis (80)*
17) *Osteopathic Manipulation for Low Back Pain (81)*
18) *Moxibustion for Breech Presentation (82)*
19) *Acupuncture for Recurrent Headaches (83)*
20) *Acupuncture for Post-operative Nausea (84)*
21) *Acupuncture for Fibromyalgia (85)*
22) *Distant Healing (86)*
23) *Intercessory Prayer (87)*
24) *Massage for Low-Back Pain (88)*
25) *Agnus Castus Extract for Premenstrual Syndrome (89)*

26) Tai Chi for Balance Disorders (90)

27) Selected Herbal Therapies (e.g., Gingko, St. John's Wort and Saw Palmetto) (91)

28) Adjunctive Non-pharmacological Analgesia for Invasive Medical Procedures (92)

Selected Clinical Trials Suggesting That CAM Therapies May Lack Efficacy

1) Acupuncture for Peripheral Neuropathy (93)
2) Hydroxycitric Acid for Obesity (94)
3) Chiropractic vs. Physical Therapy vs. Education for Low Back Pain (95)
4) Acupuncture for Tinnitus (96)
5) St. John's Wort for Major Depression (97)
6) Homeopathy for Warts on the Hands (98)
7) Homeopathy for Muscle Soreness (99)
8) Herbal Remedies for Asthma (100)
9) Hair Analysis of Trace Minerals (101)
10) Chiropractic for Infantile Colic (102)
11) Group Psychosocial Support for Metastatic Breast Cancer (103;104)

Selected Articles Describing Significant Drug-Herb Interactions and/or Toxicity

Over the past two years, the medical literature has included several reports of clinically significant adverse events caused by the direct or indirect toxicity of herbal products. Notable examples include:

1) Case Studies Involving the Most Commonly Used Medicinal Plants (105);

2) Adverse Reactions Between St. John's Wort and Prescription Drugs (106);

3) Open-label Study Showing St. John's Wort Decreases Indinavir Concentrations (107);

4) Association of a Chinese Herb (Aristolochia fangchi) with Renal Failure and Urothelial Carcinoma (108);

5) Letter to Lancet Editor regarding St. John's Wort Induced Heart Transplant Rejections (109); and

6) Summary of Ephedra's Toxicity (110).

Selected Articles Relating to the Mechanisms of CAM Interventions and Placebo-Related Phenomena

Investigating the mechanisms of actions of CAM therapies is now a high priority for the NIH and NCCAM. Notable examples of recent publications in this area include:

1) Expectation and Dopamine Release: Mechanism of the Placebo Effect in Parkinson's Disease (111);

2) Changes in Brain Function of Depressed Subjects During Treatment with Placebo (112);

3) Functional MRI Studies of Acupuncture in Normal Subjects—Localization of Processing (113);

4) Functional MRI Studies of Acupuncture in Normal Subjects (114);

5) Is the Placebo Powerless? (115);

6) Response Expectancies in Placebo Analgesia and Their Clinical Relevance (116); and

7) MRI Imaging of Placebo (117).

V. HOW CAM/INTEGRATIVE MEDICINE RESEARCH HAS FOLLOWED AN UNUSUAL TRAJECTORY

Conventional biomedical research typically follows a trajectory that begins with basic science and animal research, followed by Phase I, II, and III clinical (human) trials. If effective, new therapies are then evaluated for their cost-effectiveness and appropriate health care policy is ultimately developed.

This has not been the case, however, for much of complementary and integrative medicine therapies, the majority of which have not yet been formally evaluated in terms of their mechanism of action (i.e., basic science research) and clinical or cost-effectiveness (health services research). Ernst has documented the relative absence of cost-effectiveness research involving CAM Integrative Medicine interventions (118). Both basic science and health services research are emerging as high priorities for both governmental (e.g., NIH) and private sector sponsored research in this area (e.g., research sponsored by pharmaceutical companies, insurance carriers, Fortune 500 corporations).

In a recent article, Vandenbroucke and de Craen argue that CAM research provides a "mirror image" for scientific reasoning in conventional medicine. More specifically, they provide several examples in which physicians discard a theory because of new facts, or, alternatively, cling to a theory despite the facts (119).

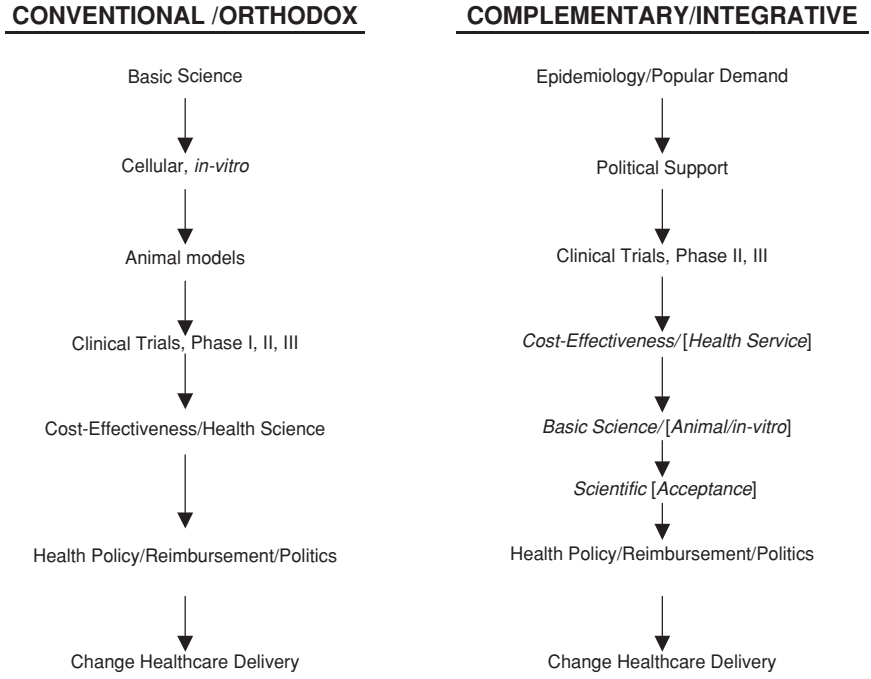

FIGURE 1

VI. CREDENTIALING AND MALPRACTICE LIABILITY CONCERNS

The oversight of educational requirements, credentialing, malpractice insurance, and scope of practice vary from state to state (120;121) (122). A tabular summary of state licensing patterns for chiropractic, acupuncture, massage therapy, homeopathy, and naturopathy is available elsewhere (120;121).

David Studdert, J.D., Ph.D., et al. examined malpractice insurance claims data from both the conventional (MD) and CAM (i.e., chiropractic, acupuncture, massage) communities (123). Their findings, published in *JAMA* included the observation that claims against licensed CAM practitioners occurred less frequently and typically involved injury that was less severe than claims against physicians during the same period. This article also described specific situations in which referral by a medical doctor to a licensed CAM practitioner will or will not likely be construed as negligent. The texts by Michael Cohen (124;125) also highlight many

CAM related legal concerns. An article by Cohen and Ernst addresses issues of informed consent involving CAM (126). *The Annals of Internal Medicine* special series on CAM has scheduled the publication of individual papers on CAM-related malpractice, credentialing and ethics in the spring of 2002. In addition, the Federation of State Medical Boards is scheduled to vote on model guidelines for the use of CAM therapies in medical practice later this year (2002).

VII. EMERGING MODELS FOR THE CLINICAL DELIVERY OF COMPLEMENTARY AND INTEGRATIVE MEDICAL THERAPIES

Increasingly, hospitals, managed care organizations, health insurers and large, self-insured corporations are developing models whereby CAM/integrative therapies are made available to members, subscribers, and employees. The spectrum of existing models, all relatively new, is broad and includes:

- The establishment of networks of "credentialed" complementary and alternative therapy practitioners.
- Reduced "fee-for-service" models whereby members/subscribers/employees receive a discount on routine CAM services provided by "credentialed" networks of identified practitioners in a given geographic area. (Note: This model does not typically include reimbursement for or liability assurance regarding the delivery of CAM services.)
- Covered benefits, which include a predetermined maximum of complementary and alternative therapy services for selected medical conditions (usually with a required referral from an MD).
- Covered CAM benefits without a required referral from an MD.
- "Integrated" medical services which typically include both conventional and complementary/alternative services, usually in an outpatient (ambulatory) setting. Reimbursement options vary as do referral requirements.
- "Integrated" consultation services, i.e., the provision of complementary and alternative therapies for inpatients in hospitals.
- The incorporation of complementary and alternative (a.k.a. "integrative") services as part of an individual medical practice, a group medical practice, a managed care organization, a PPO, an insurance product, a community hospital, or university-affiliated teaching hospital.
- Specialized integrative care teams consisting of conventional and complementary care providers working within a medical institution or group practice. Notable examples include integrative care teams at Beth Israel Hospital (NY), University of Maryland, Stanford University, Cedars-Sinai, and Memorial Sloan Kettering hospitals.

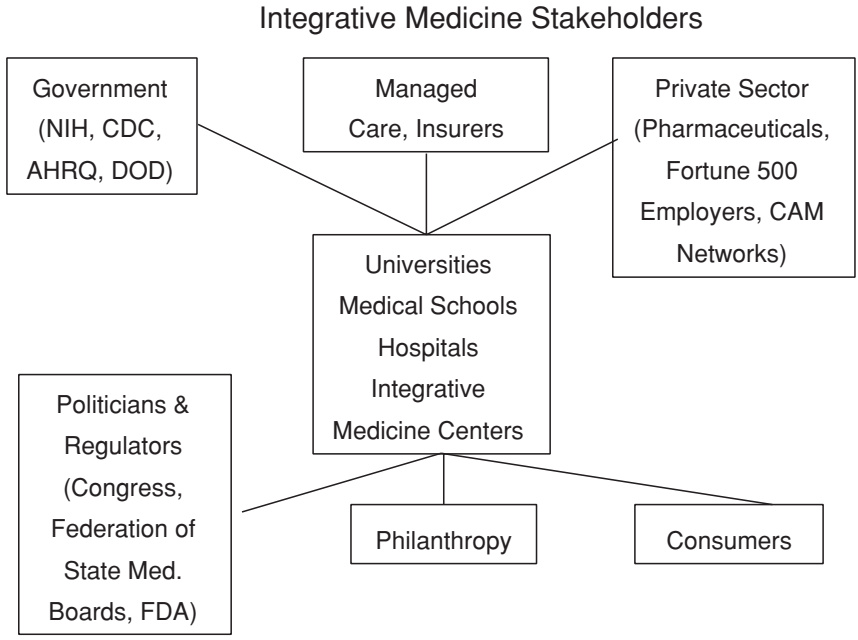

FIGURE 2

Unlike hospitalizations and physician services, complementary and alternative therapies are only infrequently included in insurance benefits. With the exception of chiropractic, CAM therapies are typically not covered by third-party reimbursement. The percentage of CAM users who paid entirely out-of-pocket for these services did not change significantly between 1990 (64 percent) and 1997 (58.3 percent) (19). Even when alternative therapies are covered, they tend to have high deductibles and copayments and tend to be subject to stringent limits on the number of visits or total dollar coverage. Because the demand for health care (and presumably alternative therapies) is sensitive to how much patients must pay out-of-pocket, current use is likely to under represent utilization patterns if (and when) insurance coverage for alternative therapies increases in the future (19). Trends involving insurance coverage for CAM therapies have recently been reviewed by Pelletier et al. (127;128). A survey by John Weeks of 27 hospital-sponsored integrative medicine clinics provides descriptive information on services, practitioners, provider mixes, and profitability issues (129).

While models of "integrative care" have recently begun to develop

nationwide, a variety of barriers to their success have become apparent. Many of these barriers were highlighted in a recent NIH request for proposals and include: 1) the need for more research; 2) the ability to translate research findings into clinical practice; 3) fiscal constraints and the absence of a financially sustainable model; 4) ignorance about CAM therapies on the part of referring physicians; 5) provider competition; 6) liability issues; 7) cultural bias and prejudice; and 8) the lack of standards pertaining to credentialing, patient triage, and third-party reimbursement. In October 2001, the NIH NCCAM issued eight awards (four RO1s and four R21s) to a spectrum of institutions and investigators to develop innovative models of integrative care.

VIII. CHALLENGES AND OPPORTUNITIES FOR STAKEHOLDERS

Further development of CAM/Integrative Medicine research will require:

- Additional resources and an expanded commitment from both the public and private sectors to promote additional:

  — Clinical research;
  — Health services research; and
  — Basic science research.

It should be emphasized that all three are essential; moreover, basic science and health services research need to be prioritized at this time.

- Recruitment of additional research leadership across disciplines and constituencies (e.g., more basic scientists, clinical investigators, economists, toxicologists, etc.).
- Improved quality assurance of dietary supplements. Can botanicals be standardized for research purposes? Can the FDA, NIH, and Congress revisit current regulatory statutes in order to promote reproducible scientific inquiry as well as consumer safety?
- A critical mass of university-affiliated CAM/Integrative Medicine programs with sufficient resources to pursue:

  — Research (clinical, basic, health services)
  — Educational reform and training
  — Clinical delivery of CAM/Integrative Medical services at university-affiliated hospitals

Note: The Consortium of Academic Health Centers for Integrative Medicine is currently being developed. This consortium currently includes medical school faculty from the Universities of Maryland, Arizona, Michigan, Minnesota, Massachusetts, Duke, Columbia, Albert Einstein, Thomas Jefferson, Georgetown, UCSF, and Harvard. The consortium is developing an agenda which relates to CAM/Integrative Medicine education, research, and clinical care.

- A commitment to primarily pursue inter-disciplinary, inter-institutional, and, where appropriate, international collaboration wherever possible.

Note: Harvard Medical School and the UCSF School of Medicine have jointly developed an Annual International Scientific Conference on CAM/Integrative Medicine Research. This meeting is sponsored, in part, by a grant from the NIH NCCAM. (The next research conference is scheduled for April 12-14, 2002 in Boston. For information, contact 781-245-3010.)

The successful delivery of CAM/Integrative Medical services will require:

- More consistent standards for credentialing of CAM providers.
- More consistent tracking of clinical and financial outcomes.
- The establishment of appropriate guidelines regarding the use (or avoidance) of herbs, vitamins, and supplements for outpatients and inpatients.
- Demonstration projects that provide evidence of financial and clinical offsets.
- Demonstration projects that provide evidence of financial sustainability.
- Demonstration projects with revenue streams that include self-pay, third-party reimbursement, philanthropy, and income from sponsored research.
- Demonstration projects that are functionally integrated into existing medical delivery models (e.g., hospitals, clinics, group practices, MCOs, etc.).
- Models that include access for CAM services for those with less expendable income and/or lack of medical insurance.
- Medical-legal guidelines for conventional and CAM practitioners, institutions and third party payers so as to minimize liability exposure.
- Partnerships and incentives involving government, the academic community, and the private sector.

Paradoxes and Policy Decisions Involving CAM and Integrative Medical Therapies

1. Is third party reimbursement for CAM/Integrative services a beneficial objective? What is the "dark side" of third party reimbursement for the CAM professions?
2. Is CAM/Integrative Medicine:
   a. a valuable refinement of mainstream, conventional medical care?;
   b. a "disruptive technology"?;
   c. a (potentially) disruptive reconfiguration of health care delivery models?; or
   d. none of the above?
3. Should academic medical centers launch model integrative care centers in the absence of scientific consensus on the efficacy, safety, and mechanism of action of each modality used? Conversely, are these model integrative care centers necessary engines of research to discern CAM efficacy and safety?
4. Can/should/will increased governmental regulation (and/or legal incentives for pharmaceutical companies) be required to address quality assurance issues regarding dietary supplements? How can the issue of intellectual property (i.e., patents) be addressed in light of existing DSHEA legislation? Should DSHEA be revisited? Amended? What would prompt Congress to do so?
5. Can reproducible models of credentialing, billing, and data tracking be devised and can existing electronic medical records systems be refined to build a national data warehouse/registry of integrative care outcomes?
6. How best to distinguish quackery/fraud/deception

   from

   Responsible delivery of CAM (by an individual or institution)

   from

   The responsible co-management of patients with a (licensed) CAM provider?

   Each creates unique liability exposure and relates to specific professional sanctions.
7. How best to incorporate relevant information regarding CAM into required core curricula and training of MDs/RNs/PharmDs/dieticians, and other allied health professional at the undergraduate and postgraduate levels? Can appropriate, web-based, interactive CME programs be jointly developed across professional disciplines? Isn't the same "core" information needed by each medical discipline?

8. How to incorporate clinically relevant CAM/Integrative Medicine examination questions into the board examinations of physicians, nurses, pharmacists, dieticians, and other health professionals, including licensed CAM providers?

9. How best to improve the quality of relevant CAM information on the Internet? For clinicians, for researchers, for patients?

10. How to pursue "integration" in the absence of co-optation of one professional discipline by another? Are there successful models of integration across (medical) disciplines? What can be learned from these?

Postscript

"Doing everything for everyone," wrote David Grimes, "is neither tenable nor desirable. What is done should be inspired by compassion and guided by science and not merely reflect what the market will bear." (130).

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The Extraordinary Case of Dietary Supplements

Catherine Woteki

I have been asked this evening to talk about one particular case of complementary and alternative medicine, dietary supplements. Dietary supplements are an extraordinary case because of the amount of attention Congress has given to them and because of the regulatory framework that has been established.

The legal definition of a dietary supplement is: a product that is intended to supplement the diet; that contains a vitamin, a mineral, an amino acid, an herb; or a dietary substance for use to supplement the diet, by increasing the total dietary intake (that last phrase is generally taken to mean substances like enzymes, glandular extracts, or other types of substances that might be present in foods, but are not a nutrient or herb); of a concentrate, metabolite, constituent, extract or combination of any ingredient above; and are intended for ingestion as a capsule, powder, soft gel or gel cap; and not a conventional food or sole item of the meal or the diet (Table 1).

When people talk about dietary supplements these days, they are talking about an incredibly wide range of different substances that can be assigned to two large categories. The first category is those substances for which there are demonstrated health benefits. Clearly, the vitamins and minerals, and some of the herbal products, to which Dr. Eisenberg referred, do fit into that category. The second category is everything else, for which a thorough understanding of the health benefits and risks associated with ingesting them does not exist.

We do know that the dietary supplement market has become a very, very substantial business. A recent *Nutrition Business Journal* article de-

TABLE 1 Defining Dietary Suppements

- Products intended to supplement the diet that contain a vitamin, mineral, amino acide, herb OR;
- Dietary substances for use to supplement the diet by increasing the total dietary intake OR;
- Concentrate, metabolite, constituent, extract, or combination of any ingredient above; AND
- Intended for ingestion as a capsule, powder, softgel, or gelcap, and not a conventional food or sole item of a meal or the diet.

scribes the current state of the supplements industry (Table 2). It shows that there are, first of all, many different products marketed as dietary supplements. They include vitamins, the herbals and botanicals, sports nutrition products, meal supplements as well as minerals. Together, in 1996, those five classes of products had annual sales of $10 billion that had grown in the year 2000 to be $15 billion.

The traditional vitamin supplements and multivitamin supplements comprise about half of the market. Closely behind, are the herbals and botanicals, constituting about a third of the sales.

Who is taking these supplements? In a review of the many different surveys conducted over the last 10 to 15 years, Janet Gregor summarized the results of several population surveys. Contrary to popular opinion, the typical dietary supplement taker is a woman. She tends to be of college or higher-level education, higher income, white, and older.

Other characteristics of individuals taking dietary supplements are those that tend to believe in health promotion practices and incorporate them, or at least report that they incorporate them, into their daily activities. They tend to be non-smokers; if they drink alcoholic beverages, they

TABLE 2 Dietary Supplement Sales and Market Share, 1996

Product	Sales ($m)	% of market
Vitamins	4,900	48
Herbals & botanicals	3,000	28
Sports nutrition products	927	9
Meal supplements	618	6
Minerals	309	3
Total	10,372	100

do so moderately, but there are also a very high proportion of abstainers. Supplement users report that they do regular cancer screening tests and they tend to be healthier.

Another group frequently thought of as supplement-takers are athletes and exercisers. Indeed, Gregor's review of recent surveys does bear that finding. Seventy-five percent of marathoners, for instance, take two or more dietary supplements.

Lastly, there is a persistent impression that people who are in poor health are more likely to take dietary supplements than people who are in good health. A review of these surveys shows inconsistent information. Some studies report that people who have one or more health problems are more likely to take dietary supplements; others show that people with diagnosed hypertension, cancer, and cardiovascular disease do not take more dietary supplements than those who are not diagnosed. The question is still open as to whether people who are in ill health are more likely to take dietary supplements than those who are not.

Who makes these supplements? There are about 1,000 different companies listed by the *Nutrition Business Journal* as makers of supplements (Table 3). The vast majority are small to mid-sized companies that assemble ingredients purchased from raw material suppliers, of which there are approximately 40 in this country. Of the 40 suppliers, eight are large pharmaceutical companies that supply over 75 percent of the vitamins that are incorporated into formulations made by the smaller companies. There are about 150 suppliers of herbal and botanical raw materials.

How are the supplements marketed? The major outlets include the natural and health food chain stores, accounting for about 35 percent of the market share. They are followed by the mass merchandisers, grocery stores, and drug stores. Increasingly, grocery stores have major sections devoted to dietary supplements. The next group of vendors are multilevel marketing firms. These are direct sales companies, marketing through home parties or in door-to-door sales. Direct mail order only accounts for about six percent of the market. Surprisingly, health care

TABLE 3 Producer and Sales Numbers of Dietary Supplements

	No. of companies	Revenue ($b)
Supplement manufacturers	1,050	6.05
Vitamin raw mineral suppliers	40	0.93
Herb and botanical raw material suppliers	150	0.489

TABLE 4 Sales and Market Shares of Dietary Supplements

Outlet	Sales ($b)	% Market Share
Natural & health food chain stores	4.5	35
Mass merchandisers	3.8	30
Multilevel marketing firms	2.9	23
Mail order	0.8	6
Health care practitioners	0.7	6
Total	12.7	100

practitioners are also a small source, about six percent, of dietary supplement sales (Table 4).

As I think about alternative medicine and dietary supplements, I am reminded of Ruth Eng's description of the "clean living movement" that has been going on in the United States since the early 1970s. Antagonism to modern agricultural practices, concern about food safety, advocacy for organic food and for vegetarianism, and strident calls for dietary change to prevent disease characterize the movement.

This, though, is also part of a historical pattern. There were two early waves of clean living movements, one occurring from 1830 to approximately 1860. Some of the leading proponents of that earlier movement were William Alcott and Sylvester Graham. We remember Alcott more for being Louisa May Alcott's father than as the Christian physiologist on which his reputation was forged. He and Sylvester Graham advocated a vegetarian diet, cold water baths, and rigorous exercise as a means for maintaining good health. We remember Graham because he advocated eating whole grain crackers, and the graham crackers on grocery shelves today were his invention.

Some of the leaders in the clean living movement from 1880 to 1920 identified by Ruth Eng were John Harvey Kellogg, Horace Fletcher, and Harvey Wiley.

We remember Kellogg because of the spa and sanitarium he established in Michigan, as well as for the corn flakes he served to people who participated in his programs at the sanitarium. They liked these corn flakes so much that he sent participants home with the cereal, and he started a mail order business, sending breakfast cereal. The breakfast cereals we eat today are decendents of this earlier movement.

Fletcher, however, is largely forgotten. He advocated that everybody

chew their food until it was absolutely liquid before swallowing, though there are not many proponents of that approach.

Harvey Wiley is remembered for studying toxins in foods, particularly substances added to foods as preservatives and colors, as well as other purposes, and also for his advocacy for the Pure Food and Drug Act passed in 1906. The Pure Food and Drug Act established the regulatory framework under which dietary supplements were regulated up until 1994.

Supplements then and now were regulated as food. Thus, the only criterion on which FDA can regulate is on the basis of safety.

In 1994, Congress passed a new law, the Dietary Supplements Health and Education Act, which carved out a special niche for dietary supplements within the regulatory purview of the FDA for foods. Safety determination for dietary supplements rests with the manufacturer, and the substantiation of label claims also rests with the manufacturer. The law provides FDA no authority for premarket approval for dietary supplements with one single exception: new dietary ingredients. Lastly, there is no requirement for any manufacturer of dietary supplements to register with FDA. Thus, there is no list of companies manufacturing these particular products.

The responsibility for safety of dietary supplements rests with the manufacturer, and FDA has no authority to review for safety or for effectiveness prior to marketing. In fact, effectiveness of products does not enter into FDA's regulatory decision at all.

Once a supplement is on the market, FDA must show that the supplement is unsafe before it can take any regulatory action. Unlike drugs, manufacturers of dietary supplements are not required to record, investigate, or forward to FDA reports of any injuries or illnesses that are associated with dietary supplements.

There are some general concerns associated with the safety of dietary supplements. One is the toxicity of the products or ingredients within those products. A second is the potential for nutrient/nutrient interactions; this is the case where a large level of intake of one nutrient interferes with the absorption and/or metabolism of another nutrient. For example, high levels of zinc intake interfere with iron metabolism and with copper metabolism. A third category of problems is drug/nutrient interactions, to which Dr. Eisenberg referred, that I will mention again shortly.

Last, is the problem of contamination with pathogens or toxins, particularly in herbal products and other animal products, such as glandular products.

There is a growing history of illnesses and injuries associated with dietary supplements (Table 5). Three of the herbal products currently of

TABLE 5 Supplements Associated with Illnesses and Injuries

- Herbal and Botanicals
  —Chaparaal – liver disease
  —Comfrey – obstruction of blood flow to liver
  —Ephedra (Ma huang) – elevatned blood pressure, irregular heartbeat, nerve damage
- Vitamins, minerals, and amino acids
  —Vitamins A, Niacin, Selenium
  —L-tryptophan –eosinophilia myalgia syndrome

concern to the Food and Drug Administrations are Chaparral, which has been associated with liver disease; Comfrey, with obstruction of blood flow to the liver; and Ma Huang, associated with elevated blood pressure, irregular heartbeat, and nerve damage.

Vitamins, minerals, and amino acids can also cause adverse health outcomes if taken in inappropriate amounts (Table 6). For example, vitamin A can cause birth defects, as well as acute and chronic toxicity. Niacin causes flushing of the face and heart-related symptoms. High selenium intakes are associated with toxicity and with cancer. Well over 10 years ago, there was a very large outbreak of eosinophilia myalgia syndrome linked to an amino acid supplement, tryptophan. It was marketed as being a sleep inducer, and something "natural" that one should take at bedtime to induce sleep.

Under current law, the only recourse that FDA has to detect health effects from dietary supplements is adverse events reports. There is no responsibility on the part of the manufacturer to report adverse events to the Food and Drug Administration.

TABLE 6 Adverse Event Reports

	Dietary Supplement	Foods
Types	Many	Limited
Etiologies	Multiple	Pathogens Sensitivities
Duration	Acute Chronic	Acute
Information source	Health care providers	Consumer
Evaluation	Extensive followup	Limited

The types of adverse events reported for dietary supplements are many and varied, compared to the types of adverse events that are related to foods. The etiologies, with respect to dietary supplements, are multiple. With respect to foods, they tend to cluster in food-borne illnesses, pathogen-related problems, as well as sensitivities and allergies. The duration of effects associated with dietary supplements can be either acute or chronic. With respect to food products, they tend to be very acute, again, because of the relationship of pathogens and adverse effects. The information source of the adverse event reports for dietary supplements are predominantly healthcare providers; whereas, for foods, they tend to be consumers. The nature of the adverse events are so severe that people go to their healthcare providers who, in turn, report to FDA. Lastly, FDA is finding that follow-up on dietary supplements is very expensive and requires far more resources than the usual follow-up on food reports, which tend to be much more limited and much easier for them to do.

We are faced with a public health dilemma. Dietary supplements are now very widely used. There is a lack of industry safety and effectiveness research, largely because there is no incentive to conduct research. Under the law, as it now exists, if a substance was present in a traditional product prior to the year 1994, it is not a new ingredient. Therefore, there is no incentive for supplement manufacturers to do any research as to the safety or the effectiveness of the dietary supplement. The medical community and FDA lack knowledge about the safety of these products, their efficacy, and the substantiation for label claims. Lastly, FDA is confined to reliance on post-market surveillance and its own resource-constrained ability to investigate adverse events, which further complicates the medical community's ability to assemble a substantial database on the safety and efficacy of these products.

When a good base of science helps to inform legislation in areas of public health, we have a good public health policy. In the case of dietary supplements, excluding vitamin and mineral supplements, we do not have a sufficient base of knowledge about their safety or efficacy to inform our current policies. In fact, we have a situation where legislation has created a very perverse incentive against industry investment into the types of research that would lead to wise public policy on dietary supplements.

Discussion

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DR. SHINE: I have separate questions for David and Cathie. David, you have talked about randomized controlled trials. You have also emphasized that, in a number of the kinds of therapies we are discussing, the role of the provider is extremely important. A randomized control trial implies the notion that you are objectively evaluating an intervention and that whomever applied that intervention could show it would work. In this situation, it is the intervention and the provider together, with a particular belief, enthusiasm, or whatever is appropriate in terms of the effectiveness of what you are doing. Do you end up comparing an enthusiastic provider against a non-enthusiastic provider, or a set of enthusiastic providers doing the therapy in different ways?

I understand how one performs an herbal trial, for example, but I am puzzled as to how, in a number of these therapies, you conduct a randomized control trial when you are looking at the effect of both the intervention and the enthusiasm of the provider.

For Cathie, I am curious: has the recent emergence of a number of these toxicities and so forth had any kind of effect suggesting that Congress will revisit regulatory issues? Do you see this as not simply being on the horizon?

DR. WOTEKI: My answer is going to be quick. I don't see anything on the horizon with respect to major review or revision of the existing legislation. The single exception to that would be if there is a very large outbreak of disease associated with one of these supplements that might lead the political will to revisit it, but it doesn't seem to be there.

DR. EISENBERG: Ken, your point is well taken, and I think you point out how complex it is to design studies that provide an answer with which one can be satisfied.

Certainly, things taken orally that we can control with a credible sham placebo pill are the easiest. I think once you get into provider–dependent interventions, again, the methodologists have been very creative.

In the area where we think modality is the key to the efficacy, we try to standardize the intervention as best as possible. Even there, just to stick with it for a moment, you get into a conundrum. Do you use the same point for nausea in all patients, or do you let 10 qualified acupuncturists from five different Asian traditions pick their own, hoping there will be some overlap?

The NIH has, in a rather remarkable way, opted to fund projects to follow each of those trajectories. Some studies will standardize the acupuncture points or the massage points or the chiropractic approaches, where herbs for irritable bowel will leave it up to the practitioner to diagnose and treat, as is their normal practice.

We end up with three arm studies. The study for irritable bowel in *JAMA* was one of these studies that used that paradigm.

There is also tremendous creativity in how to appropriately blind and create controls that are credible for some of these techniques.

There are actually, I think, fairly good examples of sham placebo devices that can be used in patients who are naive to acupuncture, which are spring loaded and go through a tube.

The person who is naive to real acupuncture, when punctured by this sham acupuncture needle, which is on a spring, feels the needle touching the skin but it never touches the skin; that is one level of control. Whether that is satisfactory for all questions about acupuncture is another question.

I guess what I am trying to say, without appearing or being overly defensive, is that each study has its own limited number of questions it can ask and answer authoritatively.

That is precisely why this field needs people who are trained in clinical epidemiology, who understand the modalities as they are used—not just the rules of evidence, and why we need universities that are willing to bring in clinicians from the different professions to ask how this is actually practiced, before devising a randomized trial that meets reductionistic requirements, which has little or no bearing to the way you and your colleagues actually practice it.

This is not easy. It is very messy science. If you extend that to herbs, they are the messiest of all. Even if you can give a credible sham foul-tasting elixir that tastes like the foul-tasting elixir of herbs, the consistency

of the herbal products being used and the ability to acquire an IND for them, and then to contemplate an interaction to them, is a great challenge.

So, it is hard work, but again, I think the right people now are invested. The open-minded skeptics are asking, "what have we got here in each of these studies?"

My hope is that my colleagues will assure that the science is done well, so we don't assume prematurely that we have the answers before we actually have them.

PARTICIPANT: I was wondering, David, if you would comment on some policy that we have evolved at the Center for Substance Abuse Treatment, of the Substance Abuse and Mental Health Services Administration, that suggests the notion for the need for randomized clinical trial results, and may actually shed some light on your question of which should come first.

That is, starting in about 1994 and 1995 with a program called the Rural, Remote, and Culturally Distinct Populations Program, populations were funded for comprehensive culturally appropriate substance abuse treatments.

Community interventions were implemented, such as a program in Hawaii funded to include traditional Hawaiian healing practices, and several programs serving Native American communities were funded to include sweat lodges. There were also programs funded to include acupuncture.

What they had in common was that they were high demand, low cost, safe, but non-evidence-based treatments that were allowed to be included in a comprehensive treatment setting.

That program has become more operationalized. What we are working on at the Center for Substance Abuse Treatment is developing guidelines on acupuncture incorporation into addiction treatment programs, and we are doing a treatment improvement protocol on that.

Admittedly, the evidence for acupuncture being efficacious in addiction treatment is somewhat lacking. I find it promising but not conclusive.

At the same time, this is used by several hundred different programs. In substance abuse treatment programs in particular, we noticed that time and treatment of almost any sort has a significant improvement on the long-term outcome.

If we have a treatment, such as acupuncture or a sweat lodge, that brings people into the treatment setting, as long as it is comprehensive, then that may improve outcome, if not through efficacy, perhaps through increased utilization or compliance with treatment.

It would be hard to subject a sweat lodge to a randomized control trial. We still like to think of it as having a role, at least, in comprehensive, culturally-competent drug abuse treatment that is community oriented.

DR. EISENBERG: I don't know how to respond other than to say this is another example where the research is often complicated by the fact that we are trying to help patients in the absence of a reductionistic trial.

Sometimes these things don't lend themselves to randomized trials and credible controls as we know them or would like them.

You are talking about whole, culturally sensitive approaches to individuals who have substance abuse, and whether it is the intervention—culturally acceptable as it is—the practitioners who are providing it, the ambience, et cetera, or the ambience itself.

Again, it is nice when those kinds of things lend themselves to a randomized trial. I would say, respectfully, that acupuncture could lend itself to more randomized trials for substance abuse than it has. Historically, as you know, the data have been wanting there.

I agree with you. I don't think that all these things lend themselves to a definitive trial. Yet, if you take a step back and you say, let's look at it from a health service perspective: are we doing more good than harm if we allow access to a given population at very high risk and/or high morbidity and mortality to have access to these therapies? What does it do to their clinical outcomes and costs?—that is a different question.

I think from a public health standpoint, you get an answer to your public health question. From an NIH scientific standpoint, you don't know what the actual cause and effect relationship of the individual components is.

Alan Trachtenberg, who is the acting director of the Office of Alternative Medicine, and I have debated these and other questions for some time. I don't think there is a clear solution. I think this is one of the messy parts of the equation.

PARTICIPANT: One aspect, I think, of the solution might be trials that look at—as the unit of analysis, rather than the individual patient or subject—the treatment program.

DR. EISENBERG: Right, and at the population it serves, I agree. Unfortunately, the NIH doesn't usually fund those kinds of projects. In spite of the $200 million of resources, we don't have $200 million to look at these things from a population based or a public health vantage point, and I know that is the song you sing.

PARTICIPANT: Unfortunately, many of the other agencies don't receive that level of funding to pursue those agendas.

DR. YATES: I am Allison Yates, the director of the Food and Nutrition Board at IOM. It is interesting to see the diet supplements and then look at integrative and complementary medicine.

One aspect Dr. Woteki brought out was the specifics of the law in 1994 of the Dietary Supplement Health and Education Act, which essentially said dietary supplements are foods.

One component that might be useful to discuss is the other aspect of that enactment, which limited dietary supplements to only being discussed in terms of structure and function.

Perhaps Cathie and Dr. Eisenberg want to talk about their role in treating disease.

DR. WOTEKI: When dealing with an extract or a concentrate, in my mind, that takes it into the realm of drugs and out of the realm of foods.

Secondly, the idea that those marketing these supplements are only marketing them for the effects they will have on structure and function is kind of winking, to put it mildly, at the implicit message surrounding so many of these products that they do have a direct disease prevention or disease treatment intent or purpose.

Both of those things are inherent weaknesses in this regulatory approach, but they are ones that no leading members of Congress want to take on to revise legislation.

The end result is this enormous dilemma of a product that can only be regulated on safety, for which the labeling claims can be made for structure and function effects, but everything surrounding them, with respect to books and articles and advice from sales people, does have a direct medical implication to it.

DR. YATES: I thought Dr. Eisenberg might want to address whether these are medicines? Then, when one uses them to treat Parkinson's?

DR. EISENBERG: There is no clear delineating line between food and medicine as supplement and over the counter substances. Certainly, the line is terribly blurred for somebody who walks into Osco, CVS, or any drug store in the country. Where does the aisle begin and end?

I didn't show two slides of an article published in the *Archives of Internal Medicine* this summer by Robert Blendon on his survey of adults' perceptions on dietary supplements. One of the more remarkable findings really points to a perception disconnect, if you will. When asked whether individuals would want their dietary supplements to be proven safe and

effective before being given permission to be placed on the shelf, I forget the number, but it must be higher than 70 percent.

I think the American public is not aware of the facts that have been presented tonight, of the absence of teeth in the law that demand efficacy or safety prior to putting them on the shelves.

The language is unclear. If you speak to an audience of clinicians, doctors in white coats, and PharmDs and nurse practitioners, they are quite frustrated with the inadequacy of what is available by way of information and labeling.

When a patient says, does saw palmetto help with my benign prostatic hypertrophy? The label says: it improves urinary health. What do we have here?

Speaking only for myself, I think we should, as a nation, rally support from additional congressmen and women to revisit this.

I personally think it is not working in the service of the patient or the healthcare practitioners who are very frustrated. I do not think we have properly incentivized the private sector to make the investment to improve the quality or do the science.

If they could regain some of the investment, they might help us discover what the active ingredient or ingredients are and help promote scientific discovery. That is where I stand on it.

DR. HARAMATI: I'm Adi Haramati from Georgetown University. David, this is for you. You have presented a vision of integrative health care and listed the stakeholders and the progress, and also a series of key issues. I wonder if you could prioritize or give us a sense, in the short term, of what barriers we have to overcome to get there, to try to give us some short-term goals. Perhaps we can eventually focus on the long-term goals, but more importantly, we can leave this room with a sense of the immediate things we need to do in the next year or two.

DR. EISENBERG: I think it depends where you sit. You know, the notion that if you are a hammer, everything looks like a nail? If I were in a board room of Fortune 500 employers and their groups, I would say: you should invest in health service research to figure out which, if any, of these things should be in your benefit package or your cafeteria plan.

If I were with the pharmaceutical companies, I would say what I said five minutes ago. If I were with FDA, we would have a different conversation.

You know, as an academic, and you in particular, in the basic sciences, we both participate in the consortium where we are working with the deans of medical schools and colleagues in the medical community where we can say, this is our problem. We must lead, and we as members

of academic medical centers and universities have to do the hard work of distinguishing useful from useless, pursuing scientific discovery, following all the guidelines we follow for everything else we do when we wear white coats.

I guess I go back to that stakeholders chart and say that we have to methodically, with the help of all the stakeholders, state that each one of those groups needs its own priority list. If you are in the private sector, it may be credentialing or patent protection with input from the government. It depends where you sit.

I wish I could prioritize it. In fact, I am glad I can't. By not prioritizing it, it means that they are all equally important.

I don't think the field will develop in a satisfactory way in the absence of any one of those components. I am sorry to slice up your question.

MS. BEATTY: Hi, my name is Margaret Beatty, and I am actually an acupuncturist practicing here in D.C. I have three questions for Dr. Eisenberg.

First, are you familiar with the Japanese acupuncture tradition of Toyohari?

DR. EISENBERG: Just by its name, but I have not practiced this.

MS. BEATTY: It is a tradition of acupuncture where the acupuncture needles are just placed on the skin or maybe placed above the skin. I just toss that out as another method of acupuncture, which seems to complicate your life a little bit more.

Also, I am intrigued by this whole idea of research, since acupuncture comes from a medical tradition that has a totally different paradigm than allopathic medicine and has a much longer tradition and history. One question is: how do you study something that comes from such a totally different view of the world with something that comes from a competing kind of culture?

DR. EISENBERG: First of all, I very much appreciate the question and let me answer it in two ways. One, I have mentioned already that it makes no sense to design a trial without input from the actual practitioners. So, the practitioners have been helpful in figuring out the different credible shams. That is on one extreme.

On another extreme, the practitioners have been very helpful in the following experiment. It is known in Chinese medicine that 10 people with pneumococcal pneumonia or migraine headache on the western side might have five or 10 different diagnoses.

There are now NIH-funded trials to take a group of people with a homogeneous diagnosis by western terms and stratify them by Chinese or Japanese diagnoses.

So, you can imagine 1,000 people with migraine headaches, only 100 of whom have one particular Japanese or Chinese diagnosis, and randomize those to either real acupuncture, sham acupuncture, or conventional medicine.

My point is, these are all attempts to honor the tradition from which the therapy comes and simultaneously acknowledge that there are rules of evidence that we believe and hold dear, and believe can be beneficial in helping us understand where the most benefit is gained.

This isn't an either/or, but rather a call for collaboration between scholars and practitioners of some of these therapies and our most open-minded skeptical clinical epidemiologists.

I just want to conclude my response by saying I understand it. The 20 clinician researchers with me who do this work understand it. The NIH is increasing understanding of it. It is not an attempt to just put a round plug in a square hole and figure it out: does it work or not?

MS. BEATTY: There are just two other things I am curious about.

DR. EISENBERG: How about you and I talk about your question afterwards, because I think we are over time. Let's have one other question. I am here afterward, and maybe I could answer yours offline.

MS. BEATTY: I am curious about your partnerships with, for instance, acupuncture schools or chiropractor schools. I didn't see them on your list of integrative medicine stakeholders. There seems to be a lot of emphasis on allopathic medical schools and that also brings up the issue of doctors who are able to practice acupuncture by taking a 300-hour acupuncture course, as opposed to acupuncturists who have a much more substantial training. I think that is a concern.

DR. EISENBERG: I think my diagram needs to have another box of important stakeholders, and I thank you for that.

MS. BEATTY: I am just wondering, is anybody looking at a definition of health and looking at how we do work with people from medicine, coming from a definition of health perspective?

DR. BULGER: Could I suggest you pursue that offline? We are going to have some dietary supplements soon, be they either too warm, or too cold, or whatever. The last question.

DR. MARION: My name is Phil Marion. I am a medical director of rehab medicine at The George Washington University, up the street. A question for Dr. Eisenberg and perhaps an observation.

I am one of those allopathic physicians, who is also a medical acupuncturist, and I have noticed that patients, who come in; are not insured; and are going to pay cash, have a different enthusiasm, if you will, toward the treatment of acupuncture than someone who receives it from their managed care companies.

As a matter of fact, patients are a bit suspect if they are going to be covered by their managed care companies, and sometimes that has an effect on the results of their treatment.

The second point I wanted to make was that very often with patients, especially if you look at stakeholders for patients covered by their insurance companies, they try to fit an eastern traditional medicine into western medicine. For example, they will give you four visits and they will say, get them better in three months or they have to get another referral. You then have to fight the battle with the insurance company, if you will.

In many ways, it turns out that having them covered by their insurance company is actually a detriment to their actual treatment. I am using acupuncture as an example, but for others as well, and I wanted your comments and experience on that.

DR. EISENBERG: I think these are excellent points. There is a large literature, much of it out of RAND, looking at how patients perceive and behave in health systems where health care is free, partially covered, or self paid, and I think that translates across the modalities used.

It is clearly a very important aspect of care, as to whether (a) you choose it, (b) you have access to it, and (c) how much you pay for it.

In the same way, trying to do a randomized trial of people who have an injury and are seeking worker's compensation is very different from a population trying to get its life back and is very motivated to participate and pay any amount just to salvage a life.

I think these are factors that can and are being incorporated into some of the health service research. In all the studies I mentioned, these are some of the variables that need to be tested, not just the choice of a therapy, but the co-payment and the percentage of co-payment. I think these are part of the future of health service research in this area and your points are very well taken. Thank you.

DR. BULGER: I want to thank everybody. I will have an interesting e-mail for our members based on what we have learned tonight.

I heard from Cathie Woteki that we all need to explore the financial records of Osama Bin Laden and see whether he is in the herbal supplying

business. Perhaps that would help FDA and the academic centers who formed these 11 centers to somehow get together with the entrepreneurial divisions of the universities and allocate funds to post an authoritative internet site.

I think you have raised a tremendously important set of points. Please join me in thanking them once more.

Biosketches

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Dr. Eisenberg's major research interests include the evaluation of complementary and alternative medical therapies in terms of their prevalence, safety, efficacy, cost-effectiveness, and mechanisms of action.

Dr. Eisenberg is also the Director of two Harvard Medical School courses devoted to complementary and alternative medicine. One course is offered through the Department of Medicine and the other through the Department of Continuing Education.

From 1994-1998 he served as a member of the National Institutes of Health Alternative Medicine Program Advisory Council. He is currently a member of the FDA subcommittee responsible for postmarket surveillance of dietary supplements. He has authored numerous scientific articles involving complementary and alternative medicine practice.

CATHERINE E. O'CONNOR WOTEKI, PH.D., R.D.

Catherine Woteki is Senior Research Scientist with the College of Agriculture and Natural Sciences at the University of Maryland and Professor of Nutrition and Food Safety at the University of Nebraska. She holds appointments in the Department of Nutrition and Food Science and the Joint Institute for Food Safety and Applied Nutrition at the University of Maryland. A nutritional epidemiologist, she served from August 1997 until January 2001 as the first Under Secretary for Food Safety in the U.S. Department of Agriculture. In that capacity she was responsible for development of U.S. food safety policies through the work of the President's Council on Food Safety and the Codex Alimentarius Commission, and for the safety of meat, poultry, and egg products under the regulatory authority of the Food Safety and Inspection Service. Prior to being appointed as Under Secretary, for two years Dr. Woteki was Deputy Under Secretary for Research, Education, and Economics at the USDA where she led strategic planning activities. She also was Deputy Associate Director for Science in the White House's Office of Science and Technology Policy from January 1994 until January 1996.

As Director of the Food and Nutrition Board, Dr. Woteki led one of the Institute of Medicine's most active programs. Under her direction from 1990-1993, the Board published 30 studies of food safety and human nutrition. Dr. Woteki co-authored three of the studies, one of which, *Eat for Life: The Food and Nutrition Board's Guide to Reducing Your Risk of Chronic Disease*, was a Book of the Month selection. Dr. Woteki's research interests include food safety and nutrition policy, chronic disease prevention, and population health surveillance and monitoring. She is the author of over 50 articles and 12 technical reports and books on these topics.

Dr. Woteki received a Bachelor of Science degree in biology and chemistry from Mary Washington College (1969), and Master of Science (1971) and Doctor of Philosophy (1974) degrees in human nutrition from Virginia Polytechnic Institute and State University. She did post-doctoral studies in nutrition and gastroenterology at the University of Texas Health Science Center at San Antonio and in epidemiology at the Johns Hopkins University School of Hygiene. Dr. Woteki is a registered dietitian and a member of the Institute of Medicine.

Moderator:
Roger J. Bulger, M.D.
President
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