WHITE HOUSE COMMISSION ON COMPLEMENTARY AND ALTERNATIVE MEDICINE POLICY

Meeting Site: Academy for Educational Development
1825 Connecticut Avenue, NW, Room 800, Washington, DC

May 14-16, 2001

PRELIMINARY AGENDA*

****Final Agenda will be posted by May 10, 2001***

DAY ONE: Monday, May 14, 2001

7:30 a.m. **Registration Opens**

Meeting Topic I.
Complementary and Alternative Medicine: UNDERSTANDING COVERAGE AND REIMBURSEMENT

8:15 a.m. Opening Remarks and Introductions
- **Stephen C. Groft, PharmD**, Executive Director, White House Commission on Complementary and Alternative Medicine Policy
- **James S. Gordon, MD**, Chair

8:30 a.m. **Panel I: Overview of Health Care Financing in the US**

(1) Michael O'Grady, Project Hope

- *Discussion*

9:25 a.m. **Panel II: Federal Purchasers**

(2) John Whyte, MD, Health Care Financing Administration

(3) Abby Block, US Office of Personnel Management

- *Discussion*

10:45 a.m. – 11: 00 a.m. **BREAK**

11:00 a.m. **Panel III: State and National Perspectives**

(4) Joy S. Wilson Johnson, National Conference of State Legislators

(5) Marilyn Francis, American Association of Health Plans
(6) Alan Korn, MD, Blue Cross Blue Shield Association

- *Discussion*

12:00 p.m. – 1:00 p.m. **LUNCH BREAK**

1: 00 p.m. **Panel IV: Employer Perspectives**

(7) Tom Sawyer, William M. Mercer
(8) Mary Jane England, Washington Business Group on Health
(9) TBA

- *Discussion*

2:10 p.m. **Panel V: Health Plan Perspectives**

(10) Rick Gallion, Blue Cross Blue Shield of South Carolina
(11) John Kelly, MD, Aetna/U.S. Healthcare
(12) John Weeks, *The Integrator*

- *Discussion*

3:10 p.m. – 3:25 p.m. **BREAK**

3:25 p.m. **Panel VI: Special Populations: Minorities, Uninsured, Underinsured**

(13) Nathan Stinson, MD, PhD, Office for Minority Health, DHHS
(14) TBA

- *Discussion*

4:15 p.m. **Breakout Groups: Access and Delivery***
**(review of December 4-5, 2000 meeting discussion)*

5:15 p.m. **Group Reports and Discussion**

6:00 p.m. **Adjourn**

DAY TWO (Topic I Continued): Tuesday, May 15, 2001

7:15 a.m. **Registration Opens**

Meeting Topic I.
CAM: UNDERSTANDING COVERAGE AND REIMBURSEMENT continued

8:00 a.m. **Opening Remarks**

- **Stephen C. Groft, PharmD**, Executive Director
- **James S. Gordon, MD**, Chair

8:05 a.m. **Panel VII: Issues and Ideas**

(15) Melinna Gianninni, Alternative Link, Inc.
(16) Linda Bedell-Logan, Solutions in Integrative Medicine
(17) Wayne Sickles, Massage Therapist

- *Discussion*

(18) Max Heirich, Professor Emeritus, University of Michigan

- *Discussion*

9:25 a.m. **Break/Breakout – Small Group Discussion (CAM Reimbursement)**

10:50 a.m. **Group Reports and Discussion**

11:30 a.m. – 12:30 p.m. **Lunch Break/Adjourn Meeting Topic I.**

DAY TWO: Tuesday, May 15, 2001

Meeting Topic II.
Complementary and Alternative Medicine: RESEARCH CHALLENGES

12:30 p.m. **Opening Remarks**

12:40 p.m. **Panel I: Overview of CAM Research Challenges**

(19) David Eisenberg, MD, Harvard University

- *Discussion*

1:25 p.m. **Panel II: Foundation Support for CAM Research**

(20) M. Bridget Duffy, MD, Medtronic Foundation
(21) Dorianne C. Miller, MD Robert Wood Johnson Foundation

(22) Susan Braun, Susan G. Komen Breast Cancer Foundation
(23) Ronald Chez, MD Samueli Institute for Information Biology

- *Discussion*

2:35 p.m. – 2:50 p.m. **BREAK**

2:50 p.m. **Panel III: Approaches to Evaluating Research Literature**

(24) Donald A. Lindberg, MD, National Library of Medicine
(25) Douglas B. Kamerow, MD, MPH, Agency for Healthcare Research and Quality
(26) Brian Berman, MD, University of Maryland

- *Discussion*

4:10 p.m. **Panel IV: Concerns about CAM and CAM Research**

(27) William M. London, EdD, MPH, National Council Against Healthcare Fraud
(28) Simeon Margolis, MD, PhD, Johns Hopkins University
(29) Arthur P. Grollman, MD, State University of New York at Stonybrook

- *Discussion*

5:30 p.m. **Adjourn**

DAY THREE (Topic II Continued): Wednesday, May 16, 2001

7:15 a.m. **Registration Opens**

Meeting Topic II.
CAM: RESEARCH CHALLENGES continued

8:00 a.m. **Panel V: Research Methodology**

(30) John A. Chabot, MD, Columbia University
(31) Marcia Angell, MD, Editor-in-Chief Emeritus, New England Journal of Medicine
(32) Jennifer Jacobs, MD, MPH, American Institute of Homeopathy
(33) B. Alex White, DDS, DrPH, Kaiser Permanente Center for Health Research
(34) Bruce Rabin, MD, PhD, University of Pittsburgh

- *Discussion*

9:25 a.m. **Panel VI: Training of Conventional and CAM Investigators**

(35) Nancy Pearson, PhD, National Center for Complementary and Alternative Medicine
(36) Neal West, PhD, National Center for Complementary and Alternative Medicine
(37) Robert H. Blanks, PhD, University of California at Irvine
(38) Russell Phillips, MD, Harvard University
(39) Richard Hammerschlag, PhD, Oregon College of Oriental Medicine

- *Discussion*

10:35 a.m. – 10:50 a.m. **BREAK**

10:50 a.m. **Panel VII: Publication of Peer-Reviewed CAM Research Results**

(40) Edward W. Campion, MD, New England Journal of Medicine
(41) Jackie C. Wootton, MEd, Journal of Alternative and Complementary Medicine
(42) Phil B. Fontanarosa, MD, Journal of the American Medical Association
(43) David Riley, MD, Alternative Therapies in Health and Medicine
(44) Christine Laine, MD, MPH, Annals of Internal Medicine
(45) Arnold Relman, MD, Editor-in-Chief Emeritus, New England Journal of Medicine

- *Discussion*

12:30 p.m. – 1:30 p.m. **LUNCH BREAK**

1:30 p.m. **Breakout – Small Group Discussion (CAM Research Challenges)**

2:50 p.m. **Group Reports and Discussion/Adjourn Meeting Topic II.**

4:00 p.m. **BREAK**

4:15 p.m. **Public Comment Session – 3-Minute Oral Statements***
**this list will be revised and posted on the website no later than May 10*

(46) Audrey Di Maria, Art Therapy Credential Board
(47) Katherine Jane Gorton, American Dietetic Association

(48) Su Liang Ku, FITCM
(49) Matt Ward Russell, National Integrative Medicine Council
(50) Carolyn Jones Sabatini, Pharmavite Corporation

- *Discussion*

(51) James Sensenig, American Association of Naturopathic Physicians
(52) Nancy Kristine Haller, Feldenkrais Guild of North America
(53) Diane Davis Cole, University of Virginia Cancer Center

- *Discussion*

5:00 p.m. **Adjourn**

DRAFT QUESTIONS Date: 4/9/01

Questions for Foundations:

Does your foundation support CAM research and/or research training? If so, how does your foundation determine what (CAM) research or research training it will fund?

What types of research are you currently funding or are considering funding?

What role can foundations play in stimulating CAM research, e.g., seed money, research grants, publication of research results, research training support, conferences?

What are the obstacles and possible solutions to accomplishing your foundation's goals regarding CAM in this area?

How can CAM research coordination be enhanced between the Federal government and the not-for-profit sector?

Do you work collaboratively with other foundations to stimulate CAM research and research training?
would needs to be done to enhance collaboration ⊂ Fndns not active in area
What policy recommendations can your foundation offer regarding CAM research for the Commission's consideration as it develops its report to the President and Congress?

Questions for Approaches to Evaluating Research Literature:

What criteria are used when deciding to include a peer-reviewed journal or other information sources in the NLM database?

Has AHRQ conducted evidence-based assessments of CAM practices and products? What criteria are used by the agency when deciding on topics for evidence-based practice reports? What evidence-based assessments in CAM have you conducted?

Does the Cochrane Collaboration for Evidence-based Medicine include in its database information on CAM practices and products? What criteria are used in your selection process with regard to CAM topics?

What policy recommendations can you offer regarding the evaluation of research literature in CAM for the Commission's consideration as it develops its report to the President and Congress?

Questions for the Research Panel:

In discussing approaches to increasing the safety and effectiveness of CAM practices and products, in addition to data collection and clinical trial methodology, consider 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 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?

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

What training do conventional investigators need to conduct CAM research?

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

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

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

Research Training Panel:

What training do CAM professionals need to evaluate their own clinical efficacy and conduct high quality research?

What training do CAM professionals need to design and conduct high quality research projects.

What training do CAM professionals need to contribute as members of research teams, including the collection of valid data, etc.

How can CAM practitioners become better educated in the critical evaluation of CAM product claims and the results of CAM protocols and clinical research?

What policy recommendations can you offer the Commission on the training of conventional investigators and CAM investigators and clinicians to strengthen the pool of highly qualified CAM researchers?

Are there special issues involved in the training of conventional researchers in the research of CAM

Questions on Peer Reviewed Journals:

What criteria are used by your journal for accepting articles on CAM research?

How do you choose your reviewers; what qualifications must they have?

Are the criteria used by conventional journals in accepting CAM studies similar to or different from criteria used for acceptance of conventional studies?

What are the unique challenges facing CAM acceptance in conventional peer-reviewed journals?

Are the criteria used by CAM journals in accepting research studies comparable to the standards used by conventional journals?

What are the unique challenges facing CAM peer-reviewed journals?

What are the most common reasons articles are rejected?

On average, how many revisions are made before publication?

What is the average length of time from receipt of an article to publication?

What are the gaps in reporting CAM research results?

Does your audience include both CAM practitioners; conventional practitioners? What percentage of your readership do you believe falls into either category?

What policy recommendations can you offer regarding the publication of CAM practices and products in peer-reviewed journals for the Commission's consideration as it develops its report to the President and Congress?

What are conventional journals doing to reach out to the CAM Research Community

General Questions for Federal Agencies (DoD, NSF, AHRQ, Dept. Of Ed, CDC, USDA, and NASA):

How can coordination be established or strengthened among and between Federal agencies that have research and research-related responsibilities, and how can it be enhanced with the not-for-profit and private sectors?

What are the obstacles (conceptual or otherwise) and possible solutions to accomplishing

integration of CAM into mainstream research?

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

Additional Questions for DoD:

Does DoD support any research on CAM practices and programs?

How and why were these selected as the most promising areas of research on CAM interventions?

Does DoD coordinate CAM research efforts across the services?

Does DoD include any CAM practices and products in its clinical programs? If so, how are they selected?

What does DoD consider as the most promising areas of CAM practice 1) to study; 2) to incorporate into military health care?

Additional Questions for NSF:

Does NSF support any research related to CAM practices and products? What can CAM perspectives and approaches contribute to research in the biological, physical, social, and behavioral sciences? Are there areas of research related to CAM that NSF considers promising?

Additional Questions for CDC:

Does CDC support any epidemiologic research or surveillance projects on CAM practices and products? Are there areas of research related to CAM that CDC considers promising?

Additional Questions for USDA, Dept. of Education, NASA, Dept. of Energy:

Does (*agency*) support any research or research-related activities on CAM practices and products? Are there areas of research related to CAM that (*agency*) considers promising?

* Contact Tom Harkin for Presence

RESEARCH II **DRAFT** 4/6/01

Tuesday, May 15, 01

Overview

12:30-1:15 David Eisenberg ***(45 minutes-25/20/ reimbursement, clinical, basic, and health services research)***

Foundation
Not-for-Profit Support for CAM Research*

1:15
- Medtronic and George Foundations-Bridget Duffy, M.D., ***confirmed***
- RWJ Foundation-Dorianne Miller, M.D. ***confirmed***
- Susan G. Koman Breast Cancer Foundation- Susan Braun, ***confirmed***

two to three more speakers from list below, others respond in writing

- Fetzer Foundation, Jeremy Waletzky, ***left message*** (Tom Inui, Lynn Underwood cannot attend)
- Cummings Foundation (Andrea Kydd/letter)
- ~~Kohlberg Foundation (Jerry?/Columbia/letter)~~
- Bill and Melinda Gates Foundation, ***e-mailed Gordon Perkin, per Dean Ornish***
- Kaiser Family Foundation
- H and S (Henry/Susan Samueli) Foundation, ***will call 4/10***
- Rockefeller Family Foundation, Melissa Berman, ***sent e-mal message***

2:15 DISCUSSION

Approaches to Evaluating Research Literature

2:45 NLM Selection Process for Peer-reviewed Journals- Donald Lindberg ***confirmed***
Evidence-based Practice Centers and CAM-John Eisenberg, AHRQ, ***confirmed, if hearing date changes, he will send Doug Kamerow***
(other Federal agency support to be handled in writing. See ** below.)
Cochrane Collaboration-Brian Berman, ***will send agenda and questions, waiting for an answer***

3:15 DISCUSSION George Lundberg

3:45 BREAK

4:00 Scientific Basis of CAM

~~Wallace Sampson~~, Saul Green, Steven Barrett, etc

6:00 Adjourn

Wednesday, May 16, 01

The ~~Challenges~~ of CAM Research and Research Training

8:30 Research methodology:

- John Chabot, PI on Columbia/Gonzalez study-***confirmed***
- Marcia Angell-***confirmed***
- Jennifer Jacobs, M.D., MPH, American Institute of Homeopathy- -***confirmed***
  rep. from NCCAM-supported Oregon Center on CAM, ***Steve***
- Bruce Rabin, U of Pittsburgh, ***confirmed***

~~Robert Blanks~~

(Andrew Vickers; ***cannot attend but will send written material by 4/25***)

Training of conventional and CAM investigators:

Richard Nahin, NCCAM, ***Steve***

Richard Hammerschlag, Soc. for Acupuncture Research, ***waiting for confirmation***

~~Elizabeth Targ, UCSF, cannot attend~~

Marilyn Schlitz, SF Noetic Society, ***call back 4/10***

9:50 DISCUSSION

10:30 BREAK

Publication of Peer-Reviewed CAM Research Results

10:45 NEJM-Edward Campion, Deputy Editor, ***confirmed*** (Jeffrey Drazen)

JAMA-Phil Fontanarosa-***confirmed*** (Catherine DeAngelis)

- Arnold Relman-***confirmed***

Alternative Therapies in Health and Medicine-Larry Dossey ***cannot make it, emailed David Riley at Dossey's suggestion***

The Journal of Alternative and Complementary Medicine, Jackie Wootton-***confirmed***

Annals of Internal Medicine- Frank Davidoff-***will attend himself or will send deputy editor working with him on a series of papers on CAM***

George Lundberg, CBS Healthwatch, former editor of JAMA ***??***

12:00 DISCUSSION

12:40 LUNCH

1:40 Discussion Groups/breakouts

Federal agency support
Not-for profit support
Evaluating research results
Research challenges and research training
Journal publication of CAM results

Two breakout groups (members and chair assigned prior to meeting):
1) give Commissioners as much material a possible ahead of time.
2) strongly encourage Commissioners to review materials and transcripts from first research meeting and research-related testimony/discussion at town hall and other meetings.
3) suggest that Commissioners keep breakout sessions in mind when listening to testimony and taking notes.
4) task Commissioners with developing draft recommendations for all the above areas.
5) allow time for access and delivery recommendations.

3:00 Full Commission Discussion

4:00 Public Session

5:30 Adjourn

**(Letters to the following Federal Agency Support for CAM Research: responses in writing)

NSF- ***Michael Sieverts for Rita Colwell***
Dept of Ed ***call Theresa SanAgustin***
DoD ***Acting Asst Sec for Health, J. Jarred Clinton***
CDC-***Bill Dietz***
USDA- ***Orville Levander***
NASA- ***Kathy Olson***
Dept. of Energy-***Jim Decker***
HRSA-

Read + Respond to the

RESEARCH II **DRAFT** 4/6/01

Tuesday, May 15, 01

Overview

12:30-1:15 David Eisenberg ***(45 minutes-25/20)***

Not-for Profit Support for CAM Research*

1:15 Medtronic and George Foundations-Bridget Duffy, M.D., ***confirmed***
RWJ Foundation-Dorianne Miller, M.D. ***confirmed***
Susan G. Koman Breast Cancer Foundation- Susan Braun, ***confirmed***
two to three more speakers from list below, others respond in writing
Fetzer Foundation, Jeremy Waletzky (Tom Inui, Lynn Underwood cannot attend)
Cummings Foundation (Andrea Kydd/letter)
Kohlberg Foundation (Jerry?/Columbia/letter)
Bill and Melinda Gates Foundation, speak to Gordon Perkins, mention Dean Ornish
Kaiser Family Foundation
H and S (Henry/Susan Samueli) Foundation
Rockefeller Family Foundation, Melissa Berman, sent e-mal message

2:15 DISCUSSION

Approaches to Evaluating Research Literature

2:45 NLM Selection Process for Peer-reviewed Journals- Donald Lindberg ***confirmed***
Evidence-based Practice Centers and CAM-John Eisenberg, AHRQ, sent e-mail (other Federal agency support to be handled in writing. See ** below.)
Cochrane Collaboration-Brian Berman ***confirmed*** Steve

3:15 DISCUSSION

3:45 BREAK

4:00 Scientific Basis of CAM

Wallace Sampson, Saul Green, Steven Barrett, etc

6:00 Adjourn

Wednesday, May 16, 01

The Challenges of CAM Research and Research Training

8:30 Research methodology:

John Chabot, PI on Columbia/Gonzalez study-***confirmed***
Marcia Angell-***confirmed***
Jennifer Jacobs, M.D., MPH, American Institute of Homeopathy- -***confirmed***
rep. from NCCAM-supported Oregon Center on CAM, Steve
Bruce Rabin, U of Pittsburgh
Robert Blanks
David Eddy-***medical economist/will be invited to reimbursement mtg.***
(Andrew Vickers; ***cannot attend but will send written material by 4/25***)

Training of conventional and CAM investigators:
Richard Nahin, NCCAM, Steve
Richard Hammerschlag, Soc. for Acupuncture Research, Corinne
Elizabeth Targ, UCSF
Marilyn Schlitz, SF Noetic Society

9:50 DISCUSSION

10:30 BREAK

Publication of Peer-Reviewed CAM Research Results

10:45 NEJM-Jeffrey Drazen ***out of country/sent e-mail***
JAMA-Phil Fontanarosa-***confirmed*** (Catherine DeAngelis)
Arnold Relman-***confirmed***
Alternative Therapies in Health and Medicine-Larry Dossey-***call David Riley***
The Journal of Alternative and Complementary Medicine, Jackie Wootton-***confirmed***
Annals of Internal Medicine- Frank Davidoff-***will attend or send deputy editor working with him on a series of papers on CAM***
George Lundberg, CBS Healthwatch, former editor of JAMA ***??***

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12:40 LUNCH

1:40 Discussion Groups/breakouts

- Federal agency support
- Not-for profit support
- Evaluating research results
- Research challenges and research training
- Journal publication of CAM results

Two breakout groups (members and chair assigned prior to meeting):
1) give Commissioners materials ahead of time
2) task Commissioners with developing draft recommendations for (all) the above areas, including issues of access and delivery associated with Federal agencies
3) encourage Commissioners to review transcripts (on whccamp web site), briefing book materials, and notes of previous meetings, as well as current plenary session presentations and questions as reference material for breakout session discussion.

3:00 Full Commission Discussion

4:00 Public Session

5:30 Adjourn

**(Letters to the following Federal Agency Support for CAM Research: responses in writing)

NSF- ***Michael Sieverts for Rita Colwell***
Dept of Ed ***call Theresa SanAgustin***
DoD ***Acting Asst Sec for Health, J. Jarred Clinton***
CDC-***Bill Dietz***
USDA- ***Orville Levander***
NASA- ***Kathy Olson***
Dept. of Energy-***Jim Decker***

DRAFT QUESTIONS Date: 4/6/01

Questions for Foundations:

Does your foundation support CAM research and/or research training? If so, how does your foundation determine what (CAM) research it will fund?

What types of research are you currently funding or are considering funding?

What role can foundations play in stimulating CAM research, e.g., seed money, research grants, publication of research results, research training support, conferences?

What are the obstacles and possible solutions to accomplishing your foundation's goals in this area?

How can CAM research coordination be enhanced between the Federal government and the not-for-profit sector?

Do you work collaboratively with other foundations to stimulate CAM research and research training?

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

Questions for Approaches to Evaluating Research Literature:

What criteria are used when deciding to include a peer-reviewed journal or other information sources in the NLM database?

Has AHRQ conducted evidence-based assessments of CAM practices and products? What criteria are used by the agency when deciding on topics for evidence-based practice reports? What evidence-based assessments in CAM have you conducted?

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What policy recommendations can you offer regarding the evaluation of research literature in CAM for the Commission's consideration as it develops its report to the President and Congress?

Questions for the Research Panel:

In discussing approaches to increasing the safety and effectiveness of CAM practices and products, in addition to data collection and clinical trial methodology, consider the complex questions inherent in CAM that require study such as multiple interventions; complex systems and complex compounds; individualization; the placebo effect; provider/patient interaction; multiple populations including culture/race, gender, age; and so forth.

How can good data 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, chronic conditions, pain management, self care, care for the terminally ill?

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

What training do conventional investigators need to conduct CAM research?

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

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

Research Training Panel:

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What training do CAM professionals need to design and conduct high quality research projects.

What training do CAM professionals need to contribute as members of research teams, including the collection of valid data, etc.

How can CAM practitioners become better educated in the critical evaluation of CAM product claims and the results of CAM protocols and clinical research?

What policy recommendations can you offer the Commission on the training of conventional investigators and CAM investigators and clinicians to strengthen the pool of highly qualified

CAM researchers?

Questions on Peer Reviewed Journals:

What criteria are used by your journal for accepting articles on CAM research?

How do you choose your reviewers; what qualifications must they have?

Are the criteria used by conventional journals in accepting CAM studies similar to or different from criteria used for acceptance of conventional studies?

What are the unique challenges facing CAM acceptance in conventional peer-reviewed journals?

Are the criteria used by CAM journals in accepting research studies comparable to the standards used by conventional journals?

What are the unique challenges facing CAM peer-reviewed journals?

What are the most common reasons articles are rejected?

On average, how many revisions are made before publication?

What is the average length of time from receipt of an article to publication?

What are the gaps in reporting CAM research results?

Does your audience include both CAM practitioners; conventional practitioners? What percentage of your readership do you believe falls into either category?

What policy recommendations can you offer regarding the publication of CAM practices and products in peer-reviewed journals for the Commission's consideration as it develops its report to the President and Congress?

General Questions for Federal Agencies (DoD, NSF, AHRQ, Dept. Of Ed, CDC, USDA, and NASA):

How can coordination be established or strengthened among and between Federal agencies that have research and research-related responsibilities, and how can it be enhanced with the not-for-profit and private sectors?

What are the obstacles (conceptual or otherwise) and possible solutions to accomplishing integration of CAM into mainstream research?

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

Additional Questions for DoD:

Does DoD support any research on CAM practices and programs?

How and why were these selected as the most promising areas of research on CAM interventions?

Does DoD coordinate CAM research efforts across the services?

Does DoD include any CAM practices and products in its clinical programs?

What does DoD consider as the most promising areas of CAM practice 1) to study; 2) to incorporate into military health care?

Additional Questions for NSF:

Does NSF support any research related to CAM practices and products? What can CAM perspectives and approaches contribute to research in the biological, physical, social, and behavioral sciences? Are there areas of research related to CAM that NSF considers promising?

Additional Questions for CDC:

Does CDC support any epidemiologic research or surveillance projects on CAM practices and products? Are there areas of research related to CAM that CDC considers promising?

Additional Questions for USDA, Dept. of Education, NASA, Dept. of Energy:

Does (*agency*) support any research or research-related activities on CAM practices and products? Are there areas of research related to CAM that (*agency*) considers promising?

WHF. Based on
TCM - Different systems
- Portland - CAM Clinics -
- Training Qum
- Modules - of NCCAM (Herbacops)
45 Col of Acy + TCM / TOM
- Return Green to Body of Material to permit practice to continue

Rep ① Office of Herbal Products at FDA (Office of Natural Products)

U.S. F + A. Service
Conservation, Endangered Species / Herbal Medicine

- Therapeutic Agents
- UK - crushed products - permits (Purity & Identity
Australia - Therapeutic Goods Act / Contaminants
2000 — Good / Active Herbals

* Levels of training + inform consumers of education level of emphasis + referral

Task Force on Curriculum —
- Survey courses - in Conventional Medical, Pharmacy, Nursery, Dentistry

- Fed. Funding for Collaborative Clinics
- R13 Grant Applications
- HCFA
-

RESEARCH II **DRAFT 3/30/01**

Tuesday, May 15, 01

All Aspects Research Research Training Reimbursement

Overview

12:30-1:15 David Eisenberg ***(45 minutes-25/20)***

Not-for Profit Support for CAM Research*

1:15 Medtronic and George Foundations-Bridget Duffy, M.D., ***confirmed***
RWJ Foundation-Dorianne Miller, M.D. ***confirmed***
Susan G. Koman Breast Cancer Foundation- Susan Braun, ***confirmed***
two to three more speakers from list below, others respond in writing

Frontier Research Integrative Medicine

- Fetzer Foundation (Tom Inui cannot attend, will speak to Lynn Underwood, director of research program (Jeremy Waletzky) Mind-Body
- Cummings Foundation (Andrea Kydd/____)
- Kohlberg Foundation (Jerry ___/Columbia $s)
- Bill and Melinda Gates Foundation, speak to Gordon Perkins, mention Dean Ornish
- Kaiser Family Foundation
- H and S (Henry/Susan Samueli) Foundation
- ~~Rockefeller Family Foundation, Melissa Berman~~
- Alberto Vilar Foundation

2:15 DISCUSSION

Approaches to Evaluating Research Literature

2:45 NLM Selection Process for Peer-reviewed Journals- Donald Lindberg ***confirmed***
Evidence-based Practice Centers and CAM-John Eisenberg, AHRQ
(other Federal agency support to be handled in writing. See ** below.)
Cochrane Collaboration-Brian Berman

International Aspects Research + training

3:15 DISCUSSION

3:45 BREAK

4:00 Scientific Basis of CAM

Wallace Sampson, Saul Green, Steven Barrett, etc*

Journal

* Ursula Goodenough Paul

6:00 Adjourn

Wednesday, May 16, 01

The Challenges of CAM Research and Research Training

8:30 Research methodology: David Eddy; Andrew Vickers; rep from NCCAM-supported Oregon Center on CAM; John Chabot, PI on Columbia/Gonzalez study-***has accepted***; Steven Hyman, Director NIMH; ~~Ian Colter, Rand Corp.~~; ~~George Lewith, England~~; ~~Richard Horton, England~~; ~~Stephen Mayers, Australia~~

Training of conventional investigators- Richard Nahin, NCCAM

Training of CAM professionals, ~~Bill Mecker~~, Tim Callahan, Leannna Standish, Marilyn Schlitz, Richard Hammerschlag, Soc. for Acupuncture Research

American Institute of Homeopathy-Jennifer Jacobs, M.D., MPH-***confirmed***

~~Robert Blanks, conventional researcher looking at wellness, Veronica Gutierrez's suggestion~~

Bruce Rabin, conventional researcher with considerable experience re. CAM research questions-U of Pittsburgh, George Bernier suggestion

9:50 DISCUSSION

10:30 BREAK

Peer-Reviewed Publication of CAM Research Results

10:45 NEJM-Jeffrey Drazen

- JAMA-Catherine DeAngelis
- Marcia Angell
- Arnold Relman

Alternative Therapies in Health and Medicine-Larry Dossey

- The Journal of Alternative and Complementary Medicine-Jackie Wootton ***confirmed*** ~~(Kim Jobst, Scotland)~~
- Annals of Internal Medicine- Frank Davidoff
- George Lundbergh, CBS Healthwatch, former editor of JAMA

12:00 DISCUSSION

12:40 LUNCH

1:40 Public Session (patients, people who have tried to get research support?)

2:40 Discussion Groups/breakouts

- Federal agency support
- Not-for profit support
- Evaluating research results

Research challenges and research training
Journal publication of CAM results

3:40 Full Commission Discussion

4:20 Adjourn

**(Letters to the following Federal Agency Support for CAM Research: responses in writing)

NSF- ***call Michael Sieverts***
Dept of Ed ***call Theresa SanAgustin***
DoD ***write to Acting Asst Sec for Health, J. Jarred Clinton*** (Maureen)
CDC- ***Michele***
USDA- ***Ken, Orville Levander***
NASA- ***Kathy Olson***
Dept. of Energy-***Jim Decker***

RESEARCH II **DRAFT** 3/30/01

Tuesday, May 15, 01

Overview

12:30-1:15 David Eisenberg ***(45 minutes-25/20)***

Not-for Profit Support for CAM Research*

1:15 Medtronic and George Foundations-Bridget Duffy, M.D., ***confirmed***
RWJ Foundation-Dorianne Miller, M.D. ***confirmed***
Susan G. Koman Breast Cancer Foundation- Susan Braun, ***confirmed***
two to three more speakers from list below, others respond in writing
Fetzer Foundation (Tom Inui cannot attend, will speak to Lynn
Underwood, director of research program (Jeremy Waletzky)
Cummings Foundation (Andrea Kydd/____)
Kohlberg Foundation (Jerry ___/Columbia $s)
Bill and Melinda Gates Foundation, speak to Gordon Perkins, mention Dean Ornish
Kaiser Family Foundation
H and S (Henry/Susan Samueli) Foundation
Rockefeller Family Foundation, Melissa Berman
Alberto Vilar Foundation

2:15 DISCUSSION

Approaches to Evaluating Research Literature

2:45 NLM Selection Process for Peer-reviewed Journals- Donald Lindberg ***confirmed***
Evidence-based Practice Centers and CAM-John Eisenberg, AHRQ
(other Federal agency support to be handled in writing. See ** below.)
Cochrane Collaboration-Brian Berman

3:15 DISCUSSION

3:45 BREAK

4:00 Scientific Basis of CAM

Wallace Sampson, Saul Green, Steven Barrett, etc

6:00 Adjourn

Wednesday, May 16, 01

The Challenges of CAM Research and Research Training

8:30 Research methodology: David Eddy; Andrew Vickers; rep from NCCAM-supported Oregon Center on CAM; John Chabot, PI on Columbia/Gonzalez study; Steven Hyman, Director NIMH; Ian Colter, Rand Corp.; George Lewith, England; Richard Horton, England; Stephen Mayers, Australia
Training of conventional investigators- Richard Nahin, NCCAM
Training of CAM professionals, Bill Meeker, Tim Callahan, Leannna Standish, Marilyn Schlitz
American Institute of Homeopathy-Jennifer Jacobs, M.D., MPH-***confirmed***
Robert Blanks, conventional researcher looking at, Veronica Gutierrez's suggestion
Bruce Rabin, conventional researcher looking at attitude and cancer- U of Pittsburgh, George Bernier suggestion

9:50 DISCUSSION

10:30 BREAK

Peer-Reviewed Publication of CAM Research Results

10:45 NEJ-Jeffrey Drazen
JAMA-Catherine DeAngelis
Marcia Angell
Arnold Relman
Alternative Therapies in Health and Medicine-Larry Dossey
The Journal of Alternative and Complementary Medicine-Jackie Wootton ***confirmed***
Annals of Internal Medicine- Frank Davidoff
George Lundbergh, CBS Healthwatch, former editor of JAMA

12:00 DISCUSSION

12:40 LUNCH

1:40 Public Session (people who have tried to get research support)

2:40 Discussion Groups/breakouts
Federal agency support
Not-for profit support
Evaluating research results

Research challenges and research training
Journal publication of CAM results

3:40 Full Commission Discussion

4:20 Adjourn

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Dept. of Energy-***Jim Decker***

3/30/01

DRAFT QUESTIONS

Questions for Foundations:

How does your foundation determine what (CAM) research it will fund?

What types of research are you currently funding or are considering funding?

What role can foundations play in stimulating CAM research, e.g., seed money, grants, publication of research results, research training support, conferences?

What are the obstacles and possible solutions to accomplishing this goal?

How can CAM research coordination be enhanced between the Federal government and the not-for-profit sector?

What policy recommendations can *your foundation* offer regarding CAM research for the Commission's consideration as it develops its report to the President and Congress?

Questions for Approaches to Evaluating Research Literature:

What criteria are used when deciding to include a peer-reviewed journal in the NLM database?

Has AHRQ's conducted evidence-based assessments of CAM practices and products?

What criteria are used by the agency when deciding on topics for evidence-based practice reports?

Does the Cochrane Collaboration for Evidence-based Medicine include in its database information on CAM practices and products?
What policy recommendations can you offer regarding...?

Questions for the Research and Research Training Panel:

In discussing approaches to increasing the safety and effectiveness of CAM practices and products, in addition to data collection and clinical trial methodology, consider and the complex questions inherent in CAM that require study such as multiple interventions, complex systems and complex compounds, individualization, the placebo effect, provider/patient interaction, and so forth.

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, chronic conditions, pain management, self care, care for the terminally ill?

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

What training do conventional investigators need to conduct CAM research?

What training do CAM professionals need to evaluate their own clinical efficacy and conduct high quality research?

How can CAM practitioners become better educated in the critical evaluation of CAM product claims and CAM protocols and clinical research?

How can research collaborations between conventional and CAM institutions be facilitiated.

What policy recommendations can you offer

Questions on Peer Reviewed Journals:

What criteria are used by (*journal*) for accepting articles on CAM research?

Are these criteria similar to or different from criteria used for acceptance of conventional research studies?

What are the unique challenges facing CAM acceptance in conventional peer-reviewed journals?

What are the unique challenges facing CAM peer-reviewed journals?

What are the criteria for accepting a research article?

What are the most common reasons articles are rejected?

How do you choose your reviewers; what qualifications must they have?

What is the average number of revisions made before publication?

What is the average length of time from receipt of an article to publication?

What are the gaps in reporting CAM research results?

Does your audience include CAM practitioners; conventional practitioners?

What policy recommendations can you offer regarding research, evaluation and publication of CAM practices and products in peer-reviewed journals?

General Questions for Federal Agencies (DoD, NSF, AHRQ, Dept. Of Ed, CDC, USDA, and NASA):

How can coordination be established or strengthened among and between Federal agencies that have research and research-related responsibilities, and how can it be enhanced with the not-for-profit and private sectors?

What are the obstacles (conceptual or otherwise) and possible solutions to accomplishing integration of CAM into mainstream research?

What policy recommendations can *(agency)* offer regarding research on CAM for the Commission's consideration as it develops its report to the President and Congress?

Additional Questions for DoD:

Does DoD support any research on CAM practices and programs?

How and why were these selected as the most promising areas of research on CAM interventions?

Does DoD coordinate CAM research efforts across the services?

Does DoD include any CAM practices and products in its clinical programs?

What does DoD consider as the most promising areas of CAM practice 1) to study; 2) to incorporate into military health care?

Additional Questions for NSF:

Does NSF support any research related to CAM practices and products? What can CAM perspectives and approaches contribute to research in the biological, physical, social, and behavioral sciences? Are there areas of research related to CAM that NSF considers promising?

Additional Questions for CDC:

Does CDC support any epidemiologic research or surveillance projects on CAM practices and products? Are there areas of research related to CAM that CDC considers promising?

Additional Questions for USDA, Dept. of Education, NASA, Dept. of Energy:

Does (*agency*) support any research or research-related activities on CAM practices and products? Are there areas of research related to CAM that (*agency*) considers promising?

SPECIAL ARTICLE

Americans' Views on the Use and Regulation of Dietary Supplements

Robert J. Blendon, ScD; Catherine M. DesRoches, DrPH; John M. Benson, MS; Mollyann Brodie, PhD; Drew E. Altman, PhD

This article presents the views of Americans on what the government's future role should be in regulating or overseeing the growing sales of dietary supplements for health purposes. Based on results of multiple national opinion surveys, including the views of both users and nonusers of supplements, we found that a substantial percentage of Americans surveyed reported that they regularly take dietary supplements as a part of their routine health regimen. However, they reported that they do not discuss the use of dietary supplements with their physicians because they believe that the physicians know little or nothing about these products and may be biased against them. Many users felt so strongly about the potential health benefits of some of these products that they reported that they would continue to take them even if they were shown to be ineffective in scientifically conducted clinical studies. However, there also was broad public support for increased government regulation of these products. We found that a majority of Americans surveyed supported the following: to require that the Food and Drug Administration review the safety of new dietary supplements prior to their sale; to provide increased authority to remove from sale those products shown to be unsafe; and to increase government regulation to ensure that advertising claims about the health benefits of dietary supplements are true.

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One of the most striking changes in Americans' health behaviors in the 1990s was the widespread and growing use of dietary supplements for health reasons. Since 1994, dietary supplement sales have grown by nearly 80%, from $8.8 billion to an estimated $15.7 billion for 2000. Sales of specific herbal remedies, such as echinacea, ginseng, *Ginkgo biloba*, and St John's wort, exceeded $200 million per product per year, and these supplements are taken routinely by millions of Americans.[1]

The sharp rise in the use of these supplements has raised concerns in the medical community and the media about the potentially serious health risks of the mostly untested and unregulated products. Various reports[2,3] from poison control centers and practicing physicians have indicated examples of individuals being harmed by taking these supplements. Others[4] have raised the concern that the use of these products may be leading some to forgo proven conventional medical treatment when they are seriously ill.

Furthermore, the issue has been raised that as these products are increasingly advertised in the media and sold in drug stores and supermarkets the public may be given a false sense of security about their safety. They may believe that supplements are subject to existing government regulations similar to those applicable to over-the-counter medications sold to the public without a prescription. In fact, dietary supplements are subject to a less stringent government standard of safety testing than other over-the-counter medications.[1,3,5]

After receiving thousands of letters from supplement users in a heated advocacy campaign, Congress passed the Di-

From the Department of Health Policy and Management, Harvard School of Public Health, Boston (Drs Blendon and DesRoches and Mr Benson), John F. Kennedy School of Government, Harvard University, Cambridge (Dr Blendon), Mass; Henry J. Kaiser Family Foundation, Menlo Park, Calif (Drs Brodie and Altman).

etary Supplement Health and Education Act[6] of 1994, which freed dietary supplement manufacturers from many existing Food and Drug Administration (FDA) regulations. In the Nutrition Labeling and Education Act[7] of 1990, Congress gave the FDA the authority to require manufacturers of dietary supplements to provide evidence that their products were safe prior to sale and to approve the health claims made about these products before they could be used in marketing. After the 1994 legislation was enacted, the burden of proof concerning the safety of dietary supplements shifted. Instead of the manufacturer having to show that a supplement was safe, the FDA had to prove that it was unsafe. Also, as a result of the legislation, manufacturers have been able to make general health claims about products as long as they do not contain references to preventing or curing specific diseases. These supplements are now sold under the same oversight standard as vitamins and are categorized under a separate FDA category as "foods."[8,9]

Recently, the question of the need for stricter regulation of these products has been raised in editorials, medical journals, and articles in the media, particularly on the issue of safety and the specific health claims that can be made by the manufacturers.[2,10,11] What has been missing in this growing debate over what the government's role should be in regulating dietary supplements are the views of the American public, both users and nonusers of these products.

In this article, we seek to fill this void by summarizing the available public opinion survey data on the dietary supplement issue. We used national opinion survey data to answer the following questions: (1) What are the characteristics of people who use dietary supplements regularly, and how are users different from nonusers? (2) How are regular users' attitudes about dietary supplements and their usefulness different from those of nonusers? (3) What are Americans' attitudes toward government regulation, and are there differences between the attitudes of regular users and nonusers? (4) What are the policy implications of these differences, and how might they affect the debate on the national level?

DATA AND METHODS

Relatively few polls investigating Americans' views of dietary supplement use and regulation have been conducted. The data presented herein came primarily from 2 sources.

The first source consisted of specific results drawn from 4 national opinion surveys conducted from 1996 to 1999. These surveys did not differentiate between the views of regular users and nonusers of dietary supplements. These data were compiled from the public opinion database at the Roper Center for Public Opinion Research in Storrs, Conn.[12-15]

The second source consisted of 2 surveys that differentiated the views of users and nonusers of dietary supplements. One survey was designed by researchers at National Public Radio, the Henry J. Kaiser Family Foundation, and the John F. Kennedy School of Government. Telephone interviews were conducted with 1200 randomly selected US adults by Princeton Survey Research Associates between February 19 and 25, 1999.[16] The second survey was designed by researchers at the Henry J. Kaiser Family Foundation and the Harvard School of Public Health. International Communications Research conducted interviews via telephone with 1013 randomly selected US adults between December 16 and 21, 1999.[17]

In the analysis of data from these latter 2 surveys, *regular users* were defined as respondents who reported that they regularly use products, such as echinacea, ginseng, over-the-counter hormones, or amino acids. Respondents who reported using dietary supplements sometimes were classified as *sometimes users*. Lastly, *nonusers* were defined as those respondents who reported that they never use these products. We compared the views of both sometimes users and nonusers with regular users. Differences between these groups were tested using a χ^2 test, and significance is noted in the individual tables.

All surveys were subject to sampling and nonsampling errors. Results may have differed from what would have been obtained if the whole population of adults had been interviewed. The size of this error varied with the number surveyed and the magnitude of difference in the responses to each question. These surveys had sample sizes of approximately 1000 to 1200 persons. With a sample this size, the results, with a 95% degree of confidence, have a statistical precision of ± 3 to 3.5 percentage points compared with what would have been obtained if the entire population had been interviewed. Possible sources of nonsampling error include nonresponse bias and question wording and ordering effects.

RESULTS

DEMOGRAPHIC CHARACTERISTICS

A review of the findings of these surveys showed that approximately half (48%) of all American adults surveyed reported taking some type of nonprescription vitamin, dietary, or mineral supplements regularly.[11] One in six (16%-18%) reported regularly using dietary supplements, like echinacea, ginseng, amino acids, or over-the-counter hormones.[16,17]

Table 1 displays the differences between demographic groups in terms of the frequency of dietary supplement use. American respondents with higher levels of education reported greater use than those with less education. Regular users were also more likely to be white (non-Hispanic). Americans older than 45 years were more likely to use supplements regularly than those who were younger (24% vs 14%, respectively).[16]

Also, uninsured American respondents were significantly more likely than those with insurance to use dietary supplements (21% vs 15%, respectively).[17] Of note, 1 (18%) of 6 parents reported giving dietary supplements to their children.[16]

BELIEFS ABOUT DIETARY SUPPLEMENTS

The surveys found that a substantial percentage of the Americans sur-

veyed held positive views of the health benefits derived from taking dietary supplements. A 1997 survey found that one third (36%) of the American adults thought that there was a dietary supplement that could help them live longer.[12] Overall, 85% of regular users reported that dietary supplements are good for people's health and well-being. The figure was lower for those who were not regular users.[16]

Regular users differed significantly from nonusers in their belief that dietary supplements could help with the treatment of a wide range of medical conditions (**Table 2**). About half of the American respondents believed that supplements are helpful for people with colds (61%), arthritis (53%), depression (52%), and influenza (49%). Respondents viewed dietary supplements as helpful in the treatment of cancer (35%) and acquired immunodeficiency syndrome (16%).[16] Not surprisingly, regular users were significantly more likely than nonusers to believe that supplements could help people with all the conditions the survey asked about; however, rates were also high among the nonusers. Another study[14] found that 82% of the Americans surveyed said that they would seriously consider trying alternative treatments, such as herbal medicines, if they were terminally ill.

The surveys also found that those who were regular users believed strongly in the usefulness of various dietary supplements irrespective of the scientific evidence. When asked what they would do if a government agency said that the supplement they use most often was ineffective, 71% of regular users reported that they would continue to use it (**Table 3**).[16] In the follow-up survey, respondents were asked what they would do if the FDA specifically said that the supplement they use most often was ineffective to see if using the FDA's name vs an unknown government agency would alter the result. The addition of the FDA did not lead to different responses (Table 3). Once again, two thirds (67%) of regular and sometimes users said that they would continue to take the supplement.[17]

Given how beneficial most regular users believed dietary supple-

Table 1. Demographics of US Respondents*

	Total (N = 1196)	Frequency of Dietary Supplement Use: Regular (n = 235)	Sometimes (n = 381)	Never (n = 580)	P
National	...	18	15	66	...
Income, $†					
<20 000	19	20	30	50	
20 000-29 999	15	20	27	53	
30 000-50 000	18	16	37	48	...
>50 000	25	17	34	49	
Education					
Less than high school graduate	17	16	28	56	
High school graduate	34	15	28	57	<.001
Some college	27	22	36	42	
College or more	23	22	33	45	
Race or ethnicity					
White, non-Hispanic	80	20	30	50	
Black, non-Hispanic	10	8	33	60	
Hispanic	7	14	34	53	.03
Other	3	24	45	31	
Insurance status					
Insured	83	15	10	74	.05
Uninsured	16	21	16	64	
Age, y					
18-34	33	16	34	50	
35-44	22	14	32	54	
45-64	28	24	31	45	<.001
≥65	17	22	26	52	
Sex					
Male	48	18	30	52	
Female	52	19	32	49	...

*Data are expressed as percentages unless indicated otherwise. Percentages may not equal 100% because of rounding. The values sum horizontally. National indicates the percentage of the national population in each group; ellipses, not applicable. Data are from a survey conducted by Princeton Survey Research Associates.[16]
†Percentages do not equal 100% because of missing data.

Table 2. Dietary Supplements' Effect on Health and Well-being According to US Respondents*

	Total (N = 1196)	Frequency of Dietary Supplement Use: Regular (n = 235)	Sometimes (n = 381)	Never (n = 580)
Supplements are good for health and well-being				
Yes	52	85	62†	34†
No	17	3	10	27
Some are, some are not‡	17	9	18	20
Do not know	14	3	9	19
Supplements are helpful for people with				
Influenza	49	64	58§	40†
Colds	61	77	73	48†
Cancer	35	54	41†	24†
Acquired immunodeficiency syndrome	16	21	20	12†
Arthritis	53	71	61†	42†
Depression	52	72	58†	42†
How important is access to supplements?				
Very important	35	73	40†	19†
Somewhat important	24	18	32	22
Not too important	17	7	18	21
Not at all important	22	2	9	37

*Data are expressed as percentages. Percentages may not equal 100% because of rounding. Data are from a survey conducted by International Communications Research.[17]
†Significantly different from regular users (P<.001).
‡Respondents volunteered answer; it was not given as an option in the survey.
§Significantly different from regular users (P = .02).

Table 3. US Respondents' Use of Dietary Supplements Considered Unsafe by Government Agencies*

	Total (N = 1196)	Frequency of Dietary Supplement Use: Regular (n = 236)	Frequency of Dietary Supplement Use: Sometimes (n = 381)
If a government agency said that the dietary supplement is ineffective, what would you do?			
Stop using the supplement	25	24	25
Keep using the supplement	72	71	72
Do not know	4	4	3
If the FDA said that the dietary supplement you use most often is ineffective, what would you do?			
Stop using the supplement	33	32	33
Keep using the supplement	66	67	65
Do not know	1	1	1

*Data are expressed as percentages. Percentages may not equal 100% because of rounding. The first question was from a survey conducted by Princeton Survey Research Associates.[16] The second question was from a survey conducted by International Communications Research.[17] FDA indicates Food and Drug Administration.

Table 4. US Respondents' Opinions on the Safety of Dietary Supplements*

	Total (N = 1196)	Frequency of Dietary Supplement Use: Regular (n = 235)	Frequency of Dietary Supplement Use: Sometimes (n = 381)	Frequency of Dietary Supplement Use: Never (n = 580)
Supplements are adequately tested				
Yes	37	49	38†	33†
No	48	39	47	53
Do not know	15	12	15	14
Advertising for supplements is				
Not true	49	29	48†	60†
Generally true	37	57	45	25
Do not know	15	14	12	16
How often are people harmed by supplements?				
Often or sometimes	47	38	46	51†
Rarely or never	44	53	48	38
Do not know	10	9	6	11

*Data are expressed as percentages. Percentages may not equal 100% because of rounding. Data are from a survey conducted by Princeton Survey Research Associates.[16]
†Significantly different from regular users ($P<.001$).

ments to be, it is not surprising that access to them is very important for regular users. Of those who reported that they regularly use dietary supplements, 91% said that access to them is "very" or "somewhat" important. Of note, 72% of sometimes users and 41% of nonusers felt this way (Table 2).[16]

CONFIDENCE IN PHYSICIANS' OPENNESS TOWARD AND KNOWLEDGE OF DIETARY SUPPLEMENTS

The respondents who reported regular use of dietary supplements were divided in their assessment of their physician's level of knowledge of and openness toward these products. More than two thirds (70%) of those who reported taking supplements regularly said that they had shared this information with their regular physician. However, the survey did not provide a measure of the extent of information shared between patients and physicians, and many regular users were skeptical of their physician's knowledge of and attitudes toward supplements. Nearly half (49%) of regular users believed that physicians are prejudiced against supplement use and 44% believed that their own physician knows only a little or not much at all about these products.[17]

SAFETY OF DIETARY SUPPLEMENTS

Regular users of dietary supplements had much more confidence in the safety of these products than nonusers. As shown in **Table 4**, only 37% of the respondents believed that dietary supplements are adequately tested. However, regular users were more likely (49%) than nonusers (33%) to believe that there is adequate testing of these products. Also, the majority of regular users (53%) believed that people are "rarely or never" harmed by taking dietary supplements. In contrast, 51% of nonusers reported that people are "often or sometimes" harmed by these supplements.[16]

ROLE OF ADVERTISING INFORMATION

Commercial advertising has been shown to be an important source of information about over-the-counter medications.[16] One recent survey[15] found that 39% of the respondents reported that television commercials are the most influential source of information in their decision about which cold medicine to buy. In the area of dietary supplements, data are not available on the frequency of use of commercials as an important information source. However, a majority (57%) of regular users thought that the claims made by supplement manufacturers in the advertisements are generally true (Table 4). Those who were not regular users were less likely to believe the claims made by these advertisements.[16]

ATTITUDES TOWARD GOVERNMENT REGULATION OF DIETARY SUPPLEMENTS

A substantial percentage of the respondents were confused about the role that the government currently plays in regulating dietary supplements. Slightly more than half (53%) of the respondents were aware that supplements are not regulated by the government (**Table 5**). One third (35%) of the respondents believed that supplements are currently regulated, and 12% reported that they did not know. The results were similar for regular users.[16]

However, even with this level of public confusion, a majority of respondents expressed support for increased government regulatory efforts to ensure that dietary supplements are not harmful and are pure, that doses are consistent, and that advertising claims are true (**Table 6**).[16] As shown in Table 5, 81% of the respondents supported giving the FDA the authority to allow new supplements to be sold only if the safety of the supplements has been tested by the FDA; 80% supported giving the FDA the authority to remove dietary supplements from the market if they are proved unsafe. Similar levels of support were found among regular users.[17]

CONCLUSIONS

It is clear from the rapid growth in sales that dietary supplements have become a big business. Millions of Americans now regularly take these products as part of their routine health regimen. This phenomenon is being driven by a widespread belief that these untested products contain substances that can lead to better health. Many users feel so strongly about the potential health benefits of some of these products that they reported that they would continue to take them even if they were shown to be ineffective in scientifically conducted clinical studies.

Although only 16% to 18% of the respondents were regular users, the majority of the respondents thought that access to these products is important. This finding suggests that Americans want to be able to use supplements if needed. It also may be due to a belief that there are therapeutic or beneficial substances that the medical community is not aware of.

However, the growing enthusiasm for dietary supplements does not mean that there is not support for stronger regulation that would require FDA review of the safety of new dietary supplements prior to their sale and that would give the FDA ample authority to remove from the market those products shown to be unsafe. Broad support also exists for increased government regulation to ensure that advertising claims about the health benefits are true, that the ingredients in the products are pure, and that dose levels are consistent with the labeling.

The caveat is that a substantial number of the respondents were not prepared to be denied access to existing dietary supplements that have not been previously tested for safety. Many respondents held skeptical views about physicians' and most likely scientists' motivations and knowledge about dietary supplement issues and will likely want clear evidence of a safety hazard before supporting the removal of supplements from the market.

Table 5. US Respondents' Attitudes Toward FDA Regulation of Supplements*

	Total (N = 1185)	Frequency of Dietary Supplement Use: Regular (n = 235)	Sometimes (n = 381)	Never (n = 580)
Does the government regulate dietary supplements?				
Yes	35	32	42†	33
No	53	58	49	54
Do not know	12	11	9	13
Allow new dietary supplements to be sold only if they have been tested by the FDA				
Favor	81	70	80	84
Oppose	14	24	17	10
Do not know	5	6	3	6
Remove dietary supplements from the market if the FDA shows that they are unsafe				
Favor	80	78	79	80
Oppose	16	18	19	14
Do not know	5	3	1	6

*FDA indicates Food and Drug Administration. Data are expressed as percentages. Percentages may not equal 100% because of rounding. Data are from a survey conducted by Princeton Survey Research Associates.[16]

†P = .003 compared with regular users.

Table 6. US Respondents' Attitudes Toward Levels of Regulation*

Level of Regulation	Total (N = 1198)	Frequency of Dietary Supplement Use: Regular (n = 235)	Sometimes (n = 381)	Never (n = 580)
To make sure that supplements are not harmful				
Too much	7	9	7	5†
Not enough	59	55	59	62
Right amount	24	27	26	22
Do not know or refused to answer	10	9	8	11
To make sure that supplements are pure and doses are consistent				
Too much	6	9	4‡	6§
Not enough	60	55	61	62
Right amount	23	25	25	21
Do not know or refused to answer	11	10	10	12
To make sure that advertising claims are true				
Too much	7	10	6	5‖
Not enough	64	62	65	64
Right amount	20	19	21	20
Do not know or refused to answer	10	9	7	11
Supports more regulation for children's supplements	77	78	77	77

*Data are expressed as percentages. Percentages may not equal 100% because of rounding. Data are from a survey conducted by Princeton Survey Research Associates.[16]

†Significantly different from regular users (P = .005).

‡P = .002 compared with regular users.

§P = .007 compared with regular users.

‖P = .004 compared with regular users.

Thus, efforts to increase FDA oversight may not gain support from a critical segment of the public if there is not a clear understanding that any proposed expanded FDA authority is narrowly focused on the testing of either new products or those in use in which there is evidence of potential hazards or untruthful health claims.

These findings also point to the importance for physicians of becoming both more involved with patients in discussing their use of dietary supplements and more knowledgeable about them, particularly in regard to safety issues. The fact that 1 of 6 parents reported giving these supplements to their children should prompt physicians to devote more attention to discussing this practice with parents as they seek health care for their children.

Finally, although the question was not asked directly in the surveys, the findings suggested that there is considerable support for increased research efforts by the government and industry to test and evaluate dietary supplements, particularly for safety purposes. Given how quickly these products are moving into mainstream use, more research seems warranted.

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REVIEW ARTICLE

Garlic Shows Promise for Improving Some Cardiovascular Risk Factors

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Objectives: To summarize the effects of garlic on several cardiovascular-related factors and to note its adverse effects.

Methods: English and non-English citations were identified from 11 electronic databases, references, manufacturers, and experts from January 1966 through February 2000 (depending on the database searched). Reports of cardiovascular-related effects were limited to randomized controlled trials lasting at least 4 weeks. Reports of adverse effects were not limited by study design. From 1798 pertinent records, 45 randomized trials and 73 additional studies reporting adverse events were identified. Two physicians abstracted outcomes and assessed adequacy of randomization, blinding, and handling of dropouts. Standardized mean differences of lipid outcomes from placebo-controlled trials were adjusted for baseline differences and pooled using random effects methods.

Results: Compared with placebo, garlic preparations may lead to small reductions in the total cholesterol level at 1 month (range of average pooled reductions, 0.03-0.45 mmol/L [1.2-17.3 mg/dL]) and at 3 months (range of average pooled reductions 0.32-0.66 mmol/L [12.4-25.4 mg/dL]), but not at 6 months. Changes in low-density lipoprotein levels and triglyceride levels paralleled total cholesterol level results; no statistically significant changes in high-density lipoprotein levels were observed. Trials also reported significant reductions in platelet aggregation and mixed effects on blood pressure outcomes. No effects on glycemic-related outcomes were found. Proven adverse effects included malodorous breath and body odor. Other unproven effects included flatulence, esophageal and abdominal pain, allergic reactions, and bleeding.

Conclusions: Trials suggest possible small short-term benefits of garlic on some lipid and antiplatelet factors, insignificant effects on blood pressure, and no effect on glucose levels. Conclusions regarding clinical significance are limited by the marginal quality and short duration of many trials and by the unpredictable release and inadequate definition of active constituents in study preparations.

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AMERICAN CONSUMER use of complementary and alternative medicine is escalating rapidly. Out-of-pocket expenditures for herbal therapies are estimated at more than $5 billion per year in the United States alone.[1] Garlic (*Allium sativum*) is clearly one of the most popular herbal remedies worldwide today. Animal studies suggest that garlic has potential antilipidemic, antihypertensive, antiglycemic, antithrombotic, and antiatherogenic properties.[2-7] Although some small studies in humans corroborate the findings of animal studies, the results are often conflicting.[5,8-14] Several previous reviews summarize trials in humans, but they cite different original studies, emphasize single cardiovascular factors (eg, lipid levels or hypertension only), and provide variable attention to specific garlic preparations and constituents.[15-21]

Inabilities to blind subjects to the smell and taste of garlic as well as unpredictability in the release of potential active ingredients have limited clinical applicability of prior trial results. Some investigators have simply conducted nonblinded trials with various odor-containing garlic preparations. Others have used "odor-free" commercial preparations, such as dehydrated tablets (eg, Kwai, Lichtwer Pharmaceuticals, Berlin, Germany; Sapec, Lichtwer Pharmaceuticals; Pure-Gar Deodorized Garlic, Essentially Pure Ingredients, Chatsworth, Calif) and "aged garlic extract" (eg, Kyolic, Wakunage of America, Mission Viejo, Calif), or have instead compared garlic with matching odor- or taste-containing placebos. Dehydrated preparations are used most commonly and reportedly contain most constituents found naturally in whole garlic. Many

dehydrated preparations are further "standardized" according to particular constituents, most commonly to the compound S-allyl cysteine–S-oxide (alliin). Standardization to alliin is believed to provide a greater potential for liberation of the thiosulfinate compound allicin, which is produced enzymatically from alliin following hydration. Allicin has been shown in animal models to have significant antilipidemic potential.[22,23] Alternatively, aged garlic extract (Kyolic) is based on the content of S-allyl cysteine, as it is reportedly prepared by allowing more volatile compounds found in chopped garlic (eg, allicin) to slowly evaporate in the presence of aqueous alcohol. Throughout the remainder of this review, "standardized" will refer to commercial garlic preparations that are marketed by their potential to liberate a weight-based percentage of allicin after human consumption.

This systematic review will carefully scrutinize the internal validity of trials using oral garlic preparations, focus on the importance of differences among various preparations, and comprehensively summarize multiple reported cardiovascular-related effects and potential adverse effects of various oral garlic preparations.

MATERIALS AND METHODS

DATA SOURCES

English and non-English citations were identified from 11 electronic databases, references of pertinent articles, symposia, manufacturers, and experts. Electronic databases, including AMED, CISCOM, the Cochrane Library, EMBASE, MEDLINE, and NAPRALERT, were searched from January 1996 through July 1999 (depending on the database) using the following terms: "2-propenesulferic acid," "aglio," "ajo," "ajoene," "alisat," "allicin," "allinase," "*Allium sativum*," "allyl mercaptan," "diallyl disulphide," "diallyl sulfide," "diallyl sulphide," "dipropyl disulphide," "dipropyl sulphide," "garlic," "garlic extract," "garlic oil," "knoblauch," Kwai, Kyolic, "S-allyl cysteine," "thioallyl derivative," "thiosulfinates," and "vinyl dithiin." This search was updated on PubMed in February 2000.

STUDY SELECTION

Reports of effects on cardiovascular outcomes were limited to randomized controlled human trials, lasting at least 4 weeks, and comparing garlic with placebo, no garlic, or another active agent. Reports of adverse effects included any human study that identified adverse clinical symptoms or events associated with garlic exposure. From 1798 possible pertinent records, 2 independent reviewers (C.D.M. and V.A.L.) identified 45 randomized trials and 73 additional studies reporting adverse effects. One additional trial, available only in abstract form, was not reviewed.[24]

DATA EXTRACTION

Two independent physicians (R.T.A. and C.D.M.) abstracted data from trials, and one physician (L.M.) abstracted studies of adverse effects. Original authors were contacted and requested to provide information when data were unreported. No formal reliability tests of abstractions were conducted; disagreements were resolved by consensus (R.T.A., C.D.M., and L.A.).

DATA SYNTHESIS

Placebo-controlled randomized trials with lipid level outcomes were quantitatively pooled because (1) multiple small to moderate-sized studies with lipid level outcomes were available, (2) similar control groups were used, and (3) lipid level outcomes were measured using similar parameters at similar follow-up times. Standardized mean differences, adjusted for baseline differences, were used as the effect size measure rather than mean differences.[25,26] Effect sizes calculated as mean differences can be variably influenced by underlying population values when studies exhibit substantial heterogeneity at baseline; greater absolute effects are more likely, for example, to occur among patients with high baseline cholesterol levels than among those with lower baseline cholesterol levels.[26] We tried to identify outlier studies with Galbraith plots, a standard χ^2 test, and funnel plots. Studies were considered outliers if the χ^2 test was $P<.10$ and/or if they fell outside of the Galbraith or funnel plot.

Data were pooled using a random effects estimate both with and without studies that were identified as outliers.[27] (Results presented in the text are without outliers, while figures give results of both analyses.) Subgroup analyses were conducted for trials that (1) used similar dried standardized preparations of garlic, (2) enrolled subjects with hypercholesterolemia, and (3) used double-blind designs. A study that evaluated a garlic and fish oil combination was not pooled because of possible independent effects of fish oil on lipid levels. Effect sizes were converted to clinical laboratory units using the following weighted average pooled SDs: total cholesterol level, 1.05 mmol/L (40.8 mg/dL); low-density lipoprotein cholesterol level (LDL-C), 0.75 mmol/L (29.1 mg/dL); high-density lipoprotein cholesterol level (HDL-C), 0.29 mmol/L (11.4 mg/dL); and triglyceride levels, 0.97 mmol/L (85.9 mg/dL).

RESULTS

OVERVIEW OF TRIAL QUALITY

Randomized trials were published in scientific journals (n=37), symposia proceedings (n=5), a book chapter (n=1), a thesis (n=1), and an abstract (n=1; full report was obtained from the corresponding author). Details of randomization procedures were scant. Whether 2 trials were actually randomized was unclear; attempts to contact the original authors for clarification were unsuccessful.[28,29] Equivalencies between randomized groups for baseline lipid levels, blood pressure, body mass, diet, or activity levels were reported in 16 trials.[21,30-44]

Of 34 trials with double-blind designs, only one, which used an odor-free dehydrated tablet, assessed adequacy of blinding through direct questioning. Blinding was reportedly not successful.[33] Eight trials reported adverse effects clearly

attributable to garlic (ie, body odor, breath, or taste) that occurred significantly more frequently in garlic-treated subjects than in those receiving placebo; all of these trials used standardized dehydrated tablets.[21,33,39,40,43,45-47] Four trials specifically used a placebo with garlic odor or taste.[30,35,48,49] One of these, which involved a nonstandardized dehydrated preparation, reported that an insignificant number of subjects correctly guessed their assignment.[30]

Four trials had dropout rates that were 20% or greater.[40,43,50,51] Five excluded subjects from the statistical analysis due to insufficient compliance, protocol violations, or missed visits,[34,38-41] and 3 reported rates of compliance that were less than 80%.[21,50,52] Only 6 specifically conducted intention-to-treat analyses or reported no dropouts.[21,34,37,53,54]

INTERVENTION AND CONTROL GROUPS

Twenty-two studies evaluated dehydrated garlic preparations that were standardized to an alliin content of 1.3% of the weight of active powder within each tablet (**Table 1**).* Other preparations were standardized to a minimum release of 0.3% allicin,[62] and 4.6 mg of alliin per tablet.[45] The remainder used various nonstandardized preparations alone,† or in combination with either fish oil, hawthorn, soya lecithin, gingko biloba, or other lesser ingredients.[35,37,41,67,68] Compliance of preparations with gastrointestinal dissolution standards were rarely reported.[46]

Placebos were used as control comparisons except for a no-garlic control,[65] an antilipidemic agent,[34] an antihypertensive agent,[59] and a head-to-head comparison of 2 different garlic preparations.[57] Ten studies specified low-fat, low-cholesterol, high-fiber diets.‡ Other studies defined no specific dietary measures and generally allowed usual diets. Seven trials reported no changes in diet during follow-up,[30,33,42,44,47,49,52] 15 reported no changes in body mass,§ and 2 reported no changes in physical activity.[30,52] Trials used various lipid measurement protocols; a few clearly followed current suggested guidelines.[21,30,42,44,45,58]

TRIAL OUTCOMES

Antilipidemic Effects

Meta-analyses of placebo-controlled trials that reported total cholesterol level outcomes at 4 to 6 weeks, 8 to 12 weeks, and 20 to 24 weeks are shown in the **Figure**. Combining all studies regardless of garlic preparation showed that compared with placebo the total cholesterol level was reduced on average by 0.19 mmol/L (7.2 mg/dL) (95% confidence interval [CI], 0.03-0.34 mmol/L [1.2-13.15 mg/dL]) after 4 to 6 weeks of therapy (n=14) and 0.44 mmol/L (17.1 mg/dL) (95% CI, 0.32-0.57 mmol/L [12.37-22.04 mg/dL]) after 8 to 12 weeks (n=24). Studies evaluating standardized dehydrated garlic preparations revealed average reductions of 0.26 mmol/L (10.2 mg/dL) (95% CI, 0.08-0.45 mmol/L [3.09-17.40 mg/dL]) after 4 to 6 weeks (n=8) and 0.50 mmol/L (19.2 mg/dL) (95% CI, 0.34-0.66 mmol/L [13.15-25.52 mg/dL]) after 8 to 12 weeks (n=12). Average reductions after 20 to 24 weeks of treatment were not statistically significant (all garlic preparations [n=6]: 0.03 mmol/L (1.2 mg/dL) 95% CI, −0.21 to 0.28 mmol/L (−8.12 to 10.83 mg/dL); standardized dehydrated garlic preparations only [n=3]: 0.07 mmol/L (2.8 mg/dL) (95% CI, −0.22 to 0.37 mmol/L (−8.51 to 14.31 mg/dL).

At 8 to 12 weeks, average triglyceride level reductions from placebo-controlled trials, regardless of garlic preparation type (n=17), were 0.21 mmol/L (19.1 mg/dL) (95% CI, 0.09-0.34 mmol/L [3.48-13.15 mg/dL]); average reductions among trials evaluating standardized dehydrated garlic tablets (n=13) were 0.24 mmol/L (21.1 mg/dL) (95% CI, 0.09-0.38 mmol/L [3.48-14.69 mg/dL]). At 8 to 12 weeks, average LDL-C level reductions across all garlic preparation types (n=13) were 0.16 mmol/L (6.2 mg/dL) (95% CI, 0.02-0.30 mmol/L [0.77-11.6 mg/dL]), and standardized dehydrated garlic tablets alone (n=10) were 0.17 mmol/L (6.7 mg/dL) (95% CI, 0-0.34 mmol/L [0-13.15 mg/dL]). At 8 to 12 weeks the average HDL-C level *reduction* from all garlic preparations combined (n=14) was 0.02 mmol/L (0.9 mg/dL) (95% CI, −0.03 to 0.07 mmol/L [−1.2 to 2.70 mg/dL]), whereas reduction from standardized dehydrated garlic preparations (n=10) was 0.01 mmol/L (0.2 mg/dL) (95% CI, −0.05 to 0.06 mmol/L [−1.93 to 2.32 mg/dL]). Analyses limited to trials with only subjects with hyperlipidemia or that used double-blind methods did not vary significantly from those presented earlier.

The only head-to-head trial compared a standardized dehydrated preparation (Kwai) to garlic oil (Hoefels Original Garlic Oil with Rutin; Seven Seas Limited, Marfleet Hull, England). This unblinded trial found a statistically significant reduction in LDL-C level, but not total cholesterol or HDL-C level, favoring the dehydrated preparation after 4 months of therapy.[57] The one trial that compared a commercial antilipidemic agent (bezafibrate) with a garlic preparation (Kwai) found no differences in lipid level outcomes after 3 months of therapy.[34]

Antihypertensive Effects

Of 30 trials measuring blood pressure outcomes, 23 reported results from placebo comparisons (3 did not report results[29,39,43]; 4 used nonplacebo controls[34,57,59,60]). Three trials focused on subjects with hypertension and studied blood pressure as the primary outcome.[55,59,60] Seven clearly excluded use of additional antihypertensive agents.[32,33,47,55-57,67] Although several trials reported significant reductions in blood pressure among subjects given garlic (within group comparisons), only 3 demonstrated statistically significant reductions in diastolic blood pressure (range, 2%-7%),[33,54,55] and 1 in systolic blood pressure (approximately 3%)[33] between persons given garlic and those given placebo. These data were not pooled because about

*References 9, 21, 32-34, 38-40, 43, 44, 46, 47, 51, 52, 54-61.

†References 28-33, 36, 42, 48-50, 53, 57, 63-66.

‡References 21, 34, 44, 45, 47, 50, 52, 56, 58, 62.

§References 9, 30, 33-35, 38, 42, 44, 47, 49-52, 56, 58.

Table 1. All Randomized Trials With Serum Lipid Endpoints of 4 Weeks or Longer Comparing Garlic to Placebo or Other Therapy

Source, y	Sample Size (N)	% of Male Subjects	Mean Age (Range), y	Recruitment Setting	Characteristics of Subjects*	Randomization Process†
Adler and Holub,[32] 1997	25	100	46	Unclear	Hyperlipidemia	Unclear
Auer et al,[65] 1990	47	45	58	11 General practices	Hypertension; 45% of the subjects had a total cholesterol level >6.46 mmol/L	Unclear
Barrie et al,[48] 1987	20	Unclear	26	Student volunteers	All previously healthy; total cholesterol levels ranged from 3.36-6.98 mmol/L	Unclear
Berthold et al,[49] 1998	26	54	58	Community volunteers	Hyperlipidemia	Probably adequate
Bordia et al,[64] 1981	25	100	55	Unclear	Known coronary artery disease; hyperlipidemia	Unclear
Bordia,[29] 1989	432	Unclear	Not given	Unclear	History of myocardial infarction	Unclear (potentially inadequate)
Bordia et al,[28] 1998	60	Unclear	Not given	Unclear	History of myocardial infarction	Unclear (potentially inadequate)
Buhaihan et al,[66] 1979	25	100	(18-35)	Unclear	Hyperlipidemia	Unclear
Chutani and Bordia,[50] 1981	30	Unclear	50	Unclear	Ischemic heart disease	Unclear
Czamy and Samochowiec,[67] 1996	100	65	55	Unclear	Hyperlipidemia; atherosclerotic disease; and hypertensive	Unclear
Gardner et al,[30] 1999	58	51	52	Unclear	Hyperlipidemia	Unclear
Holzgartner et al,[34] 1992	98	39	57	5 General practices	Hyperlipoproteinemia types IIa, IIb, or IV; 35% of the subjects had hypertension	Probably adequate
Isaacsohn et al,[68] 1998	50	54	58	Specialty clinic	Hyperlipidemia	Probably adequate
Jain et al,[5] 1993	42	45	52	Community volunteers	Hyperlipidemia	Unclear
Kandziora,[52] 1988	40	Unclear	(43-65)	Unclear	Hypertension; hyperlipidemia	Unclear
Kandziora,[69] 1988	40	88	56	Unclear	Hypertension; hyperlipidemia	Unclear
Kannar,[40] 1998	46	54	(30-74)	Community volunteers	Hyperlipidemia; no diabetes mellitus	Adequate
Kenzelmann and Kade,[35] 1993	46	33	43	Volunteers and 4 general practices	Hyperlipidemia	Probably adequate
Kiesewetter et al,[32] 1991	60	30	24	Volunteers	Elevated spontaneous platelet aggregation	Unclear
Kiesewetter et al,[40] 1993	80	67	60	Unclear	Peripheral vascular disease; hyperlipidemia	Unclear
Koscielny et al,[43] 1999	280	71	60	Unclear	Asymptomatic advanced atherosclerosis; hyperlipidemia; and 38% of the subjects had hypertension	Unclear
Lash et al,[33] 1998	85	49	45	Unclear	Hyperlipidemia; all after renal transplantation	Unclear
Lau et al,[36] 1987‖						
1	32	56	52	Community or clinic volunteers	Hyperlipidemia; 44% of the subjects were vegetarians	Unclear
2	14	56	26	Community or clinic volunteers	Normolipidemia; 57% of the subjects were vegetarian	Unclear

Intervention (Daily Garlic Dosage)‡	Control Group	Double-blind Study	Endpoints§					Trial Length, wk	% of Dropouts per Group
			Clinical Symptoms	Lipid Levels	Blood Pressure	Glucose Level	Thrombotic State		
Dehydrated tablet: Kwai (900 mg)	Placebo	Yes		X	X			12	Garlic treated, 8; placebo, 8
Dehydrated tablet: Kwai (600 mg)	Placebo	Yes		X	X	X		12	Unclear
Oil macerate (18 mg)	Placebo	Yes		X	X		X	4‖	Unclear
Garlic distillate: Tegra (5 mg)	Placebo	Yes		X				12‖	Pooled, 4
Garlic ether extract (0.25 mg/kg of body weight)	Placebo	Yes		X				48	Pooled, 9
Garlic ether extract (6-10 g)	Habitual coronary therapy	Unclear	X	X	X			156	Unclear
Garlic ether extract (1 g)	Placebo	Unclear		X		X	X	13	Unclear
Raw garlic (10 g)	No garlic treatment	No		X				8	Unclear
Raw or fried garlic	No garlic treatment	No					X	4	Unclear
A combination of oil macerate, soya lectin, hawthorn oil, and wheat germ (400 mg)	Placebo	Yes	X	X	X	X	X	16	Unclear
Dehydrated tablet: (500 mg and 1000 mg)	Placebo	Yes		X	X			12	Garlic treated, 4; placebo, 0
Dehydrated tablet: Kwai (900 mg)	Antilipidemic	Yes		X	X			12	0 (4% Excluded for protocol violations)
Dehydrated tablet: Kwai (900 mg)	Placebo	Yes		X	X			12	Garlic treated, 14; Placebo, 18
Dehydrated tablet: Kwai (900 mg)	Placebo	Yes		X	X	X		12	Unclear
Dehydrated tablet: Kwai (600 mg)	Placebo	Yes		X	X	X		12	Unclear
Dehydrated tablet: Kwai (600 mg)	Antihypertensive	Single		X	X	X		12	Unclear
Dehydrated tablet: Garlic 100 (680 mg)	Placebo	Yes		X	X			12	Garlic treated, 9; placebo, 4
Dehydrated tablet with ginkoba extract: Allium Plus (200 mg)	Placebo	Yes		X				8	Garlic treated, 4; placebo, 9
Dehydrated tablet: Kwai (600 mg)	Placebo	Yes		X	X	X	X	4	Unclear
Dehydrated tablet: Kwai (600 mg)	Placebo	Yes	X	X	X		X	12	Garlic treated, 20; placebo, 20
Dehydrated tablet: Kwai (900 mg)	Placebo	Yes		X	X	X	X	208	Garlic treated, 40; placebo (at 6 mo), 21
Dehydrated tablet: Pure-Gar (1360 mg)	Placebo	Unclear		X				12	Unclear
Aged garlic extract: Kyolic (4 mL of extract = 1000 mg)	Placebo	Unclear		X				26	Garlic treated, 6; placebo, 25
Aged garlic extract: Kyolic (4 mL of extract = 1000 mg)	Placebo	Unclear		X				26	Unclear

(Continued)

Table 1. All Randomized Trials With Serum Lipid Endpoints of 4 Weeks or Longer Comparing Garlic to Placebo or Other Therapy (cont)

Source, y	Sample Size (N)	% of Male Subjects	Mean Age (Range), y	Recruitment Setting	Characteristics of Subjects*	Randomization Process†
Luley et al,[53] 1986‖						
1	34	Unclear	Not given	Unclear	Hyperlipoproteinemia types IIa, IIb, or IV	Unclear
2	51	Unclear	Not given	Unclear	Hyperlipoproteinemia types IIa, IIb, or IV	Unclear
Lutomski,[41] 1984	102	49	52	Unclear	Nonspecific functional complaints; 44% of the subjects had hypertension and normolipidemia	Unclear
Mader,[60] 1990	261	44	59	Community clinic	Hyperlipidemia; 47% of the subjects had hypertension	Probably adequate
Mansell et al,[46] 1996	60	77	63	Unclear	All subjects had type 2 diabetes mellitus	Unclear
McCrindle et al,[52] 1998	31	52	14	Specialty clinic	Hyperlipidemia; family history of high lipid levels; and early coronary artery disease	Probably adequate
Melvin,[51] 1996	34	47	54	Volunteers	Hyperlipidemia	Unclear
Morcos,[59] 1997	40	58	53	Community clinic volunteers	Hyperlipidemia	Unclear
Neil et al,[21] 1996	115	61	59	Community clinic	Hyperlipidemia; obesity	Adequate
Piengvidhya et al,[43] 1988	30	47	49	Unclear	Hyperlipidemia	Unclear
Rotzsch et al,[61] 1992	24	42	37	Unclear	HDL-C2 level: <0.26 mmol/L, men; <0.39 mmol/L, women	Unclear
Santos and Grunwald,[56] 1993	60	39	52	Community clinic	Hyperlipidemia	Unclear
Santos and Jones,[57] 1995	80	35	57	Single specialist practice	Hyperlipidemia	Unclear
Saradeth et al,[58] 1994	72	31	39	Community volunteers	Hyperlipidemia	Unclear
Simons et al,[47] 1995	91	53	54	Community volunteers	Hyperlipidemia	Unclear
Sitprija et al,[31] 1987	40	33	50	Outpatient clinic	All subjects had diabetes mellitus without complications	Unclear
Steiner,[50,66] 1996	52	100	(32-68)	Unclear	Hyperlipidemia	Unclear
Superko and Krauss,[44] 2000	50	Unclear	53	Unclear	Hyperlipidemia	Unclear
Ventura et al,[62] 1990	40	38	59	Community volunteers	Hyperlipidemia; peripheral vascular disease	Unclear
Vorberg and Schneider,[54] 1990	40	43	50	Community clinic	Hyperlipidemia	Unclear
Yeh et al,[42] 1997	84	100	48	Collegiate community	Hyperlipidemia	Unclear

*To convert the total cholesterol high-density lipoprotein cholesterol-subfraction 2 (HDL-C2) levels to milligrams per deciliters, multiply by 0.02586.

†The randomization process was classified as follows: unclear, probably adequate, and adequate. Unclear indicates that the process was not described in significant enough detail to ensure adequacy. Probably adequate indicates the use of sealed envelopes but not sequentially numbered or opaque; list of random numbers read by someone enrolling the subject into the trial (open list); description suggests adequate concealment but other features such as markedly different characteristics among intervention and control groups are suspicious. Adequate indicates centralized randomization by telephone; randomization scheme controlled by pharmacy; numbered or coded identical containers administered sequentially; on-site computer system that can only be accessed after entering the characteristics of an enrollee; and sequentially numbered, sealed, and opaque envelopes.

‡The manufacturers of the garlic products mentioned in this column are as follows: Kwai, Lichtwer Pharmaceuticals, Berlin, Germany; Tegra, Hermes Pharmaceuticals, Munich, Germany; Garlic 100, Cotter Foods, Melbourne, Australia; Allium-Plus, Zeller AG, Romanshorn, Switzerland; Pure-Gar Deodorized Garlic, Essentially Pure Ingredients, Chatsworth, Clif; Kyolic, Wakunaga of America, Mission Viejo, Calif; Ilja Rogoff Garlic Tablets with Rutin, Woelm Pharmaceuticals GmbH & Company, Eschwege, Germany; LipoGuard, Viva America Incorporated, Costa Mesa, Calif; and Fitoaglio, Farmaceutici Procemsa, Torino, Italy.

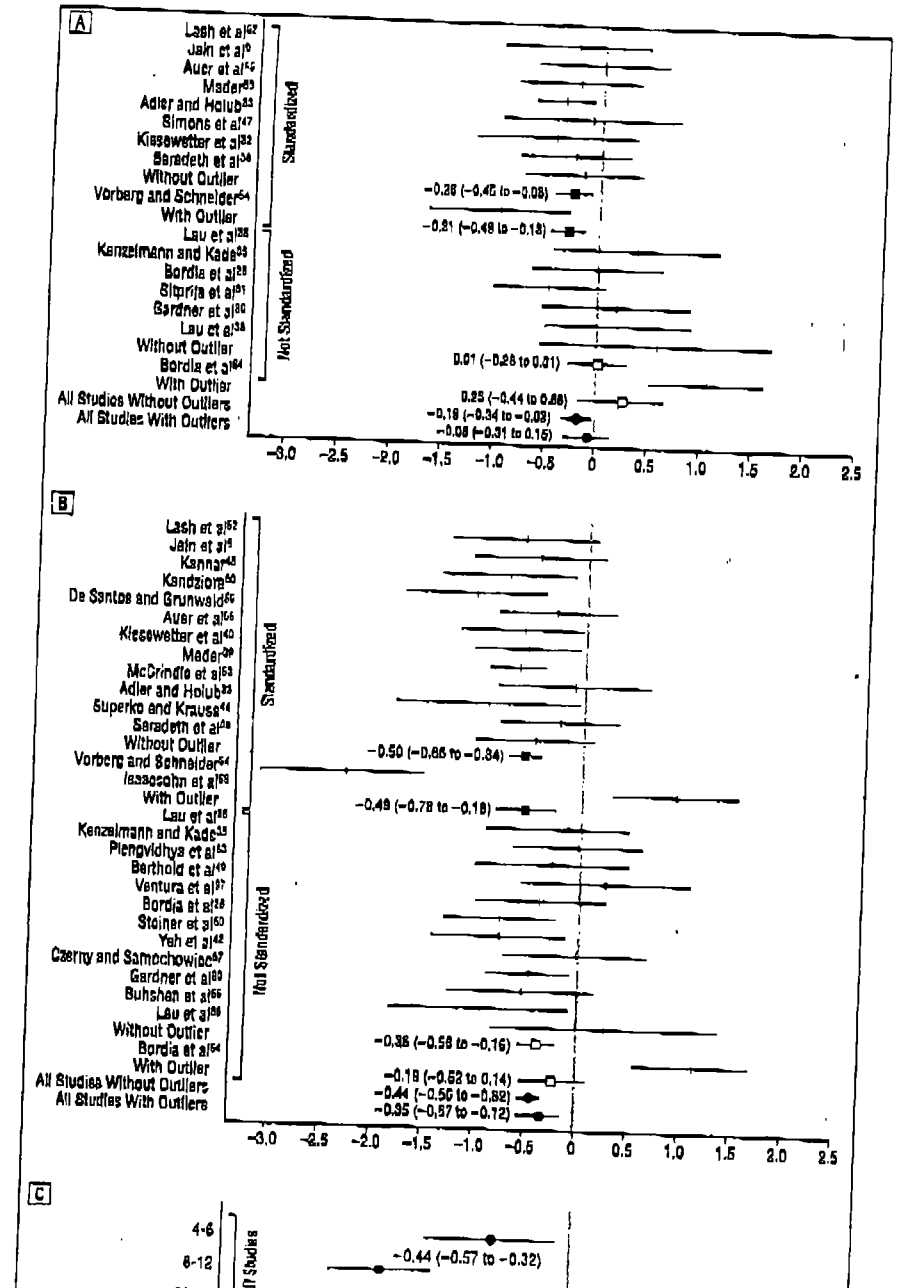
§An X indicates that that particular outcome was reported by the original authors.

‖Publication contained 2 distinctly different studies presented in a single publication; therefore, the same reference has been assigned.

¶This was a crossover study.

#These were clearly stated to not be commercial tablets.

Intervention (Daily Garlic Dosage)‡	Control Group	Double-Blind Study	Endpoints§					Trial Length, wk	% of Dropouts per Group
			Clinical Symptoms	Lipid Levels	Blood Pressure	Glucose Level	Thrombotic State		
Dehydrated tablet (594 mg)	Placebo	Yes		X	X	X		6‖	0
Dehydrated tablet (1350 mg)	Placebo	Yes		X	X	X	X	6‖	0
Dehydrated tablet/other: Ilja Rogoff Garlic Tablets with Rutin (300 mg)	Placebo	Yes		X	X			12	Pooled, 5 (15% excluded for protocol violations)
Dehydrated tablet: Kwai (800 mg)	Placebo	Yes		X	X			16	Garlic treated, 4; placebo, 7 (10% excluded for protocol violations)
Dehydrated tablet: Kwai (900 mg)	Placebo	Unclear		X	X	X		12	Unclear
Dehydrated tablet: Kwai (900 mg)	Placebo	Yes		X	X		X	8	Pooled, 3
Dehydrated tablet: Kwai (900 mg)	Placebo	Yes		X				4¶	Pooled, 44 (excluded for protocol violations)
Dehydrated tablet with fish oil: LipoGuard (1200 mg)	Placebo	Single		X				4¶	Unclear
Dehydrated tablet: Kwai (900 mg)	Placebo	Yes		X				24	Pooled, 8
Dehydrated tablet (700 mg)#	Placebo	Yes		X				6¶	Unclear
Dehydrated tablet: Kwai (900 mg)	Placebo	Yes		X				6	Unclear
Dehydrated tablet: Kwai (900 mg)	Placebo	Yes		X	X			24	Garlic treated, 17; placebo, 10
Dehydrated tablet: Kwai (600 mg)	Garlic oil: Hoefels Original Garlic Oil (1.98 mg/d)	No		X	X			16	Tablet treated, 10; oil treated, 15
Dehydrated tablet: Kwai (600 mg)	Placebo	Yes		X	X			15	Garlic treated, 1; placebo, 4 (22% excluded for incomplete data)
Dehydrated tablet: Kwai (900 mg)	Placebo	Yes		X	X			12¶	Pooled, 6
Dehydrated tablet (700 mg)#	Placebo	Yes		X		X		4	Garlic treated, 15; placebo, 20
Aged garlic extract: Kyolic (7200 mg)	Placebo	Yes		X	X			26¶	21 (cumulative)
Dehydrated tablet: Kwai (900 mg)	Placebo	Yes		X	X			12	Unclear
Dehydrated tablet, hawthorn, and other: Fitoaglio (450 mg)	Placebo	Yes		X	X			8	0
Dehydrated tablet: Kwai (900 mg)	Placebo	Yes		X	X			16	0
Aged garlic extract: Kyolic (7200 mg)	Placebo	Yes		X	X			22	Pooled, 6



Forest plot of studies with total cholesterol level results at 4 to 6 weeks (A) and at 8 to 12 weeks (B). C, Forest plot of pooled results of total cholesterol level findings at different periods. All Forest plot levels are measured in millimoles per liter. To calculate the conventional units of milligram per deciliter for the total cholesterol levels multiply by the conversion factor of 38.67. The numbers in parentheses indicate 95% confidence intervals for the pooled standardized mean differences (in millimoles per liter). The minus signs indicate that these levels were reduced relative to placebo changes over the intervention period. Solid squares indicate those studies using standardized preparations; open squares, those studies using nonstandardized preparations; and solid circles, all preparations together.

half of the studies did not present numerical data that could be used in a quantitative analysis, multiple different methods of blood pressure measurement were used, and few studies had a priori hypotheses related to blood pressure.

Antiglycemic Effects

Twelve trials assessed the effect of garlic on the serum glucose level.* Two studied adults with diabetes mellitus and considered serum glucose level as a primary outcome.[31,46] Only one 4-week trial, conducted in nondiabetic persons, reported a statistically significantly greater reduction in the serum glucose level with standardized dehydrated garlic tablets (Kwai) compared with placebo.[32] No statistically significant effects were reported for glycosylated hemoglobin,[46] serum insulin and C-peptide levels,[46] and responsiveness of serum insulin levels to an oral glucose challenge.[31]

Antithrombotic Effects

Ten trials assessed the effectiveness of garlic on potential prothrombotic risk factors.† Of 6 of these 10 trials measuring effects on spontaneous platelet aggregation, 5 provided results[32,40,48,67,69]; 4 of these 10 trials, all prohibiting intake of additional antiplatelet medications, reported modest but significant decreases in platelet aggregation with garlic treatment compared with placebo,[32,40,48,67] and the other reported significant decreases in epinephrine-induced, but not adenosine diphosphate–induced, platelet aggregation.[69] Mixed effects on fibrinolytic activity[28,53,66] and plasma viscosity were reported, while no trials assessing serum fibrinogen levels[28,32,52,53] or serum homocysteine levels[52] reported significant results.

Effects on Cardiovascular Morbidity and Mortality

Clinical trial data for cardiovascular morbidity outcomes are limited. Two trials assessed improve-

*References 9, 28, 31, 32, 43, 46, 53, 55, 59, 60, 67.

†References 28, 32, 40, 43, 48, 52, 53, 66, 67, 69.

Table 2. Su / of / Effects

Adverse Effect	Type of Garlic Exposure	Level of Evidence
Breath or body odor	Oral use of standardized dehydrated tablet	Randomized controlled trials
Skin manifestations: contact dermatitis, ulcerus necrotic lesions; and blisters, bullae, and vesicles	Oral use for 1 case of contact dermatitis; topical use for the remaining lesions	Case series and multiple case reports with resolution of lesions after discontinuation of garlic treatment; no rechallenge tests
Allergic manifestations: asthma, rhinitis, conjunctivitis, urticaria, and anaphylaxis; angioedema	Oral use for 1 case of asthma and rhinitis; garlic dust inhalation for the remaining cases	Case series and multiple case reports with resolution of symptoms after discontinuation of garlic treatment; positive rechallenge test results for asthma
Cardiovascular dysfunction: myocardial infarction	Oral use	1 Case report
Coagulation dysfunction: postoperative bleeding, spontaneous spinal epidural hematoma, increased International Normalized Ratio, clotting time prolongation, and failure of platelet aggregation test	Oral use	Case reports
Gastrointestinal tract dysfunction: small-intestine obstruction, epigastric and esophageal pain, and flatulence; hematemesis and hematochezia	Oral use	Case reports and case series
Other: Meniere disease	Oral use	Case report

ment in pain-free walking distance in subjects with lower extremity peripheral vascular disease treated with garlic vs placebo.[40,67] Although the authors of one trial reported significant increases in the walking distance with standardized dehydrated tablets (Kwai), there was a 20% dropout rate with no intention-to-treat analysis, significant disparities in the reporting of a garlic taste between garlic-treated and placebo groups that suggested possible inadequate blinding, and a reanalysis using baseline walking distances from the time of randomization rather than during a run-in phase no longer yielded significant results.[40] The second trial reported statistically significant increases in pain-free walking but used a garlic oil macerate–soya lecithin–hawthorn oil–wheat germ oil combination, making it difficult to assess the independent effect of garlic on this end point.[67]

One 3-year trial assessing reinfarction rates in 432 patients with evidence of a prior myocardial infarction reported 11 deaths and 15 reinfarctions in 222 subjects randomized to a garlic extract (0.1 g/kg per day for body mass) and 20 deaths and 22 reinfarctions in the 210 placebo recipients.[29] Although the author reported significant differences, reanalysis of between-group comparisons using a χ^2 test revealed no statistically significant differences in total mortality ($P=.07$) or myocardial infarction ($P=.13$). The trial was not published in peer-reviewed literature, and details of randomization processes, blinding, and handling of dropouts could not be obtained despite attempts to contact the original author.

Original authors of a placebo-controlled trial with standardized dehydrated tablets (Kwai) involving 280 subjects have reported statistically significant ($P<.001$) regression in atherosclerotic plaque volume over 48 months.[43] As of February 2000, the authenticity of this trial was under investigation owing to concerns regarding the validity of the ultrasound images accompanying the published text, unsuccessful randomization procedures, an unusually high (46%) unequal dropout rate, and inappropriate analyses.[70]

Adverse Effects

Approximately half of the trials reported adverse effects. Of those reporting adverse effects, 8 reported significantly greater numbers of subjects assigned garlic treatment had malodorous breath or body odor (as perceived by themselves or others) compared with subjects assigned placebo.[21,33,39,40,43,45-47] The other trials that reported adverse effects stated that persons assigned to dehydrated garlic tablets self-reported malodorous breath or body odor, abdominal pain, fullness, anorexia, or flatulence, but had too few numbers to statistically compare differences between groups. In addition to the trials, 73 further studies were found that addressed adverse effects (**Table 2**). Most (97%) were case reports or small case series. Reported adverse effects of garlic ingestion (dietary and supplements) were dermatitis, rhinitis, Meniere disease, asthma, myocardial infarction, bleeding, epidural hematoma, increased International Normalized Ratio in persons taking warfarin sodium, small-intestine obstruction, esophageal and abdominal pain, and flatulence. The frequency of adverse effects and whether they varied by particular preparations were not studied.

COMMENT

Although inconclusive, randomized controlled trial data are compatible with the hypothesis that garlic supplementation may produce mild short-term benefits on the levels of total cholesterol, triglycerides, and LDL-C, and on platelet aggregation. Several small short-term trials show mixed, but never large, effects of garlic on blood pressure outcomes, and no effects on glycemic-related outcomes. Given the overall marginal quality of many trials with respect to adequacy of randomization and blinding, as well as an inadequate definition of the specific biologically active garlic constituents in tested preparations, these results have limited clinical applicability. Although multiple adverse effects of garlic ingestion have been

reported, causality is established only for malodorous breath and body odor. The most serious potential adverse effect that has been cited is spontaneous epidural bleeding. The expected frequency of adverse effects, whether they are "dose-related," and whether they are specific to or occur more commonly with particular garlic preparations than others are unclear.

Few trials clearly reported error-free randomization procedures. Blinding of subjects was impossible in many trials that evaluated odor-producing preparations, and several double-blind trials that used odor-free coated preparations still reported adverse effects discernable to subjects that were clearly attributable to garlic. The inability to adequately blind subjects may have led to systematic overestimation or underestimation of garlic's effects. For example, it is possible that true putative health benefits of ingesting garlic are attributable to the presence, concentration, and form of its many sulfur-containing compounds. These sulfur-containing compounds generate the unique taste and odor of garlic. Studies of garlic treatment that successfully blind subjects to group assignments may be using garlic products that not only have undetectable taste and odor but that also have low levels of active sulfur-containing compounds. If benefits are tied to sulfur-containing compounds, such studies might underestimate them.

Concealment of random allocation from investigators, blinding of subjects, and proper handling of missing data are the only quality variables that have been empirically shown to affect trial outcomes.[71] Because of unclear adequacy of double-blinding techniques and because very few trials performed intention-to-treat analyses or reported no dropouts, distinguishing higher-quality trials was infeasible for performing sensitivity analyses. These methodological limitations affect the clinical relevance of even statistically significant results and further limit the use of attempting to rationalize the significance of trends in the pooled data analyses.

Several issues related to the intrinsic qualities of garlic further complicate interpretation of current human studies. First, there is no universal consensus regarding exactly which constituents of garlic have major effects on particular cardiovascular risk factors in vivo and by what mechanism these effects are achieved. Second, the relative ingredient content of whole garlic is affected by growth conditions such as soil composition. Finally, variation in the methods of preparing particular garlic preparations results in significant differences in final composition. For instance, crushing or cutting whole garlic commingles the ingredient alliin with an enzyme, allinase, resulting in liberation of allicin, which is believed by most garlic researchers to be the major ingredient responsible for potential antilipidemic effects. The herbal industry is unable to guarantee allicin content within tablets because of limitations in the stability of this compound. Most allicin-based preparations are, therefore, designed to generate allicin enzymatically from alliin after ingestion. Although commercial tablets are standardized to fixed amounts of alliin and allinase with the intention of maximizing allicin production after consumption, allinase quickly denatures at low gastric pHs. Maximal allicin release, therefore, depends not only on high alliin concentration and alliinase activity in the tablet, but also protection of allinase from gastric acid pH followed by rapid tablet dissolution in enteric pH. Despite the addition of tablet coatings to prevent premature dissolution, most preparations have not been systematically tested against *US Pharmacopeia* methods for compliance with enteric-coating standards. Notably, differential liberation of allicin from otherwise identical standardized dehydrated garlic tablets, produced by the same manufacturer but in differen batches, has been demonstrated.[72] This variability in allicin liberation, despite standardization, has recently been suggested to correlate with variability in antilipidemic effects among many recent trials using particular standardized dehydrated garlic tablet preparations.[73]

Additionally, although several trials reported equivalent baseline body mass, diet, or activity level between groups, few assessed whether these factors remained matched throughout the trial intervention. The presence of confounding effects is supported by several trials that reported significant,[39,40] or a trend toward significant,* benefit from placebo administration alone. Even accounting for regression to the mean, some investigators argue such effects are more likely attributable to unanticipated cointerventions or poor control for bias than true placebo effects.[74-76] Several trials used volunteer subjects who may potentially be seeking lifestyle modifications for poor baseline dietary and activity habits. Studying such populations could increase the perception of beneficial short-term effects simply as a result of drift toward a more average lifestyle during the intervention period—an effect that may be greater in a motivated group that is aware of receiving a presumably beneficial study medication.[74,75]

Pooled analyses of trials do show reductions in the total cholesterol level at 4 to 6 weeks with trends toward further reductions at 8 to 12 weeks, although this trend did not persist at 20 to 24 weeks. Despite several possible explanations for these trends, the marginal statistical significance of observed short-term benefits and the generalized methodological shortcomings of trials make further conjecture unwarranted. Pooled analyses also suggest that standardized dehydrated preparations may result in greater mean short-term (4-12 weeks) cholesterol level reductions than other preparations, but this difference is neither clinically (approximately 0.12-0.26 mmol/L [5-10 mg/dL]) nor statistically ($P>.10$) significant. Absence of a significant disparity between preparations believed to contain distinctly different ingredients might generally suggest that there is a common active constituent among all preparations or that reported results are actually due to something other than garlic itself, such as an unmeasured lifestyle modification. Alternatively, it is also possible that the expected differences in ingredient availability after ingestion were minimized by in-

*References 9, 28, 36, 37, 48, 51, 54-56, 58, 59, 63, 68.

advertent selection of particular preparations that have been shown to have substantially limited capabilities of liberating allicin under gastrointestinal conditions.

Studies with significant results, written in English, or funded by pharmaceutical companies historically have been more likely to be published.[77] Of 45 randomized trials in our analysis, 36 (80%) were published in peer-reviewed journals, 38 (84%) were published in the English language only, and 35 (78%) were sponsored, to some degree, by herbal manufacturers. Although we believe our search was comprehensive, and significant efforts were made to retrieve unreported data from investigators, the potential for missing data and publication bias in our review is still real.

CONCLUSIONS

One of the most readily apparent problems with human research about the effects of garlic treatment is inadequate definition of biologically active constituents and predictable availability of these constituents after ingestion. Delineating major active ingredients and their mechanisms of action are essential before conducting more trials. Although studies in humans report promising potential lipid-lowering and antithrombotic benefits, they are limited by unclear randomization procedures, short durations, and unclear adequacy of blinding to treatment administration and outcome assessments. Further studies with similar design features are useless. Rather, a few well-designed trials of longer duration are warranted. Such trials should detail a clear and unbiased recruitment and selection process, a clearly adequate randomization procedure, and assessment of the successfulness of blinding techniques. Additional emphasis on controlling cointerventions that can affect outcomes, clearly defining the constituents and dissolution properties of garlic preparations being studied, and using intention-to-treat analyses are also necessary.

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For Pharmacology Master File

- Govt does studies / NTP
(support)
Abbreviated NDA

- Retain OTC status
but can identify uses in labeling

→ Companies reference Drug Master File

- Provide language for those who go through the process

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Notices

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Notice 2	Information regarding the NCCAM's guidelines for investigator-initiated applications.
Notice 3	Information on expanding the use of the Modular Grant Application and Award.

Current RFAs

Title	RFA	Letter of Intent Receipt Date	Application Receipt Date
NCCAM Institutional Research Training Program (T32) for Minority Researchers	AT-01-003	04/16/01	05/14/01

This NRSA RFA will fund research training at minority and minority-serving institutions for individuals who are training for careers in biomedical, behavioral and clinical research related to complementary and alternative medicine (CAM).

Complementary/Alternative Medicine (CAM) at the End of Life for Cancer and/or HIV/AIDS	AT-01-01	02/26/01	04/12/2001

The primary objective of this initiative is to identify and evaluate CAM interventions for patients with advanced, terminal disease associated with cancer or HIV/AIDS. This research is expected to generate scientific knowledge on complementary and alternative medicine (CAM) therapies that will ultimately lead to improved care and quality of life for individuals at the end of life. Possible patient outcomes would include:

1. Managing or reducing the symptoms associated with the conditions of end stage disease for cancer and HIV/AIDS;
2. Preventing or reducing side effects of medications such as antiretrovirals, steroids and chemotherapy/radiotherapy; and
3. Enhancing the psychological, social, spiritual well-being, and quality of life at the end of life.

RFA Archive

Title	RFA	Letter of Intent Receipt Date	Application Receipt Date
Integration of Complementary and Alternative Medicine: A Health Services Research Perspective	AT-01-01	12/08/2000	01/24/2001
	The intent of this RFA is to 1) identify barriers and facilitators to the integration of CAM and conventional health care practices; 2) determine whether CAM research results obtained from studies conducted under ideal conditions (efficacy studies) can be translated to real-world settings (i.e., effectiveness) within an integrated model; and 3) support the evaluation of currently planned or recently initiated programs, goals of which are to improve the outcomes, quality, effectiveness, and/or cost-effectiveness of health care through the integration of CAM and conventional health care.		
Botanical Drug Interactions	AT-00-004	11/10/00	01/12/01
	The main objective of this initiative is to encourage biomedical research in order to prevent adverse botanical/drug interactions during therapy or anesthesia, to establish possible synergistic combinations of botanicals with pharmaceutical drugs, and to increase our knowledge of the mechanisms of action of botanicals.		
Exploratory Program Grants for Frontier Medicine Research	AT-00-002	08/07/00	11/14/00
	This NCCAM initiative will establish Exploratory Program Grants for Frontier Medicine Research, the purpose of which will be to create an infrastructure to nurture and therefore advance this field of biomedical research by providing the institutional support and resources necessary for rigorous scientific investigation.		
Botanical Products Development: SBIR and STTR	AT-00-003	09/07/00	11/14/00
	The purpose of this Request for Applications (RFA) is to support projects that could lead to development of appropriate standardized products (valerian root, feverfew, echinacea, and milk thistle) and provision of a reliable constant supply of these products for clinical research, as well as basic research.		

Global Network for Women's and Children's Health Research	HD-00-007	04/14/00	07/13/00

The purpose of this solicitation is to establish an innovative and flexible research network that will be responsive to the most critical existing and emerging health needs and public health problems of women and children, globally.

Centers for Dietary Supplement Research: Botanicals	OD-00-004	03/25/00	04/25/00

The Office of Dietary Supplements (ODS) and the NCCAM invite grant proposals to establish Specialized Research Centers to investigate the biological effects of botanicals including, but not limited to, botanicals available as dietary supplements. The creation of such Centers is needed to advance the quality and quantity of scientific information on botanicals and to promote further research in this area.

Centers for Complementary and Alternative Medicine Research	AT-00-001	01/07/00	03/14/00

The National Center for Complementary and Alternative Medicine (NCCAM), the National Cancer Institute (NCI), and the National Heart, Lung, and Blood Institute (NHLBI) invite applications for Centers for CAM Research using the P50 Specialized Center grant mechanism. Such Centers will provide the resources necessary for the rigorous scientific investigation of CAM. It is expected that research conducted at these Centers will examine the potential efficacy, effectiveness, safety and validity of CAM practices, as well as the physiological or psychological mechanisms underlying or contributing to the effects of these practices. Applicants should propose a multidiscliplinary research focus that incorporates basic and clinical research with either an asthma or cancer theme.

Ginkgo Biloba Prevention Trial in Older Individuals	AT-99-001	04/21/99	05/21/99

The National Center for Complementary and Alternative Medicine (NCCAM) and the National Institute on Aging (NIA) invite applications for a two-arm, double-blind, randomized, placebo-controlled multi-site trial to assess whether an extract of the botanical product, Ginkgo biloba, prevents the occurrence of dementia and/or cognitive decline in older individuals.

Research on Care at the End of Life	NR-99-004	04/30/99	05/21/99

The purpose of this initiative is to generate research that will improve the quality of dying for Americans and decrease the distress for their caregivers. Research

	applications may include basic, clinical or health care studies focused on the clinical management of physical and psychological symptoms, patient-provider and patient-family communication, ethics and clinical decision-making, caregiver support, or the context of care delivery for those facing life-limiting illnesses.		
	HL-98-008	12/11/98	01/22/99
Centers for Complementary and Alternative Medicine Research			
	Applications are being sought for Centers for CAM Research using the Specialized Center (P50) grant mechanism. Such Centers will provide its resources neccessary for the rigorous scientific investigation of CAM. It is expected that research conducted at these Centers will examine the efficacy, effectiveness, safety and validity of CAM practices, as well as the physiological or psychological mechanisms underlying these practices.		
Specialized Centers of Research (SCORS) in Ischemic Heart Disease in Blacks	HL-98-015	05/07/99	09/15/99
	Interdisciplinary study of issues surrounding the expression of heart disease in Blacks. Applicants should select one of the following three themes: Sudden Cardiac Death; Microvascular Disease; Diabetic Heart Disease.		
Specialized Centers of Research in Ischemic Heart Disease	HL-98-007	06/12/98	12/29/98
	Interdisciplinary approaches to the elucidation of the etiology and pathophysiology of ischemic heart disease, sudden cardiac death, and heart failure at the molecular, cellular, and tissue levels.		
Basic and Clinical Research on Fibromyalgia	AR-98-006	05/15/98	07/15/98
	Research studies related to all aspects of pathogenesis and clinical manifestations of fibromyalgia syndrome (FMS) and to relationships between FMS and temporomandibular disorders (TMDs).		
Innovative Approaches to Disease Prevention Through Behavior Change	OD-98-002	04/01/98	05/21/98
	A four-year research grant program to test interventions designed to achieve long-term health behavior change.		
Centers for Complementary and Alternative Medicine	OD-98-003 ERRATA		01/13/98

Research			
	A **correction** issued for RFA OD-98-003, which was published in the NIH GUIDE, Volume 26, Number 34, October 10, 1997.		
Centers for Complementary and Alternative Medicine Research	OD-98-003	12/01/97	01/13/98
	The OAM, NICHD, and NIDA seek to encourage research of CAM by establishing CAM Centers of Research, which will make the resources necessary for the conduct of high quality research available to investigators interested in CAM.		
Acupuncture Treatment for Osteoarthritis	OD-97-006	08/17/97	09/19/97
	The OAM and NIAMS seek to initiate a clinical trial of acupuncture for the treatment of osteoarthritis (OA) of the knee. See correction or **ERRATA** issued on August 1, 1997.		
Center for Chiropractic Research	OD/OD-97-005	04/09/97	05/14/97
	Seeks to encourage research of chiropractic by establishing a Center for Chiropractic Research, which will make the resources necessary for the conduct of high quality research to investigators interested in chiropractic.		

Note: *RFPs, RFAs, and PAs are published in the NIH Guide for Grants and Contracts.*

NCCAM Home / For Investigators / Funding Opportunities

Menu...

Please send questions and comments to nccam-info@nccam.nih.gov.
Last Updated: February 21, 2001

Groft, Stephen (NCCAM)

From: Chang, Michele (NCCAM)
Sent: Wednesday, April 18, 2001 11:52 AM
To: Groft, Stephen (NCCAM)
Subject: RE: NCCAM EXPLORES NEW OPPORTUNITIES FOR FUTURE COLLABORATION WITH INDUSTRY

Steve:

FYI, Buford's email doesn't work, so you need to send emails to his assistant, Tierney Lancaster at
tierney334@yahoo.com

I've sent her (and all the Commissioner's assistants a copy of your e-mail.)

Mi

-----Original Message-----
From: Groft, Stephen (NCCAM)
Sent: Wednesday, April 18, 2001 10:44 AM
To: Buford Rolin; Conchita M. Paz; David Bresler; Dean Ornish; Donald Warren; Effie Chow; George Bernier; George DeVries; James Gordon; Joe Pizzorno; Joseph Fins; Julia Scott; Linnea Larson; Thomas Chappell; Tieraona Low Dog; Veronica Gutierrez; Wayne Jonas; William Fair; Xiaoming Tian; Albrecht, Joan (NCCAM); Axelrod, Corinne (NCCAM); Chang, Michele (NCCAM); Fisher, Ken (NCCAM); Jim Swyers; Kaczmarczyk, Joseph (NCCAM); Kingsbury, Doris (NCCAM); Miller, Maureen (NCCAM); Pollen, Geraldine (NCCAM)
Subject: FW: NCCAM EXPLORES NEW OPPORTUNITIES FOR FUTURE COLLABORATION WITH INDUSTRY

Attached is a meeting announcement that is concurrent with our May 14 meeting. this is for your information.

Steve Groft

-----Original Message-----
From: Kingsbury, Doris (NCCAM)
Sent: Wednesday, April 18, 2001 7:31 AM
To: Axelrod, Corinne (NCCAM); Fisher, Ken (NCCAM); Jim Swyers; Joan Albrecht; Kaczmarczyk, Joseph (NCCAM); Maureen Miller; Michele Chang; Pollen, Geraldine (NCCAM); Stephen Groft
Subject: NCCAM EXPLORES NEW OPPORTUNITIES FOR FUTURE COLLABORATION WITH INDUSTRY

FYI

NATIONAL INSTITUTES OF HEALTH

National Center for Complementary
and Alternative Medicine (NCCAM)
http://nccam.nih.gov

NIH NEWS RELEASE

NOTE TO REPORTERS AND EDITORS:
FOR IMMEDIATE RELEASE
Tuesday, April 17, 2001

Press Contact:

Anita Greene (301) 496-1712
greena@mail.nih.gov

NCCAM EXPLORES NEW OPPORTUNITIES FOR FUTURE COLLABORATION WITH INDUSTRY

The National Center for Complementary and Alternative Medicine (NCCAM), a component of the NIH, will hold a colloquium on May 14, 2001, to explore opportunities to collaborate with two key groups: Industrial stakeholders that produce, label, and market complementary and alternative medicine (CAM) therapeutics (e.g., dietary supplements and other biologically based treatments), and organizations that develop and apply standards to determine quality and safety of these products. The purpose of the meeting is to begin a dialogue on how NCCAM and industry can work together to definitively evaluate CAM therapeutic products for composition, safety, and efficacy, and to obtain input from the broad stakeholder community.

WHAT:
Senator Tom Harkin (D-IA), who spearheaded legislation to create NCCAM (formerly the Office of Alternative Medicine), will open the colloquium: "Exploring Opportunities for Collaboration with Industry" with an overview of NCCAM's legislative mandate. Stephen E. Straus, M.D., Director of NCCAM will discuss NCCAM's perspective with respect to opportunities to establish collaboration with industry. Myron S. Weinberg, Chairman of the Weinberg Group will serve as chair for this colloquium.

Leaders from key federal government regulatory agencies, major industrial, non-profit, consumers, and researcher groups will address important topics to include: (1) The role of NCCAM and the NIH Office of Dietary Supplements in studying CAM therapeutics within the context of the NIH mission, (2) The scope of interests and needs of the CAM therapeutics industry in developing and marketing CAM therapeutics, (3) Areas of interest common to NCCAM and the CAM therapeutics industry, (4) Areas of complementary expertise contributed by NCCAM and the CAM therapeutics industry, and (5) Regulatory authorities and responsibilities of other federal agencies. Ample opportunity will be provided for audience discussion of these issues.

Additional information, including an agenda and featured speakers at this meeting is available at:
http://nccam.nih.gov/nccam/colloquium

Individuals, or representatives from the following organizations should attend this meeting:

--CAM therapeutics suppliers of raw materials, manufacturers, and distributors

--Members of organizations that develop and apply standards to determine quality and safety of CAM therapeutics

--Consumers

--Practitioners of conventional and complementary and alternative medicine, and members of the allied health professions

--Researchers and research administrators

--Policy makers

--Publishers of compendia of information related to CAM therapeutics

--Regulatory lawyers

--Government regulators

WHEN:
Monday, May 14, 2001
8:00 a.m. - 5:45 p.m. EDT

WHERE:
The meeting will take place at the Washington Monarch Hotel located at 2401 M Street, N.W., Washington, D.C.

REGISTER NOW:
Registration is FREE for credentialed press only; however, SPACE IS LIMITED. Please contact Anita Greene, NCCAM Press Officer at (301) 496-1712 ASAP to make a reservation.

The National Center for Complementary and Alternative Medicine (NCCAM) is dedicated to exploring complementary and alternative medical (CAM) practices in the context of rigorous science, training CAM researchers and disseminating authoritative information. For additional information, including fact sheets, press releases, and other information about NCCAM, please visit our website at http://nccam.nih.gov.

DRAFT 4/19/01

WHITE HOUSE COMMISSION ON COMPLEMENTARY AND ALTERNATIVE MEDICINE POLICY RESEARCH CHALLENGES

Tuesday, May 15, 01

Overview

12:30-12:40 Opening Remarks- James Gordon, Steve Groft

12:40-1:25 Overview-David Eisenberg

Foundation Support for CAM Research

1:25
- Dr. Bridget Duffy, Medtronic
- Dr. Dorianne Miller, RWJ Foundation
- Ms. Susan Braun, Susan G. Komen Breast Cancer Foundation

TBA (Samueli)

2:05 DISCUSSION

Approaches to Evaluating Research Literature

2:35 BREAK

2:50 Dr. Donald Lindberg, NLM-Selection Process for Peer-reviewed Journal

- **Dr. Douglas Kamerow**, Agency for Healthcare Research and Quality-Evidence-based Practice Centers and CAM
- Dr. Brian Berman, University of Maryland-Cochrane Collaboration

3:30 DISCUSSION

4:10 Concerns about CAM and CAM Research

Dr. William London, Council Against Healthcare Fraud
Dr. Simeon Margolis, Johns Hopkins University

MEPS
Medical Expenditure Panel Survey

Dr. Arthur Grollman, SUNY/Stonybrook

4:40 DISCUSSION

5:30 Adjourn

Wednesday, May 16, 01

The Challenges of CAM Research and Research Training

8:00 Research methodology:

Dr. John Chabot, Columbia University
Dr. Marcia Angell
Dr. Jennifer Jacobs, American Institute of Homeopathy
Dr. Alex White, Kaiser Permanente Center for Health Research
Dr. Bruce Rabin, University of Pittsburgh
(Andrew Vickers, Memorial Sloan Kettering ***cannot attend but will send written material by 4/25***)

8:50 DISCUSSION

9:25 Training of conventional and CAM investigators:

Dr. Neil West, NCCAM
Dr. Nancy Pearson, NCCAM
Dr. Richard Hammerschlag, Oregon College of Oriental Medicine
Dr. Marilyn Schlitz, Institute for Noetic Sciences
TBA

10:30 DISCUSSION

11:00 BREAK

Publication of Peer-Reviewed CAM Research Results

11:15 Dr. Edward Campion, NEJM
Dr. Phil Fontanarosa, JAMA

Dr. Christine Laine,. Annals of Internal Medicine
Dr. Arnold Relman
Dr. David Riley, Alternative Therapies in Health and Medicine
Ms. Jackie Wootton , Journal of Alternative and Complementary Medicine

12:15 DISCUSSION

12:55 LUNCH

1:55 Discussion Groups/breakouts

3:00 Full Commission Discussion

4:00 Public Session

5:30 Adjourn

Letters requesting information on CAM research activities sent to the following Federal agencies:

NSF- ***Rita Colwell***
DoD ***J. Jarrett Clinton***
CDC-***William Dietz***
USDA- ***Orville Levander/Kathleen Ellwood***
NASA- ***Kathie Olson***
Dept. of Energy-***Jim Decker***
HRSA- ***Elizabeth James Duke***
NIEHS/NIH-***Scott Masten***

Several NIH Institutes, the National Center for Complementary and Alternative Medicine/NIH, the Office of Dietary Supplements/NIH, the Federal Drug Administration, the Indian Health Service, and the Veteran's Administration testified at the WHCCAMP research meeting in October 2000.

Alternative Medicine: The Importance of Evidence in Medicine and in Medical Education

Guest Editor:
ARTHUR P. GROLLMAN, MD

●

Foreword: Is there Wheat among the Chaff?

Arthur P. Grollman, MD

Alternative medicine, sometimes called "complementary medicine," has enjoyed a remarkable resurgence of popularity in the United States. For example, in the realm of orally administered substances, the widespread belief that dietary supplements prevent illness, combined with the cost and inconvenience of conventional medical care, may explain, in part, why many people use nutraceuticals, supplements, and herbal remedies.[1] Indeed, as Beyerstein, Talalay, and Marcus make clear in this issue of *Academic Medicine*, there are a variety of reasons that increasing numbers of people are turning to alternative therapies. In doing so, they may incur substantial risks or simply waste their money.[2–4] As Frenkel and Ben Arye warn in their article in this issue, "practitioners and schools of complementary and alternative medicine (CAM) are neither regulated nor closely supervised . . . and there is little protection against charlatans." On the other hand, these authors maintain that some CAM remedies "bring comfort and relief in treating conditions where conventional treatment has failed."

Marcus states the common concern that much alternative medicine research is unreliable. He notes the "need for more high-quality research on alternative modalities to provide a basis for evaluating their safe and rational use," a view echoed by other authors in this issue. Beyerstein endorses this position when he remarks that "potential clients should ask whether any alternative treatment they are considering is supported by research published in biomedical journals where peer-review processes strive to eliminate experimental artifacts that lead to false impressions of cures."

An evidence-based medicine movement has emerged in academic medicine at the same time that the use of unproven therapies has increased. Beyerstein explores this paradox by analyzing the psychology behind the public's "flight from reason" and explains why therapists and patients alike might conclude that useless therapies work. Sampson examines the lack of critical analysis in most medical school courses that teach alternative medicine, and Marcus analyzes alleged deficiencies in medical education cited by proponents of alternative medicine and demonstrates that these claims are based on a misrepresentation of medical training.

Since ancient times, herbal medicines have been employed in the treatment of human illness. Indeed, Osler remarked that "the only thing that distinguishes man from lower animals is his desire to take drugs." Nonetheless, herbal remedies today must be evaluated in light of present knowledge of pharmaceutical sciences and medicinal chemistry. The pharmacologic principles underlying the absorption, metabolism, excretion, and mechanisms of action of drugs are well known[5]—these principles apply equally to herbals, which are simply mixtures of chemicals derived from plants. Remarkably, although governmental regulatory policy requires pharmaceutical manufacturers to show that a new drug is safe and effective, these legal safeguards do not extend to herbal medicines. In this issue, Pamela and Paul Talalay review the history of drug development, discuss the consequences of exempting herbal medicines from essential regulatory controls, and describe scientific investigations of several plants that led to the development of novel therapeutic agents.

In their reviews, Sampson, an oncologist, Marcus, a rheumatologist and immunologist, Beyerstein, a psychologist, and Talalay, a pharmacologist, highlight the lack of scientific evidence presented in support of claims made by practitioners

Dr. Grollman *is the Evelyn Glick Professor and chair of pharmacological sciences at the State University of New York at Stony Brook, Stony Brook, New York.*

Correspondence and requests for reprints should be addressed to Dr. Grollman, SUNY at Stony Brook, School of Medicine, Dept. of Pharmacological Sciences, Stony Brook, NY 11794-8651.

of alternative medicine. This presents a conundrum: if alternative medical practices are not supported by properly controlled clinical trials and are therefore unproven,[2,3] we must ask why throughout history people from diverse cultures generally held "healers" in high esteem and eagerly sought their assistance in times of medical need. I briefly consider this question in light of a hypothesis proposed by Houston[6] and extended by Shapiro and Shapiro,[7] namely, that *until recently, the history of medical treatment has been largely the history of the placebo effect*. This provocative statement rests on persuasive evidence that virtually all medical treatments used before 1900 were ineffective and that the placebo effect could account for the therapeutic responses observed.

The earliest written record of medical therapy, the Ebers papyrus, appeared around 1500 B.C. and included more than 700 drugs of animal, vegetable, and mineral origin.[8] Additionally, comprehensive pharmacopoeias describing the ancient medicines used in China and India have been compiled. Galen categorized the drugs used in the Greco-Roman era and may have anticipated the placebo effect when he wrote: "He cures most successfully in whom the people have the greatest confidence."[9] Marcus acknowledges the power of the placebo effect in discussing differences between traditional and alternative medicine.

A few of the drugs used for centuries produce more than a placebo effect, *but only when properly administered*. For example, in the 15th century the father of modern pharmacology, Paracelsus, introduced extracts of opium and the use of heavy metals for the treatment of syphilis.[9] In the 18th century, Lind demonstrated the effectiveness of limes in treating and preventing scurvy.[10] About the same time, Withering's keen observations revealed the power of foxglove to treat patients with dropsy.[11] In recognizing the signs and symptoms of digitalis toxicity, Withering alerted physicians to the critical importance of using the correct dose.[11] Missionaries and soldiers also played roles in drug discovery by recognizing the therapeutic properties of cinchona bark and ipecacuanha root and bringing these plant remedies from the New World to Europe, where they were used by physicians to treat fevers and dysentery.

What can we learn from the early history of medical treatment? Considering all sources, some 20,000 prescribed remedies and 5,000 specific chemical entities have been identified.[7] Yet the list of demonstrably effective herbals today would consist only of opium poppy, cinchona, ergot, ipecacuanha, foxglove, cocoa, belladonna, and ma huang. The active principles of these herbals are uniformly toxic and their therapeutic "windows" are exceedingly narrow. Methods for preparing standardized extract of these plants and an intimate knowledge of their clinical pharmacology—information that is critical to the safe and effective use of any drug—appeared only in the 20th century. In earlier times, it seems highly unlikely that therapeutic levels of these potentially effective agents could be maintained for the lengths of time required to significantly affect the course of disease.

In the 19th century, Oliver Wendell Holmes and Sir William Osler were leading voices for academic medicine. Holmes, dean of Harvard Medical School and an outspoken critic of homeopathic medicine, argued eloquently against the use of ineffective treatments.[12] "It always does very great harm to the community to encourage ignorance, error, and deception in a profession which deals with the life and health of our fellow creatures."[13] Holmes also expressed skepticism about the effectiveness of most drugs of his day, declaring: "If the whole materia medica, as now used, could be sunk to the bottom of the sea, it would be all the better for mankind—and the worse for the fishes."[13] He recommended quinine for malaria, mercury for syphilis, digitalis for heart disease, colchicine for gout, iodine for goiter, and ipecac for dysentery. Osler added opium and iron to this short list of effective therapeutic agents and publicly criticized the irrational practice of polypharmacy, which he described as the use of "a large number of drugs, of the action of which we know little, yet we put them into bodies, the action of which we know less."[14]

Can we attribute clinical improvements associated with medical therapy for more than two millennia solely to the placebo effect? Placebos comprise all the forms of treatment, including drugs, surgery, psychotherapy, and religious rituals (e.g., prayer and exorcism) that are used to ameliorate a symptom or disease but that are not specifically effective for the condition being treated. Furthermore, recovery from acute illness simply may reflect the self-limited nature of most diseases.[15] In addition, psychosomatic complaints are common and tend to disappear over time. Nonetheless, the symptomatic improvements experienced by upward of 30% of patients visiting a health practitioner have been clearly shown to derive from the placebo effect.[7,16] Indeed, one of the fundamental advances in medical science in the 20th century has been the recognition of the power of the placebo, an understanding of which is fundamental to applications of clinical epidemiology and biostatistics in the design and interpretation of controlled clinical trials. Thus, while we should be eager to embrace evidence-based medicine—including its use in validating or discrediting alternative therapies—credit must be given to the placebo, a ubiquitous treatment common to all societies and cultures and an intrinsic component of both traditional and alternative medicine. Ironically, the placebo effect was recognized as a factor in therapeutics only when highly effective drugs became available and precise measurements of symptoms, such as pain, were developed, so that quantitative comparisons between placebos and active medications could be made.[16]

What is the role of medical education with respect to alternative medicine? The authors in this issue agree that teaching *about* alternative medicine is important for a variety of reasons, and that physicians need to learn more about these therapies and why some patients embrace them. The authors also agree that physicians should help patients distinguish between therapies whose efficacy and safety have been established and those that are unproven or unsafe. Marcus offers wise counsel when he maintains that "physicians need additional education to provide guidance to patients, but teaching about alternative medicine should be evidence-based and not merely the transmission of unproven practices."

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ARTICLE

How Should Alternative Medicine Be Taught to Medical Students and Physicians?

Donald M. Marcus, MD

ABSTRACT

Advocates of alternative medicine are critical of current medical curricula, and have proposed fundamental changes, including the introduction of "integrative medicine" programs to teach alternative medicine. Medical educators have not replied to these criticisms, and have not developed *basic* curricula in alternative medicine. The author analyzes the alleged deficiencies in medical education, which are based on misrepresentations of medicine and medical training. (For example, critics state that physicians ignore mind–body interactions; in response, several examples are given to show that training physicians to consider the whole person and to identify and address emotional and social problems—the biopsychosocial model—are central tenets of medical education.) The author also examines fundamental differences between traditional and alternative medicine (e.g., their different attitudes toward the importance of evidence; the vitalistic versus the biomedical models of health and disease) that are central to the issue of how alternative medicine should be taught. He concludes that physicians need additional education in order to provide guidance to patients, but teaching about alternative medicine should be evidence-based, not merely the transmission of unproven practices.

Acad. Med. 2001;76:224–229.

The popularity of alternative medicine[1,2] has encouraged its advocates to criticize traditional medicine, and to propose revisions in medical education, including the incorporation of alternative therapies into medical education and practice (integrative medicine).[3,pp 277–283,4–6] In his recent testimony,[7] Dr. Andrew Weil proposed that Congress designate funds for the introduction of integrative medicine into health care education. These calls for change are in part a result of the fact that medical educators have been slow to recognize the need for development of curricula in alternative medicine, and have not responded to the various criticisms of traditional medicine and medical education made by proponents of alternative medicine and others. In this article, I examine the most important of these criticisms, all of which misrepresent medicine and the medical curriculum and obscure the basic differences between traditional and alternative medicine. I also make proposals for educating physicians and patients about alternative treatments.

Dr. Marcus is professor of medicine and immunology, Departments of Medicine and Immunology, Baylor College of Medicine, Houston, Texas.

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CRITICISMS OF TRADITIONAL MEDICINE AND MEDICAL EDUCATION

Physicians Ignore Mind–Body Interactions

A recurrent allegation is that traditional medicine is based on Cartesian dualism—i.e., that it ignores mind–body interactions—and that physicians are not trained to assess the whole person. A typical example of this rhetoric is this comment about biomedicine (allopathic medicine) by Micozzi[8]: "The study of dead tissues, cells, components and chemicals to understand life processes are based upon a reductionistic, materialist view of health and healing." Another example is the description of the "Old Paradigm" of traditional medicine by naturopathic doctors[9]: "The body is a machine; the body and mind are separate; the physician should be emotionally neutral and detached."

Awareness of the profound influence of temperament and emotions on body functions has always been prominent in Western medicine. Prior to the 20th century most treatments had no value, and some, such as purging and bleeding, were harmful. The primary benefits resulting from the interactions between patients and healers were reassurance and relief of anxiety. As stated by Houston,[10] "the history of medicine is a history of the dynamic power of the relationship between doctor and patient."

Training physicians to consider the whole person and to identify and address emotional and social problems (the biopsychosocial model) is a central tenet of medical education. This aspect of the art of medicine was traditionally taught by the apprenticeship model during bedside teaching rounds. In recent decades, the apprenticeship method of teaching the biopsychosocial model has been supplemented by the incorporation of appropriate learning objectives into medical school curricula, and by development of techniques to teach and assess communication and interviewing skills of students. For example, a recent report of the Association of American Medical Colleges that presents guidelines for medical schools with respect to learning objectives for medical students' education[11] includes the following objective: "The medical school must ensure that . . . a student will have demonstrated, to the satisfaction of the faculty, knowledge of the important non-biological determinants of poor health and of the economic, psychological, and cultural factors that contribute to the development and/or continuation of maladies." In addition, the humanistic attributes of students and resident physicians are a prominent part of their evaluations, and are required by accrediting agencies and boards. Finally, the role of emotions in the pathogenesis and outcome of disease has received intensive study during the last 50 years,[12–16] and recent progress in neuroscience is providing insight into the molecular basis of communication between the nervous system and the immune and cardiovascular systems.[17,18]

Medical Treatment Does Not Address the Cause of Disease

A second criticism is that traditional medicine does not seek to understand the cause of illness, that it attempts to suppress symptoms by means of pharmacologic agents, and it ignores the potential of the body to heal itself. For example, Dr. Weil has written that "most of the treatments I had learned in four years of Harvard Medical School and one of internship did not get to the root of disease processes and promote healing but rather suppressed those processes or merely counteracted the visible symptoms of disease."[19, pp 13–14]

There are two allegations being made in this surprising statement. In regard to the first—that physicians are not trained to analyze the pathophysiologic basis of disease—it is enough to say that courses in the pathophysiology of disease have been taught in all medical schools for decades. Moreover, students and residents are taught to take a pathophysiologic approach to the analysis of symptoms such as dyspnea or chest pain. The initial sections of *Harrison's Principles of Internal Medicine*[20] have been devoted to this type of analysis for decades.

The second allegation—that medicine ignores the body's potential for natural healing and encourages an excessive reliance on dangerous pharmacologic agents to "merely suppress symptoms"—is, like the first, not warranted. The principle of "primum non nocere" (i.e., "first, do no harm") has been a central precept of medical care for over two thousand years. This maxim is attributed to the Greek physician Hippocrates, who wrote in *Epidemics*, "As to diseases, make a habit of two things—to help, or at least do no harm."[21] Implicit in this statement is recognition of the natural recuperative powers of the body. Prescribing antibiotics for viral respiratory infections[22] is frequently cited as an example of the inappropriate use of pharmacologic agents. However, guidelines for the appropriate use of antibiotics have been available for some time, and the shortcomings of individual practitioners cannot be attributed simply to basic defects in medical training. There are many factors that account for the overuse of antibiotics,[23,24] including pressure from patients, but the guidelines can be utilized effectively.[25] Current guidelines for the treatment of many diseases, including essential hypertension,[26] osteoarthritis,[27] and diabetes mellitus, emphasize the importance of non-pharmacologic approaches such as weight reduction and exercise.

Medicine Ignores Prevention of Disease

A third criticism is that traditional medicine ignores disease prevention and health promotion. This is not the case: preventive medicine has been taught in medical schools and postgraduate training for decades, and guidelines[28] have been formulated for immunizations and to screen for hypertension, diabetes mellitus, and breast, prostate, and colon cancer. Non-pharmacologic (life-style) approaches to health promotion, including the importance of a balanced diet, weight control, exercise, and stress reduction, have received increasing attention, and probably were not sufficiently emphasized until the last quarter of a century.[29] A recent supplement of *Academic Medicine* was devoted to the teaching of preventive medicine in the undergraduate medical curriculum.[30]

To the extent that any *basis* is provided by proponents of alternative medicine for their criticisms of medical education, it consists of undocumented anecdotes about the medical and humanistic shortcomings of traditional physicians, and of miraculous cures achieved by alternative prac-

titioners.[5,19] The medical "failures" are attributed to basic defects in what physicians are taught rather than to human fallibility, the complexity of modern medicine, and the constraints on practice imposed by managed care. Although it is evident that the alleged systematic defects in medical education do not exist, there is always room for improvement. Medical school curricula and postgraduate training programs are continually evolving,[31] and more emphasis is being placed on health promotion and physician–patient interactions.

FUNDAMENTAL DIFFERENCES BETWEEN TRADITIONAL AND ALTERNATIVE MEDICINE

Before considering the real issues that distinguish alternative from traditional medicine, it is important to decide how to define alternative medicine. In their surveys, Eisenberg and colleagues[2] defined alternative modalities as "intervention neither taught widely in medical schools nor generally available in US hospitals." Although this functional definition is useful for epidemiologic studies, it does not take into account the advocacy of alternative medicine by some medical educators, or the presence of alternative practitioners in some health science centers. A more fundamental distinction is the conceptual basis of the therapeutic modality. Truly alternative practices differ from traditional medicine in their concepts of the causes and treatment of diseases, and in their attitude toward evidence.

Two of the most important advances in medical science during the 20th century were the realization of the power of the placebo[32–35] and the development of sophisticated methods for the design and interpretation of controlled clinical trials. A more recent development is the promotion of evidence-based medicine,[36,37] i.e., use of the "best available external clinical evidence" by individual practitioners in patient care. This approach has been greatly facilitated by the development of criteria to evaluate the quality of evidence,[38] and the availability of systematic reviews of clinical data by the Cochrane Collaboration and others. Evidence-based medicine is not cookbook, automated medicine. It is a powerful approach that can be utilized to supplement clinical experience and the needs and preferences of the patient.[39] In contrast to these efforts to base diagnostic and therapeutic decisions on the best evidence available are many belief-based alternative therapies and healing systems.

Many alternative therapies, including traditional Chinese and Ayurvedic medicine, homeopathy, and healing touch, are based on a vitalistic view of health and disease,[40] and are truly alternative to evidence-based medicine. Although these healing traditions differ in their specific formulations, as well as their historical and cultural content, they share a belief in a vital energy (qi, prana, or spiritual vital force) whose disruption or imbalance causes disease, and in the cure of diseases by mobilization of the vital energy. These beliefs are shared by Western advocates of alternative medicine, including Dr. Weil: "Doctors believe that health requires outside intervention of one sort or another, while proponents of natural hygiene maintain that health results from living in harmony with natural law."[19]

Some prominent advocates of alternative medicine reject the concept that the efficacy of these therapies needs to be, or can be, validated by randomized, controlled trials. The editor of the journal *Alternative Therapies in Health and Medicine* wrote, "Many alternative interventions are unlike drugs and surgical procedures. Their action is affected by factors that cannot be specificed, quantified and controlled in double-blind designs. Everything that counts cannot be counted. To subject alternative therapies to sterile, impersonal double-blind conditions strips them of intrinsic qualities that are part of their power."[41]

A more subtle problem than outright rejection of controlled trials is the citation of publications that support the efficacy of alternative therapies without considering the quality of those studies.[8,42,43] Reviews of acupuncture,[44,45] chiropractic,[46–48] and herbal medications[49,50] conclude that although there are some data to support the efficacy of these treatments, firm conclusions cannot be drawn because of defects in study design. In the discussion of a systematic review of healing, Abbot made these comments about research into complementary therapies, "Too little research has been done, and that which is published is too often ill-conceived, ill-reported, often by experimenters with more enthusiasm than expertise."[51]

There are some investigators[45,47,52–54] who adhere to rigorous standards for evaluating alternative treatments. The new director of the National Center for Complementary and Alternative Medicine (NCCAM), Dr. Stephen Straus, has stated his strong support for analysis of alternative medicine by means of randomized controlled trials.[55] It is important to acknowledge that many therapies used by traditional medicine are not supported by the highest quality of evidence.[56] However, a fundamental difference between alternative and conventional medicine is the acceptance by the latter of the need for better trials, and a willingness to continuously rethink and revise therapeutic guidelines as new data become available,[57] in contrast to the reliance of alternative medicine on tradition and belief.

TEACHING ALTERNATIVE MEDICINE

How should medical schools respond to the prevalent use of alternative modalities by the public, and to the pressure to create programs in integrative medicine?[6] The answer is clear: by developing new educational programs for physicians

and the public, and by fostering research on alternative therapies. Physicians need to be well informed about the conceptual basis, efficacy, and safety of alternative therapies. This material should be incorporated into the required curricula of medical schools and graduate training programs, and not relegated solely to electives,[58,59] whose content may not be critically evaluated.

Without additional education about alternative medicine, physicians cannot obtain accurate information from patients about their use of alternative modalities, or provide information and guidance. Why people use alternative therapies[60,61] is a complex subject that is beyond the scope of this article. However, physicians must assist patients in making informed choices about health care, and they should be receptive to discussing alternative medicine with patients who request information. Physicians should be especially sensitive to the needs of patients with intractable medical conditions, such as cancer, chronic pain, and degenerative neurologic diseases, who seek relief and hope in alternative therapies. Eisenberg[62] has formulated thoughtful guidelines for counseling patients who seek alternative therapies.

In addition to educating health care professionals, there is an urgent need to provide more reliable information to the public. Many alternative treatments, especially herbals and nutritional supplements, are self-prescribed. There is a flood of books, articles, and advertisements that enthusiastically promote the benefits and safety of these materials. Moreover, the huge amounts of money spent on herbs and supplements, and the relative freedom from Food and Drug Administration oversight in making claims, have drawn large pharmaceutical companies into the promotion and sale of "nutraceuticals." This situation presents a unique challenge to the health care professions to communicate to the public in a more effective and dynamic manner about the uncertain benefits and potential hazards of these materials. The information must be disseminated on the Internet[63] and in lay publications that are the primary source of information for many people. In view of the broad range of alternative therapies, I suggest that societies representing health care professionals, including those in pharmacology and nutrition, as well as clinical practitioners, form working groups to develop educational materials.

There is also a need for more high-quality research on alternative modalities to provide a basis for evaluating their safe and rational use. Many valuable medications have been derived from herbs, and botanicals remain a promising source of new therapeutic agents.[64] However, recent information[65,66] about the development of renal failure and urothelial carcinoma in individuals who received the herb *Aristolochia fangchi*, and the evidence that St. John's wort increases the rates of metabolic degradation of many medications,[67] demonstrate the hazards of medicinal use of unregulated herbal preparations. Acupuncture can produce analgesia for operative procedures in some individuals, and it is plausible that it could be a useful adjunct for treatment of chronic pain syndromes, but more rigorous controlled trials are necessary. Treatments whose efficacy is demonstrated by high-quality controlled trials will inevitably be incorporated into medical practice.

Finally, I believe that "integrating" unproven alternative practices and remedies into medical school and residency training would be a mistake. It would confer undeserved legitimacy on alternative therapies, it is diametrically opposed to the development of evidence-based medical practice, and it would compromise the scientific and scholarly foundations of medical education.[68,69]

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Cover Note

THE NEVER-ENDING SEARCH

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To win a place in the armamentarium of the modern physician, a drug or any other proposed therapeutic modality must pass the tests of science. Although occasional treatments are found to benefit patients before the mechanisms of their effects are understood, sooner or later—and in most cases, very soon—the appropriate tests must be carried out.

The inadequacies of medical practices of 1,000, 500, or even only 200 years ago, amazing mixtures of accurate information, ignorance, the misdirected weight of tradition, wishful thinking, and superstition, arouse in us feelings of horror and scorn. With hindsight, we easily distinguish the valid from the spurious. However, most early practitioners can be assumed to have done the best they could with the limited tools they had and the knowledge at their disposal, which included many notions arising from the aforesaid ignorance, etc., and later proved unsound. For example, the mandrake root was thought, because of its humanoid shape, to have medical and even magical powers, and malaria, yellow fever, and bubonic plague were believed to result from the malevolent effect of "bad air"; Western physicians have not credited such beliefs for a long time. Nor, to take more recent examples, do they any longer attribute ulcers to emotional stress or schizophrenia to inadequacies in the mother-child relationship.

Our descendants will look back at today's medicine from an even more superior vantage point, possibly with pity and scorn. It is not farfetched to predict that in only a few generations, oncologists will have found present-day chemotherapy and radiotherapy to be crude, or even barbaric. Perhaps our approaches to treatment are not, in fact, at the heart of what science will eventually learn about the nature of cancer—if the concept of "cancer" holds up as meaningful in the light of new discoveries. Physicians in 2101 may find our chemotherapy nonsensical, in the same category as bloodletting to "balance the humors," which was a mainstay of medicine for several hundred years.

For an example from another direction, consider chronopharmacology, which even in the recent past would have been dismissed as ludicrous, more akin to astrology than to science. And yet the idea that drugs can have significantly different clinical effects according to the times of the day or night they are given—in the treatment of some cancers, for example—has been increasingly borne out by research. More study may disclose that these outcomes are coincidences that have explanations not currently apparent. On the other hand, future research may uncover layers of information that make it clear why the timing of administering medications is important. Whether chronopharmacology turns out to be a blind alley, as much of medicine has proved to be over the centuries, or the opening of a window into deeper understanding of human physiology is not the important point. The importance lies in the process of science—an openness to new ideas that is always linked to a rigorous research method and the logic at its heart.

—ADDEANE S. CAELLEIGH

ARTICLE

Alternative Medicine and Common Errors of Reasoning

Barry L. Beyerstein, PhD

ABSTRACT

Why do so many otherwise intelligent patients and therapists pay considerable sums for products and therapies of alternative medicine, even though most of these either are known to be useless or dangerous or have not been subjected to rigorous scientific testing? The author proposes a number of reasons this occurs: (1) Social and cultural reasons (e.g., many citizens' inability to make an informed choice about a health care product; anti-scientific attitudes meshed with New Age mysticism; vigorous marketing and extravagant claims; dislike of the delivery of scientific biomedicine; belief in the superiority of "natural" products); (2) psychological reasons (e.g., the will to believe; logical errors of judgment; wishful thinking, and "demand characteristics"); (3) the illusion that an ineffective therapy works, when actually other factors were at work (e.g., the natural course or cyclic nature of the disease; the placebo effect; spontaneous remission; misdiagnosis).

The author concludes by acknowledging that when people become sick, any promise of a cure is beguiling. But he cautions potential clients of alternative treatments to be suspicious if those treatments are not supported by reliable scientific research (criteria are listed), if the "evidence" for a treatment's worth consists of anecdotes, testimonials, or self-published literature, and if the practitioner has a pseudoscientific or conspiracy-laden approach, or promotes cures that sound "too good to be true."

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If only the ignorant and gullible were swayed by far-fetched claims, little else would be needed to explain the abundance of folly in modern society. But oddly enough, many people who are neither foolish nor ill-educated cling to beliefs repudiated by science. For example, college graduates, and even some physicians, accept certain aspects of complementary and alternative medicine (CAM), including therapeutic touch, iridology, ear candling, and homeopathy. Even highly trained experts can be misled when they rely on personal experience and informal reasoning to infer the causes of complex events.[1–4] This is especially true if they are evaluating situations to which they have an emotional, doctrinal, or monetary attachment. Indeed, it was the realization that shortcomings of perception, reasoning, and memory incline us toward comforting, rather than true, conclusions that led the pioneers of modern science to substitute controlled observations and formal logic for the anecdotes and surmises that can so easily lead us astray. This lesson seems to have been largely lost on proponents of CAM. Some, such as Andrew Weil, reject it explicitly, advocating instead what Weil calls "stoned thinking," a melange of mystical intuition and emotional satisfaction, for determining the validity of a therapy.[5]

Those who advocate therapies of any kind have an obligation to prove that their products are both safe and effective. The latter is the more difficult task because there are many subtle ways that honest, intelligent patients and therapists can be led into thinking that a useless treatment has produced a cure. CAM remains "alternative" because its practitioners depend on subjective testimonials rather than randomized clinical trials (RCTs) for support, and because most of their hypothesized mechanisms are at variance with those accepted by basic science. It is my intent here to draw

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attention to several social, psychologic, and cognitive factors that have helped convince many well-educated people that scientifically discredited or unproven treatments have merit.

In the last century, objective procedures have been developed that test the effectiveness of putative remedies and help distinguish therapeutically induced changes in an underlying pathologic condition from the subjective relief that might follow any intervention. These procedures form the basis of so-called "evidence-based medicine," and without such a demonstration that a treatment is safe and effective, it is ethically questionable to offer that treatment to the public. Since most "alternative," "complementary," or "integrative" therapies lack this kind of support, one must ask why so many otherwise savvy consumers trustingly pay out considerable sums for unproven, and possibly dangerous, health products. We must also wonder why claims of alternative practitioners remain so refractory to contrary data.

If an unorthodox therapy: (1) is implausible on a priori grounds (because its implied mechanisms or putative effects run afoul of well-established laws or empirical findings in physics, chemistry, or biology); (2) lacks a scientifically acceptable rationale of its own; (3) has insufficient supporting evidence derived from controlled clinical trials; (4) has failed in well-controlled clinical studies conducted by impartial evaluators and has been unable to rule out competing explanations for why it might *seem* to work in everyday settings; and (5) should seem improbable, even to the layperson, on "common sense" grounds, then why would so many well-educated people continue to purchase such a treatment?

Consumers of unscientific treatments can be classified broadly into two groups. Once a buyer from either group tries an unconventional treatment, the judgmental biases discussed below have a tendency to make even the most worthless interventions seem valid. Patrons of one type often gravitate to CAM because they suffer from chronic conditions that orthodox medicine does not handle to their satisfaction or because they live in morbid fear that they will lose their "wellness." They assume, erroneously, that competent authorities have validated CAM's wares. The other type of user chooses alternative treatments out of a philosophical commitment to the animistic, vitalistic cosmology of CAM, which rejects the mechanistic–empiricist underpinnings of scientific biomedicine.[6] CAM embraces subjective, emotive truth criteria, whereas its detractors demand objective evidence. Because one's concept of health is entwined with one's fundamental assumptions about reality, an attack on someone's belief in unorthodox healing becomes a threat to his or her entire metaphysical outlook. Understandably, this will be resisted fervently.

The ability to defend one's basic world-view is abetted by a number of cognitive biases that filter and distort contrary information. I shall return to these processes that incline supporters to misconstrue their experiences to bolster their belief in CAM. But first let us examine the cultural milieu that has fostered a widespread desire to espouse such practices.

SOCIAL AND CULTURAL REASONS FOR THE POPULARITY OF UNPROVEN THERAPIES

Several trends have contributed to today's popularity of CAM, in spite of (and to some degree, because of) its rejection by mainstream science. The resurgence of folk medicine can be traced, in large part, to nostalgic holdovers from the neo-romantic search for simplicity and spirituality that permeated the "counterculture" of the 1960s and 1970s.[7] The flower children of that generation now form the backbone of the "New Age" movement, which enthusiastically promotes unorthodox healing.[8] CAM suits the iconoclasm, mystical longings, desire for simpler times, and naive trust in the beneficence of "Nature" absorbed during those tumultuous earlier times. How, then, has this history benefited non-scientific medicine?

Poor scientific literacy. Surveys consistently find that, despite our overwhelming dependence on technology, the average citizen of the industrialized world is shockingly ignorant of even the rudiments of science.[9] Consequently, most people lack the knowledge to make an informed choice when they must decide whether a highly-touted health care product is sensible or not.

Anti-intellectualism and anti-scientific attitudes piggybacking on New Age mysticism. As a major New Age industry, CAM shares the movement's magical world-view.[6] In advocating emotional criteria for truth over criteria based on empirical data and logic, New Age medical gurus such as Andrew Weil and Deepak Chopra have convinced many that "anything goes."[5] Even in elite academic institutions today, there are strong proponents (mostly in humanities departments) of the notion that objectivity is an illusion and one's feeling about something determines its truth value.[10,11] By denigrating science, these detractors have enlarged the potential following for magical and pseudoscientific health products.[12,13]

Mind–body dualism permeates New Age thought, including CAM, though ironically, it is CAM's disciples who accuse their scientific critics of being dualists.[14,15] That CAM devotees are the real mystics and dualists can be seen by their constant appeal to undetectable spiritual interveners to confer "wellness" on those who deserve it. This obfuscation is needed to sell the oft-heard canard that scientific medicine undervalues the effects of mental processes on health.[6] Admittedly, there are psychologic effects on disease, but their importance has been grossly exaggerated by CAM promoters such as Herbert Benson.[16] Overstatements of this kind have

prompted a resurgence of ancient "mind cures" that assert that the real causes and cures for disease lie in the mind, conceived by New Agers to be equivalent to the soul.[17] Several good critiques have appeared recently, which expose the confusion and artifacts that dog the literature on spirituality and health.[18–20]

Another troubling supposition in New Age health propaganda is that one's moral standing alters the impact of natural forces on one's body. In accepting this anthropocentric, vitalistic worldview, alternative healers are reverting to the pre-scientific view of disease as supernatural retribution. Sad to say, it also amounts to blaming the victim, for implicitly, patients must have done something bad to "deserve" their afflictions.

Vigorous marketing and extravagant claims. According to a recent survey,[21] in the United States alone, "total 1997 out-of-pocket expenditures relating to alternative therapies were conservatively estimated at $27.0 billion, which is comparable to the projected 1997 out-of-pocket expenditures for all U.S. physician services." The annual number of visits to alternative healers now exceeds the total number of visits to all U.S. primary care physicians combined. With riches of this magnitude for the taking, it is not surprising that alternative healers have promoted themselves through aggressive marketing and intense legislative lobbying.[22] Routinely, promises are made that no ethical, scientifically trained practitioner could or would make. Unfortunately, the citizenry facing this slick promotional barrage is poorly equipped with the skills or information for evaluating such hyperbole.[9]

Inadequate media scrutiny and attacks on critics. With some notable exceptions, the mass media have tended to give CAM a free ride. Its enthusiastic claims make enchanting stories that are rarely disputed by the media, whose leaders know that challenging their audience's fond hopes hurts ratings. Another disturbing factor that deters some would-be critics of unscientific treatments is the realization that many of CAM's practices have been imported from non-European cultures and are championed by women. Thus self-promoters often sidestep valid criticisms by accusing detractors of racism and sexism. For example, scientifically rejected practices such as "therapeutic touch" are being embraced by many nursing schools. Because these are still institutions largely attended by women, doubters are often tarred with accusations of sexism. Likewise, when a collegue and I criticized aspects of traditional Chinese medicine (TCM),[22] we were accused of cultural insensitivity and racism.[23] We were chided for presuming to criticize TCM when we were not steeped in the philosophy that spawned it. To accept this absurd rebuke would be to concede that no one but gourmet cooks can tell when they've been served a bad meal. The truly racist and sexist attitude would be to hold empirically testable claims from other cultures or female proponents to a lower standard of proof. This *would* be an assertion of intellectual inferiority. Fortunately, there are many scientific critics from within these communities who find archaic, unproven practices just as dubious as do their white male colleagues.[24,25]

Social malaise and mistrust of traditional authority figures—the anti-doctor backlash. Growing cultural disillusionment has nurtured the belief that society's shortcomings must be due to active connivance by powerful, secret cabals, rather than merely the cumulative mistakes of well-intentioned planners. As these grand conspiracy theories flourish, so does sniping at those suspected of plotting against the common good.[26] Many have come to view government and the scientific and medical professions as parties to the plot. These conspiratorial musings have been reinforced by two other, not entirely unjustified, undercurrents to promote an anti-doctor backlash that CAM has exploited. One is disappointment arising from the failure of certain overly optimistic predictions of medical breakthroughs to materialize. The other is the realization that medicine, as a self-regulating profession, has not always held the public good at the top of its political agenda.[27] This has enhanced the social envy of many regarding the status, political clout, and wealth of the medical profession. The inability of many detractors to separate self-serving political actions by certain medical associations from the debate over whether scientific medicine's treatments are genuinely better than those of CAM has enriched the "alternatives." CAM also benefited by painting itself as the defender of the democratic ideal of "choice." This would be commendable if consumers had the wherewithal to make an *informed* choice.

Dislike of the delivery of scientific biomedicine. CAM has played on a widespread but exaggerated fear that modern medicine has become excessively technocratic, bureaucratic, and impersonal. The narrowing of medical specialties, the need to maximize the cost-efficient utilization of expensive facilities, the advent of third-party payment and managed care, and the staggering workloads of physicians have led some patients to long nostalgically for the simpler days of the kindly country doctor with ample time and a soothing bedside manner. They tend to forget, however, that this was often all a doctor of that era could offer.

Safety and side effects. A quaint bit of romanticism that promotes "holistic" health care is the belief that "natural" remedies are necessarily safer, gentler, and more efficacious than scientific ones.[6] Web sites such as ⟨www.quackwatch.com⟩ readily dispel such myths, however. For example, it is often claimed that herbal concoctions have no side effects, whereas, in fact, some popular herbal products can be far from benign—reports of allergic, toxic, and even lethal reactions are accumulating.[28–31] Mislabeling and serious contaminations have been discovered,[32] while the potential for

adverse interactions with prescribed pharmaceuticals is also becoming more widely recognized.

Public awareness of these perils remains spotty, however, because centralized reporting of ill effects of alternative treatments is not required. Unfortunately, under current U.S. law, the government must show that herb or supplement is unsafe before vendors can be forced to desist.[30] And when harmful effects do occur, users are likely to attribute them to other causes because of their touching belief that benevolent "Nature" would never pull such dirty tricks. Boosters of "natural" products should be reminded that tobacco is also quite natural and that plants produce some of the most deadly poisons known. On the other hand, they should know that several common drugs in scientific biomedicine were originally derived from plants.[25,30] The difference, of course, is that the active ingredients in plants that led to drugs approved by the Food and Drug Administration were identified, synthesized, and rigorously tested for efficacy and safety. Thus, unlike herbal concoctions, their purity and dosages can be closely regulated.

PSYCHOLOGICAL REASONS FOR THE POPULARITY OF CAM

Psychologists have long been aware that people generally strive to make their attitudes, beliefs, and behaviors conform to a harmonious whole. When disquieting information cannot easily be ignored, individuals have a great ability to distort or sequester it to reduce the inevitable friction. It is to these mental gyrations that we now turn.

The will to believe. We all exhibit a willingness to endorse comforting beliefs and to accept, uncritically, information that reinforces our core attitudes and self-esteem.[33] Because it would be nice if the hopeful shibboleths of CAM were true, it is not surprising that they are often seized upon with little demand for evidence. Once adopted, such beliefs will be defended strongly, by misconstruing contrary input if need be.[34,35]

Logical errors, shortcomings of judgment, and missing control groups. One of the most prevalent pitfalls in everyday decision making is the mistaking of correlation for causation. We are all prone to assume that if two things occur together one must cause the other, although, obviously, this need not be the case. This logical error underlies most superstitions. Testimonials for the ministrations of alternative healers commit the same blunder in assuming that when improvement follows a treatment, the treatment must have been responsible. The value of CAM's personal endorsements is limited by what Gilovich[36] has called the "compared to what?" problem. It cannot be known that any vaunted treatment is effective without blinded comparisons with placebo-treated controls. Although this makes user testimonials all but worthless, promoters of CAM such as Andrew Weil offer little else.[5]

Those who impugn fringe treatments are frequently dismissed by practitioners with the rejoinder, "I don't care what your research says. I have seen my treatments work hundreds of times." Unfortunately, this kind of intuitive judgment is also conducive to false conclusions.[1-4,36] These therapists ignore much research in the area of "cognitive heuristics"[36,37] that shows how mistaken causal attributions can arise when we rely on informal observations to determine what causes or alleviates symptoms. It is especially difficult to determine cause and effect when evaluating therapies because many relevant variables are interacting simultaneously—determinations that casual observation cannot reliably tease apart.

For example, Redelmeier and Tversky[38] showed how people are likely to perceive illusory correlations in random events. They then demonstrated how these "hunches" lead to false but widespread beliefs, including the concept that arthritis pain is influenced by the weather. Because CAM derives its diagnoses and treatments from just this kind of unreliable folklore, potential patrons should demand that all alternative treatments be held to the same standards of proof as those in scientific biomedicine. By introducing controlled clinical trials and epidemiologic methods, the pioneers of scientific medicine hoped to reduce the kind of false ascriptions of cause that these frailties of human reasoning can produce. A recent critique of studies purporting to show that various religious practices enhance health[20] offers good examples of how dubious causal attributions arise when the need for the simple control group is ignored.

Wishful thinking and "demand characteristics." Warping perceived reality in the service of dogma is commonplace.[33,34] According to cognitive dissonance theory,[39] mental distress is produced when new information contradicts existing attitudes, feelings, or beliefs. To alleviate the unease, we tend to distort the offending input, our memories, or both. For example, dissonance would be created if an individual received no benefit from an alternative treatment after committing time, money, and "face." Therefore, there would be strong pressure to find some redeeming value in the treatment rather than accept the psychologic implications of admitting that it had been a waste. Thus, CAM patients and therapists often remember things as they wish they had happened, rather than as they really occurred. And since CAM practitioners scorn careful record keeping and randomized clinical trials, they can be selective in what they recall, leading to an overestimation of their success rates while ignoring or explaining away their failures.

Likewise, there are many self-serving biases that help maintain self-esteem and promote harmonious social interchange. An illusory feeling that one's symptoms have abated could also be due to a number of so-called "demand char-

acteristics" found in any therapeutic setting. In all societies there exists a "norm of reciprocity," an implicit rule that obliges people to respond in kind when someone does them a good turn. Most therapists sincerely want to help their patients, and it is only natural that patients want to please them in return. Without clients necessarily realizing it, such obligations (in the form of implicit social demands) are sufficient to inflate their perceptions on how much benefit they have received. Thus, controls for these compliance effects must also be built into clinical trials.[40]

WHY MIGHT THERAPISTS AND CLIENTS CONCLUDE THAT INEFFECTIVE THERAPIES WORK?

Although the terms "disease" and "illness" are often used interchangeably, it is worthwhile to distinguish between the two. I use "disease" to refer to a pathologic state of an organism. By the term "illness" I will mean subjective *feelings* of malaise, pain, disorientation, or dysfunctionality, which might accompany a disease state. Our subjective reaction to the raw sensations we call symptoms is, like all other perceptions, a complex cognitive construction. As such, it is molded by factors such as attitudes, suggestions, expectations, demand characteristics, self-serving biases, and self-deception. The experience of illness is also affected (often unconsciously) by a host of social, monetary, and psychologic payoffs that accrue to those admitted to the "sick role" in society.[41] For certain individuals, these privileges and benefits are sufficient to perpetuate the experience of illness after a disease has abated, or even to create feelings of illness in the absence of disease. Unless we can tease apart these factors that contribute to one's perception of being ill, personal testimonials are a poor basis on which to judge whether a putative therapy has, in fact, cured anyone. Why, then, might someone mistakenly believe that he or she had been helped by an inert treatment?

The disease may have run its natural course. Many diseases are self-limiting. Thus, before the curative powers of a putative therapy can be acknowledged, it must be shown that the percentage of patients who improve following treatment exceeds the proportion expected to recover without any intervention at all (or that they consistently recover faster). Unless unconventional therapists release detailed records of successes *and failures* over a sufficiently large number of patients with the same complaint, they cannot claim to have exceeded the norms for unaided recovery.

Many diseases are cyclic. For example, arthritis, multiple sclerosis, asthma, allergies, migraines, and many dermatologic, gynecologic, and gastrointestinal complaints normally "have their ups and downs." Not surprisingly, sufferers tend to seek therapy during the downturn of any given cycle. Thus a bogus treatment will have repeated opportunities to coincide with upturns that would have happended anyway. Without randomized controlled trials, consumers and vendors alike are prone to misinterpret improvement due to normal cyclic variation as a valid therapeutic effect.

The placebo effect. *The major reason for doubtful remedies' being credited with subjective, and occasionally objective, improvements is the ubiquitous placebo effect.*[42,43] The history of medicine is strewn with examples of what, with hindsight, seem like crackpot procedures that were once enthusiastically endorsed by physicians and patients alike.[44,45] These misconceptions arose from the false assumption that changes in symptoms following treatment must have been a specific consequence of that procedure. Through a combination of suggestion, expectancy, and cognitive reinterpretation, patients given biologically useless treatments often can experience subjective relief; thus, the need for placebo controls that CAM practitioners steadfastly refuse to institute in place of their customer satisfaction surveys.

Many of CAM's treatments, while unable to affect the disease itself, do make the illness more bearable, but for psychologic reasons. Pain is one example. Modern pain clinics show that suffering can often be reduced by psychologic means, even if the underlying pathology is untouched.[46,47] Anything that can allay anxiety, redirect attention, reduce arousal, foster a sense of control, or lead to cognitive reinterpretation of symptoms can alleviate the agony component of pain.[48] It is obviously beneficial if patients suffer less, but we must be careful that purely symptomatic relief does not divert people from proven remedies for the underlying condition until it is too late for them to be effective. Importantly, procedures aimed purely at relieving symptoms should never precede the appropriate diagnostic tests and at least a reasonable provisional differential diagnosis.

Because the power of expectancy and compliance effects is so strong, both therapists and recipients must be "blind" with respect to active treatment versus placebo status.[49] Such precautions are necessary because barely perceptible cues, unintentionally conveyed by unblinded treatment providers, can bias trial results. Likewise, those who assess the treatment's effects must also be blind, for there is a large literature on "experimenter bias" showing that scrupulous, well-trained professionals can unconsciously "read in" the outcomes they expect when they evaluate complex outcomes.[49,50]

Defenders of CAM often complain that conventional medicine itself continues to use many treatments that have not been adequately vetted by these standards. This may be so in some instances, but the percentage of such holdovers is grossly exaggerated by the "alternatives."[51] At any rate, this criticism does nothing to enhance the credibility of CAM, for merely arguing that "they're as bad as we are" offers no positive evidence in favor of one's own pet belief. The crucial difference between scientific biomedicine and

CAM is that, unlike the "alternatives," scientific medicine is institutionally committed to weeding out treatments that fail to pass muster, and it does not cling to procedures and theories contradicted by the basic sciences.

Spontaneous remission. Any anecdotally reported cure can be due to a rare but possible "spontaneous remission." Even with cancers that are nearly always lethal, tumors occasionally disappear without further treatment. One experienced oncologist reports that he has seen 12 such events in about 6,000 cases he has treated.[52] Alternative therapists can receive unearned acclaim for such remissions because many desperate patients turn to them out of a feeling that they have nothing left to lose. When the "alternatives" publicize such events, they rarely reveal what percentage of their apparently terminal clientele is represented by these happy exceptions. The exact mechanisms responsible for spontaneous remissions are not well understood, but much research is being devoted to revealing and possibly harnessing the mechanisms that are responsible for these unexpected turnarounds.

Somatization and fear of losing "wellness." Many people can be induced to think they suffer from diseases they do not have. When these healthy folk receive from orthodox physicians the oddly unwelcome news that they have no sign of disease, they often gravitate to alternative practitioners, who can always find something to treat. If "recovery" should follow, another convert is born. Alternative healers also cater to the "worried well" who dwell on minor symptoms and believe they must take elaborate precautions to avoid losing their good health.

There are many physical complaints that can both arise from psychosocial distress and be alleviated by support and reassurance. At first glance, these symptoms (at various times called "psychosomatic," "hysterical," or "neurasthenic") resemble those of recognized medical syndromes.[53,54] They are, however, examples of somatization, the tendency to express psychologic concerns in a language of bodily symptoms.[55,56] Although there are many "secondary gains" (i.e., psychologic, social, and economic payoffs) that accrue to those who slip into "the sick role" in this way, we need not accuse them of conscious malingering to point out that their symptoms are nonetheless engendered and relieved by subtle psychosocial processes.[41,56] CAM offers comfort to these individuals who need to believe their symptoms have medical rather than psychologic causes (although, paradoxically, CAM teaches that all diseases stem from mental/spiritual lapses). With the aid of pseudoscientific diagnostic devices, fringe practitioners reinforce the somatizer's conviction that the cold-hearted, narrow-minded medical establishment, which can find nothing physically amiss, is both incompetent and unfair in refusing to acknowledge a very real organic condition. It is obviously worthwhile when unscientific "healers" supply the reassurance, sense of belonging, and existential support that their clients are really seeking, but these provisions need not be foreign to scientific practitioners, who have much more to offer.

CAM customers hedging their bets. In an attempt to appeal to a wider clientele, many unorthodox healers have begun to refer to themselves as "complementary" or "integrative," rather than "alternative" providers. Instead of ministering primarily to the ideologically committed or to those who have been told that conventional medicine has no further treatment, the "alternatives" have begun to advertise their ability to enhance scientific treatments. They accept that orthodox practitioners can alleviate specific symptoms but contend that alternative medicine treats the *real* causes of disease—dubious dietary imbalances and environmental sensitivities, disrupted energy fields, or even unresolved conflicts from previous incarnations.[6] If improvement follows the combined delivery of "complementary" and scientifically based treatments, the fringe practice demands, and often gets, a disproportionate share of the credit.

Misdiagnosis. Scientifically trained physicians do not claim infallibility, and a mistaken diagnosis, followed by a trip to a shrine, alternative healer, or herbalist, can lead to a glowing testimonial for the cure of a grave condition that never existed. At other times, the diagnosis may have been correct but the predicted time course might have proved inaccurate. If a patient with a terminal condition undergoes alternative treatments and succumbs at a later time than that predicted by the conventional doctor, the alternative procedure may receive credit for prolonging life when, in fact, the discrepancy was merely due to an unduly pessimistic prognosis.

Derivative benefits. Alternative healers often have enthusiastic, charismatic personalities.[57–59] Patients swept up by the messianic aspects of CAM can experience a psychologic uplift that can enhance placebo effects and engender other beneficial spinoffs. Elevating patients' mood and expectations can motivate greater compliance with, and hence effectiveness of, concurrent orthodox treatments. These secondary effects also can lead patients to improve their eating and sleeping habits and to exercise and socialize more. These changes, by themselves, could help speed natural recovery, or at the very least, make the recuperative interval easier to tolerate. Psychologic spinoffs of this kind also can reduce the stress that has been shown to have deleterious effects on the immune system.[60] Removing this added burden may speed recovery, even if it is not a specific effect of the therapy.

CONCLUSIONS

Potential clients should ask whether any alternative treatment they are considering is supported by research published

in biomedical journals whose peer-review processes strive to eliminate experimental artifacts that lead to false impressions of cures. Even then, because any single finding could always be due to an undetected confounding variable or a statistical fluke, independent replication is essential. If a supporting publication meets the foregoing criteria, clients should nevertheless always review the size of the reported treatment effect, for there are many "true but trivial effects" that are statistically significant but too small to be clinically useful.

One should be suspicious if, instead of randomized controlled trials, the "evidence" consists of anecdotes, testimonials, or self-published pamphlets or books. Supportive documentation should come from impartial scientific periodicals rather than from journals owned by promoters of the questionable practice or the "vanity press," which accepts virtually all submissions and charges a fee to the authors for publication.

Clients should be dubious of any practitioner who (1) is ignorant of or hostile to mainstream science; (2) cannot supply a reasonable rationale for his or her methods; (3) uses promotional patter laced with allusions to spiritual forces and vital energies or to vague planes, vibrations, imbalances, and sensitivities; (4) claims to possess secret ingredients or processes; (5) appeals to ancient wisdom and "other ways of knowing"; (6) claims to "treat the whole person" rather than organ-specific diseases; or (7) claims to be persecuted by the establishment and encourages political action on his or her behalf, or is prone to attack or sue critics rather than responding with valid research. Practitioners with degrees from unaccredited institutions or who sell their own proprietary concoctions in their offices and stress the need for frequent return visits "in order to stay well" are also a cause for concern. The presence of pseudoscientific or conspiracy-laden literature in the waiting room ought to set a clear thinker looking for the exit. And, above all, if the promised results go well beyond those offered by conventional therapists and it is claimed that there are no side effects, the probability is that one is dealing with a quack. In short, if it sounds too good to be true, it probably is.

When people become sick, any promise of a cure is beguiling. As a result, common sense and the willingness to demand evidence are easily supplanted by false hope. In this vulnerable state, the need for critical appraisal of treatment options is more—rather than less—necessary. Those who still think they can afford to take a chance on the hawkers of untested remedies should bear in mind Goethe's wise advice: "Nothing is more dangerous than active ignorance."

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ARTICLE

The Importance of Using Scientific Principles in the Development of Medicinal Agents from Plants

Pamela Talalay, PhD, and Paul Talalay, MD

ABSTRACT

The authors review the major scientific milestones and the legislative framework that have made possible the spectacular successes of many modern therapies that trace their origins to plants. They emphasize that drugs used in mainstream medicine, in contrast to most of those used in alternative medicine, are required to meet stringent federal requirements for purity, safety, and efficacy before they can be distributed to the public, and that the necessary testing requires much time and effort. Yet alternative medicines based on plant substances are extremely popular, even though their safety and efficacy have not been scientifically proven. Reasons for this are reviewed and numerous examples and case histories are cited illustrating both successes in the scientific development of drugs from plants and the dangers of unregulated drugs. Such drugs are more easily available because of the deregulating effect of the 1994 Dietary Supplement Health and Education Act (DSHEA), which has substantially weakened the authority of the Food and Drug Administration to ensure the safety of dietary supplements. The authors describe the rigorous scientific investigations of curcumin, from the ginger family, and of sulforaphane, from crucifers, to illustrate the long and demanding scientific process that is required to establish the safety and effectiveness of potential drugs from plants. They re-emphasize the necessity for strict scientific review of all drugs. They also recommend that all providers of care be required to question patients about their intakes of dietary supplements. The authors close by saying that the DSHEA is "a disaster waiting to happen," but warn that any attempts to strengthen current legislation will be opposed by special interests.

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Plants have played a central role in the prevention and treatment of disease since prehistoric times. It seems, therefore, paradoxical that of the many hundreds of plant remedies described in the Papyrus of Ebers, discovered in Egypt and written in about 1550 BC, only a handful of products currently appear among the accepted remedies in the United States Pharmacopoeia. But upon reflection, this disparity makes sense. The empiric process of identifying medicinal agents by trial and error is not an efficient one, and countless individuals no doubt have succumbed following treatments with plant products that were poisonous and/or ineffective. With the blossoming of scientific medicine in the 20th century, the discovery of new drugs has come to depend on the application of rational codified principles, providing an understanding of why some treatments are effective and others are not, and how we can tell the difference.

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CONTRASTING CRITERIA

A significant number of the many potent modern drugs used today trace their origins to plants. But there is a fundamental difference between such drugs used in "alternative" medicine and bona fide drugs used in mainstream medicine: all drugs of the latter type, whether of plant origin or not, must meet federally decreed stringent requirements for purity, safety, and efficacy before they can be distributed to the public.

These scientific criteria are not mandated for or met by most of the popular plant remedies used in alternative medicine. Although many plant agents have been used for centuries and are obviously "natural," the popular perception that this attribute alone guarantees safety is as naïve as are assumptions that time has proven their effectiveness. Almost no alternative treatments have been subjected to the exacting criteria mandated for conventional therapies. Many, if not most, plant products used in alternative medicine comprise multiple components that have not been rigorously characterized, are difficult to quantify, and vary qualitatively and quantitatively from plant to plant, in different plant parts, and according to stages of plant development and conditions of growth. These problems were recently addressed comprehensively in a symposium entitled "Botanicals: A Role in U.S. Health Care?"[1]

What, then, is responsible for the extraordinary explosion of interest in alternative medicines? In the 1960s, "green, organic, and natural" became buzzwords that attained maturity in the 1990s, when consumers increased their interest in self-care and in controlling their own destinies. Many turned to "holistic" medicine. People became tired of the high costs of treatment that was often impersonal, and with the difficulty in identifying compassionate and nurturing physicians. They also were disappointed by the failure of modern medicine to cure the increasingly prevalent chronic diseases, in contrast to its dramatic successes in treating acute illness.

This tide of popular dissatisfaction was seized upon by promoters of "health foods," who engaged in relentless advertising. Soon, more than half of the U.S. population was consuming health foods, including huge quantities of vitamins that most people did not need. Politicians whose states were prominent suppliers to the health food industry pursued this trend. Thus, apparently well-intentioned efforts to enact new legislation concerning health foods and supplements—to protect the public's health—were in part heavily motivated by commercial interests.

Moreover, perceptive and persuasive arguments presented by Beyerstein[2] establish why, in many cases, bogus therapies can appear to be effective. These situations include, for example, fluctuations in the natural courses of many chronic diseases and the extraordinary effectiveness of placebos.[3] Thus, the apparent successes of alternative strategies have strengthened the public's resolve to try alternative medicines and have fueled an exceptionally vigorous industry that is growing at several times the rate of the overall economy.

To put the impact of these forces into an organized framework, we trace the major scientific milestones and the legislative framework that have made the many spectacular successes of modern therapeutics possible. We then describe how these hard-won and dramatic advances suffered a substantial setback by enactment of the Dietary Supplement Health and Education Act of 1994 (DSHEA), a measure that significantly weakened regulations designed to protect the health of the public. We conclude with a discussion of two illustrations of research on potentially important plant-derived therapeutic or prophylactic agents (already present in some foods) that are being pursued through rigorous scientific methods. We emphasize the remarkably demanding, time-consuming, and expensive scientific efforts that are required to establish the safety and efficacy of such agents.

SCIENTIFIC DEVELOPMENT OF MODERN DRUGS

In the last 100 years, four major developments have played a critical role in the extraordinary achievements of modern therapeutics in the United States and throughout the world. These developments include the codification of the principles of (chemo)therapy; introduction of the controlled clinical trial; enactment of federal drug laws and regulations; and creation of the U.S. Food and Drug Administration (FDA) and similar bodies in other countries.

Codification of Principles of (Chemo)therapy

In the early 1900s, Paul Ehrlich, the "father of chemotherapy," formulated the basic principles that govern modern therapeutic discovery. He

- demonstrated that drugs could be developed by deliberate and planned chemical synthesis and did not have to be of natural origin;
- advocated systematic exploration of the relation of structure to biological activity to identify the structural features of molecules responsible for therapeutic activity and to distinguish them from the features responsible for toxicity;
- emphasized the importance of achieving selective toxicity by maximizing the ratio of the dose required to produce toxicity in the host to that required to cure the disease; and
- underscored the importance of developing animal models of diseases that provide quantitative measures of both therapeutic potency and toxicity.

The Controlled Clinical Trial

It is likely that the first randomized, placebo-controlled, blinded clinical trial was that devised in 1948 to evaluate the efficacy of streptomycin in the treatment of tuberculosis.[4] Since that time, the controlled clinical trial has become the objective scientific standard for evaluating the efficacies of therapeutic procedures. The design of controlled trials has evolved to include randomization of research subjects to

achieve uniformity of groups; inclusion of placebo controls; blinding (ideally double blinding) of subjects and researchers to the identity of the treatment group; statistical validation of results; and the requirement for informed consent by participating subjects, based on the compelling arguments advocated at the Nuremberg trials for ethical and humane treatment of participants in clinical trials.

Although controlled clinical trials are now commonplace, many advocates of alternative medicine neither follow these guidelines nor believe in their importance. Instead, they rely heavily—as does the population at large—on anecdotal reports of effectiveness of treatment. They subscribe to the notion that therapy must be individualized and that ultimately only the healer knows what is best for the individual patient. This belief is bolstered in part by the conviction that the controlled clinical trial is not capable of assessing mind–body interactions that alternative practitioners believe underlie much of human illness.

Federal Drug Laws

At the beginning of the 20th century, a plethora of medicines was available to the public to cure an extraordinary variety of real and imagined human afflictions. Moreover, extravagant testimonials and merciless advertising struck fear into the minds of the public about the prevalence of these diseases and offered improbable assurances of their curability by the countless nostrums that flooded the market. This state of affairs has been well described by Holbrook.[5] The chemical or plant constituents of these patent medicines were not disclosed, even when the preparations contained narcotics or alcohol. Foods were also often adulterated and misleadingly described.

In 1906, in response to this chaotic state of affairs, Congress passed the first Pure Food and Drug Act, which was signed into law by Theodore Roosevelt. It was in essence a *labeling* law, requiring foods and drugs in interstate commerce to be labeled with truthful descriptions of their contents. It prohibited false or misleading labeling but exercised no control over safety or promotion of extravagant health claims. The law did not apply to imported products. Interestingly, the real pressure to pass this law had little to do with its unassailable logic. Rather, impetus for this measure stemmed from public outcry against the notoriously insanitary conditions in the Chicago stockyards, described by Upton Sinclair in his novel *The Jungle*; a series of articles by Samuel Hopkins Adams, "The Great American Fraud," that appeared in *Collier's* magazine in 1905 and attacked patent medicines; and the reports of Harvey W. Wiley, chief chemist of the Department of Agriculture, who found extraordinary contaminants in human foods. As described below, the major amendments to the 1906 law have also been propelled by public pressure resulting from a series of medical tragedies.

The Federal Food, Drug, and Cosmetic Act of 1938 required, for the first time, that drugs be tested for *safety*. The manufacturer of a new drug would be required to submit to the FDA a New Drug Application (NDA) containing information about the composition, quality, labeling, and directions for administration of the drug, as well as evidence for its safety under the recommended conditions of use. In retrospect, it seems unbelievable that this rational, and even obvious, requirement that drugs be safe before permitting administration to humans was not mandated earlier.

The 1938 law contained no requirement that drugs be effective. They could be without activity (and many were), provided they were appropriately labeled and complied with safety requirements. A drug would be automatically approved in 60 days if the FDA filed no objection. Some control over advertising was vested in the Federal Trade Commission, and drugs already marketed were exempted as being Generally Recognized as Safe (GRAS). Again, the public played an important role in pushing for the introduction of a safety requirement as a result of a human tragedy, in which a pediatric "elixir of sulfanilamide" was marketed as a cherry-flavored solution in ethylene glycol. Tragically, the glycol was toxic and 107 children died. The government was able to seize and stop distribution of the "elixir" for mislabeling, because an elixir by definition is a solution in alcohol, in which sulfanilamide is not sufficiently soluble.

Another 24 years elapsed before the enactment of the Harris–Kefauver amendments (1962) to the Federal Food, Drug, and Cosmetic Act. The interesting history leading up the adoption of this legislation can be found in two monographs: *The Real Voice*,[6] by Richard Harris, published in 1964, and *In a Few Hands: Monopoly Power in America*,[7] by Estes Kefauver (published posthumously in 1965). These rational advances in drug legislation required, for the very first time, proof that drugs were *effective* for their intended uses. The law mandated, also for the first time in history, stringent adherence to scientific guidelines for testing of drugs. Preclinical toxicity studies and evidence of efficacy were both required to precede strictly phased controlled clinical trials, thus assuring maximization of information while minimizing hazards to human participants. Clinical evaluations had to be carried out by individuals who were specially qualified by training and experience, based on the concept that not all physicians were equally competent to develop such information.

The strictly formalized regulations for evaluating effectiveness for intended use also included a requirement for filing an Investigational New Drug (IND) application prior to initiating clinical studies, and if approval was given by the FDA, subsequently submitting a New Drug Application (NDA). Other major requirements were full disclosure of information about effectiveness, contraindications to use,

and side effects. Most important, careful keeping of records of adverse reactions to new drugs and their reporting to the FDA were mandated. Approval of prescription drug advertising was vested in the FDA. The FDA was also assigned the massive task of reviewing retrospectively the efficacies of all drugs marketed between 1938 and 1962. When this daunting task was finally completed, many of these entities did not survive.[8]

These laws and the ensuing regulations defined the "gold standard" for the world on how drugs should be developed scientifically to provide reasonable assurances that marketed medications were both safe and effective. Passage of the 1962 amendments was fought with acrimony by special-interest groups who predicted that their enactment would result in the demise of therapeutic innovation and of the pharmaceutical industry. However, public furor over the tragic consequences of the use in Europe of thalidomide, the notorious teratogen that caused the birth of more than 10,000 children with phocomelia ("seal limbs"), provided the impetus for passage of the amendments. Contrary to predictions, the pharmaceutical industry has never been stronger. Indeed, by setting high scientific standards for the development of new agents, these regulations were largely responsible for the rapid growth and spectacular achievements of the ethical pharmaceutical industry in the last 35 years.

These major, and now widely accepted, four principles (purity, truth in labeling, safety, and effectiveness) are at the heart of modern therapeutics. They are responsible for the usefulness of most modern drugs administered for the treatment of many serious diseases, and the amelioration of much suffering. We believe that the merits of alternative forms of treatment can and must be rigorously assessed according to the same fundamental principles if we are to avoid public tragedies similar to those described above. And yet, we are in danger of losing some of this hard-won scientific therapeutic rationalism with the recent passage of the Dietary Supplement Health and Education Act (DSHEA).

THE DIETARY SUPPLEMENT HEALTH AND EDUCATION ACT

In 1994, the U.S. Congress enacted legislation defining a new class of products that were classified as "dietary supplements," based on the belief that they provided health benefits. These products were legally neither foods nor drugs. They were defined as containing one or more of the following types of substances: a vitamin; a mineral; an herb or other botanical; an amino acid; or a concentrate, metabolite, extract, or combination of any of these ingredients. These products, intended to be ingested in pill, capsule, tablet, or liquid form, were required to be labeled as dietary supplements. The categories of agents classified by law as dietary supplements are enormously diverse, and include many substances that were already being advocated, sold, and perceived to provide health benefits. They were not a rational compilation of materials meeting specific health or medical needs.

What prompted the development of this new legislation? Since it was, and is, a top priority of the federal government to improve the public's health status, and scientific studies have documented the importance of nutrients and dietary supplements to health promotion and disease prevention, the act ostensibly was designed to ensure that safe and appropriately labeled products remain or become available to the public. Although this was a worthy goal, it seems likely that pressure from the public, and particularly from the health food industry, played a major role in the enactment of the DSHEA. Many individuals believe that they are entitled to choose their own preventive health care programs, and that the government should not impose unreasonable regulatory barriers to slow the flow of safe products to consumers (although it should act quickly against unsafe or adulterated products). Moreover, consumers were already relying increasingly on nontraditional and unusual health practices to provide a more "holistic" approach to treatment and to avoid costly traditional medical care, which was often perceived as impersonal. Indeed, almost half of the U.S. population had been consuming supplements of vitamins, minerals, or herbs in the belief that these substances improve nutrition and health. Such supplements are usually considered to be safe within a broad range of intakes. Perhaps one of the most compelling reasons for enactment of the DSHEA was that the United States was spending about 12% of its gross national product (GNP) on health care and that the nutritional supplement industry had become an integral part of the U.S. economy, showing a consistently positive trade balance and enormous annual sales. In our view, DSHEA is a form of *deregulation*, and it is by no means clear that it has led to safer "dietary supplements" being made available to the public.

Why has this situation occurred? There are two overriding reasons: First, despite requirements for precise information about specific ingredients, most of the herbal preparations now marketed contain numerous components that defy chemical characterization. Second, whereas the manufacturer of conventional drugs must provide proof of safety, the manufacturer of "natural" dietary supplements is *not* required to establish product safety. Instead, the burden of safety has been placed on the FDA, which depends on information supplied by customers or their advocates.

In order to withdraw a marketed dietary supplement, the Secretary of Health and Human Services must determine (1) that the product poses an imminent hazard to public health or safety under recommended conditions of use, or (2) that

it is adulterated. It is difficult for the Secretary to comply with these requirements because reporting of adverse effects of dietary supplements is not mandated. The dietary supplement product label must carry the disclaimer: "This statement has not been evaluated by the Food and Drug Administration. This product is not intended to diagnose, treat, cure, or prevent any disease." Nevertheless, surveys have shown that the public assumes, from mention of the Food and Drug Administration on the label, that the opposite is true, and that the FDA has condoned marketing and use of the supplement. Furthermore, although the DSHEA does not permit health claims unless there is convincing clinical evidence, claims for maintenance of healthy or normal "structure and function" are allowable.

Thus, a label may state that a product "maintains normal cardiovascular function and a healthy circulatory system" but not that it "reduces blood pressure" (unless there is proof that it does so). It may claim that it "maintains a healthy cholesterol level" but not that it "lowers cholesterol," unless the FDA accepts proof that it does. As a consequence of these claims promoting health maintenance, the dietary supplement industry is booming and herbal remedies are being combined with other over-the-counter preparations such as vitamins, many of which also qualify as dietary supplements.

DANGERS OF MANY DIETARY SUPPLEMENTS

Concerns over the toxicity of many herbal preparations and plant-derived products contained in dietary supplements are ever-present issues, especially now that the alternative medicine movement is relying increasingly on "natural" supplements, and their regulation under DSHEA has been loosened. In a recent review,[9] Ernst cites allergic reactions, toxic reactions, possible mutagenic effects, drug interactions, drug contaminations, and mistaken plant identities in his attempt to classify the scope of adverse reactions induced by botanical medications in common use in the Western world.

These issues have become of such importance that the FDA has voiced its concerns through efforts to educate health professionals and notify dietary supplement manufacturers. The reader is referred to a 1993 FDA review document entitled "Unsubstantiated Claims and Documented Health Hazards in the Dietary Supplement Marketplace,"[10] especially the section, "Illnesses and Injuries Associated with the Use of Selected Dietary Supplements." The following examples focus on some toxicities reported since 1992 and probably represent only a small fraction of their incidence, because many remain unrecognized and/or unreported.

- Jane Brody, writing in *The New York Times*, remarks that "under the new law, entitled the Dietary Supplement Health and Education Act, it is up to the FDA to take products off the market only after they have proved dangerous to people taking them. Only when a new ingredient is introduced is the company obliged to provide the drug agency with documentation of its presumed safety."[11]
- Dr. Lori Love of the FDA states that "there are currently no federal regulations that establish specific criteria for purity, identification, and manufacturing procedures of dietary supplements." The drug agency researchers have pointed out that there are no requirements to maintain pharmaceutical standards, and that there are no requirements for mandatory reporting to the FDA of adverse events by the manufacturer or distributor of these products. Rather, it is up to the agency and physicians to detect and report them.
- Many, and perhaps most, people who take over-the-counter dietary supplements never report untoward events to their physicians. Even if they suffer such adverse reactions, they often are embarrassed to tell their doctors what they have been taking. Thus, physicians mistakenly may attribute supplement-caused adverse effects to the illness or to conventional treatment that has been prescribed, which in turn can result in unwarranted and hazardous changes in the patient's medical care (e.g., withdrawal of an effective or even essential drug).[11]
- These problems are clearly illustrated in a recent article concerning the contamination of botanical dietary supplements by *Digitalis latana*,[12] in which the case histories are described of two women who were brought to the emergency room and diagnosed as having heart block. This condition was subsequently attributed to the toxicity of cardiac glycosides, although neither patient was known to be taking these substances. Instead, both patients had taken an oral regimen of dietary supplements for "internal cleansing." The supplements were marketed as a "program," which, according to the label and accompanying materials, consisted of 37 ingredients, including 14 different herbs and six species of bacteria. Analysis revealed that the "cleansing" material contained cardiac glycosides, which were then traced to plantain contaminated with *Digitalis lanata*. The plantain in question was part of a 6,000-pound shipment imported into the United States over about two years that had been received by more than 150 manufacturers, distributors, and retailers. Extensive efforts were then made to inform all of these groups. The authors of the report cite several reasons for the widespread and protracted distribution of a potentially lethal product.[12]

We also cite here a few more examples of the potentially life-threatening hazards of herbal products that may be contaminated with powerful toxins.

- One of the most graphic and devastating examples of the toxic potential of plant preparations concerns the development of renal failure and epithelial cancers of the urinary tract in humans who consumed certain Chinese herbs. The recognition of this association illustrates the extraordinary vigilance and detective work that was required to make this association.

  This still-unfolding story began almost ten years ago in a Belgian clinic that offered a weight-reduction regimen that included two Chinese herbs as well as appetite suppressants and other components. Rapidly progressive renal failure, necessitating dialysis and ultimately leading to a number of kidney transplants, was observed in a large number of young women. Deft detective work revealed a strong association of these cases of renal failure with the inclusion of certain Chinese herbs in the weight-reduction program. The condition became known as "Chinese herb nephropathy," and in Great Britain two cases of end-stage renal failure requiring dialysis were attributed to a Chinese herbal eczema remedy that contained known nephrotoxins.[13]

  In the case of the Belgian clinic, there seems to have been some confusion over similarities of herbs and their Chinese names.[14–16] Apparently one of the Chinese herbs (*Aristolochia fangchi*) contains known nephrotoxins (aristolochic acids: nitrophenanthrene carboxylic acids). These compounds were also well recognized carcinogens in laboratory animals. It was therefore not surprising that cancers of the urinary tract were reported to occur in individuals who consumed the aforementioned herbs. Urothelial neoplastic lesions were detected in the urinary tracts of patients undergoing renal transplantation for Chinese herb nephropathy. A number of these patients were offered the option of prophylactic nephrectomy of the remaining kidney. Among the 39 who accepted the surgical procedure, 18 were found to have urothelial carcinoma (17 cases of carcinoma of the ureter or of the renal pelvis, or both, and one case of carcinoma of the bladder).[17]

  In an editorial commenting on this report, David A. Kessler, a former Commissioner of the FDA, wrote, "Congress has shown little interest in protecting consumers from the hazards of dietary supplements, let alone from the fraudulent claims that are made, since its members apparently believe that few of these products place people in real danger. Nor does the public understand how potentially dangerous these products can be."[18]

- Other examples of contamination of nonprescription medicines include Asian patent medicines collected from retail herbal stores in California that were found to be contaminated with dangerously high levels of heavy metals.[19] For example, of 251 products analyzed, 35 contained from 22.4 to 5,070 ppm of mercury. The U.S. Pharmacopoeia limits heavy metals to 30 ppm, and even lower levels for lead, arsenic, and mercury.

- In 1990, the U.S. Centers for Disease Control summarized information about 1,536 cases of eosinophilia–myalgia syndrome reported to them from all parts of the United States, with 27 deaths at that time.[20] These illnesses were associated with the consumption of L-tryptophan-containing dietary supplements advocated to improve sleep. Eosinophilia–myalgia is a serious connective tissue disease characterized by severe muscle pain, elevated white blood cell counts, and a variety of neuromuscular and skin abnormalities. The number of contaminating impurities found in these tryptophan preparations was very large. While the precise identity of the agent(s) causing the syndrome was unclear in the absence of a suitable animal model, tryptophan itself or a condensation product of two molecules of tryptophan with acetaldehyde may have been the major culprit.[21] The contaminants arose during the production of tryptophan by microbial fermentation and/or subsequent processing. Since the surveillance definition for reporting eosinophilia–myalgia required not only severe debilitating myalgia but also a massive eosinophilia, it seems highly likely that many more individuals were affected with less severe forms of the syndrome.

- Ephedrine alkaloids, derived from ephedra herbs, sometimes called ma huang, are amphetamine-like compounds with powerful stimulant effects on the nervous system and heart. Between 1994 and 1997, the FDA investigated more than 800 reports of adverse events associated with the use of ephedra products, most of which occurred in young to middle-aged adults who were otherwise healthy. These adverse events included high blood pressure, irregular heart rate, insomnia, nervousness, tremors and seizures, paranoid psychoses, heart attacks, strokes, and death.[22] In 1997, the FDA proposed limiting the daily intake of ephedra alkaloids to 24 mg and required labels that warned consumers not to take ephedra products for more than seven days and that taking more than the recommended dosage could result in heart attack, stroke, seizure, and death. Following a strong lobbying effort by the dietary supplement industry (annual sales of ephedra-containing products last year exceeded $1-billion), the FDA was requested to provide "stronger evidence" of the relationship between ingestion of ephedra-containing food supplements and their reported adverse effects. Meanwhile, in the absence of an official FDA safety warning, in

thousands of Internet postings, users continue to praise ephedra for raising their energy, helping them lose weight, and sharpening their muscle tone.

- St. John's wort (*Hypericum perforatum*), an over-the-counter herbal extract, is being widely used for the treatment of clinical depression, although its effectiveness has not been demonstrated in controlled clinical trials. As with most other folk remedies, little information is available regarding the basic pharmacology of this herbal. It contains many biologically active components, of which the hypericins may be responsible for effects on the central nervous system.

  Recently, a routine pharmacokinetic study in human volunteers showed that addition of St. John's wort to several therapeutic regimens reduced markedly the blood levels of indinavir, a protease inhibitor used in the treatment of AIDS,[23] and of cyclosporin, a drug used to prevent transplant rejection.[24] Following these reports, the FDA issued a public health advisory warning that St. John's wort appears to induce cytochrome P-450 enzymes—a key pathway for the metabolism of prescription drugs, including many of those used to treat heart disease, depression, seizures, and certain cancers, or to prevent transplant rejection or pregnancy (oral contraceptives). These important drugs, often prescribed for life-threatening conditions, can lose their therapeutic effects when given concomitantly with St. John's wort. A review of the effects of St. John's wort in decreasing the effectiveness or increasing the toxicity of conventional drugs recently appeared in the *Medical Letter*.[24]

  Thus, a routine pharmacokinetic study (one required for drugs subject to FDA approval, but not for herbal remedies), revealed the potentially serious consequences associated with the co-administration of a supposedly harmless natural product. All herbals contain many chemical components, some of which induce drug-metabolizing enzymes, and many more drug interactions with herbal remedies are likely to surface in the future.

- Even normally safe products can be harmful if they are consumed together with certain conventional drugs prescribed for specific medical conditions. Thus, plant estrogens in herbal preparations used for treatment of prostate cancer were present at sufficiently high levels to affect patients who were already prescribed estrogenic steroids.[26]

In a recent issue of *The New England Journal of Medicine*,[27] the Editors called for vigorous testing of all products, stating, "It is time for the scientific community to stop giving alternative medicine a free ride." This request was echoed by articles in *JAMA*[28] and other responsible publications. The loosening of regulatory requirements by the DSHEA has been a bonanza for the already wildly successful health food industry, and has deprived the FDA of its ability—and reversed its statutory responsibility—to guard the health of the public. Unfortunately, it is likely that sooner or later another public health crisis will force Congress to reexamine and reformulate the provisions of the DSHEA.

PROGRESS IN SCIENTIFIC DEVELOPMENT OF DRUGS FROM PLANTS

While stressing the dangers of inadequately regulated herbal remedies, we should not forget that plants have provided a multitude of life-saving drugs. List 1 provides examples of plants and other sources producing important drugs that have been in use for centuries. Fourteen of the drugs in current use for cancer chemotherapy occur naturally, and of these, five originate from plants. Nevertheless, the long and arduous scientific journey from the discovery of the pharmacologic activity of a plant or tissue extract to the development of a useful drug of proven efficacy and safety is not widely appreciated by the many individuals who seek "cures" for their ailments or wish to "buy insurance" against becoming ill.

List 1

Drugs That Are, or Were Originally, Obtained from Plants or Other Natural Sources

Important drugs from plants that grow in the wild

Colchicine: from *Colchicum autumnale*, to treat gout
Digitalis: from *Digitalis purpurea*, for congestive failure
Opium: from *Papaver somniferum*, analgesic
Quinine: from *Cinchona* (Peruvian fever tree), antimalarial

Chemotherapeutic agents for cancer and their original sources

Plants as sources:
Etoposide and podophyllotoxin (Mayapple rhizome)
Taxol (Pacific yew bark)
Vinblastine and vincristine (Madagascar periwinkle)

Molds and bacteria as sources:
Actinomycins
Bleomycin
Daunorubicin

Animals as sources:
Interferons
Interleukins
Steroids

Two Case Studies

To illustrate the scientific development of a proven drug from plants, we have selected two representative examples of phytochemicals that are currently being developed as potential therapeutic and/or disease-protective agents. These are curcumin, an ancient spice, which continues to occupy a place in our diet and to be widely used in Asian medicine for a variety of medical conditions; and sulforaphane and its glucosinolate precursor, which were recently isolated from broccoli and other cruciferous vegetables in a search for chemoprotective agents that reduce the risk of developing cancer.

Curcumin. Curcumin is a spice that is widely used as a bright yellow coloring and flavoring agent. It is the major yellow pigment obtained from turmeric, the powdered rhizome of *Curcuma longa*, a Southeast Asian member of the ginger family. References to the healing power of *C. longa* are found in early Asian texts, in which the component of this plant was known by a variety of names, the most common of which is the Sanskrit term, haridra. In the West, where it is used as a constituent of curry, the more familiar name is turmeric.

In Chinese medicine, it is one of the herbs that "invigorate" the blood and stimulate the Qi, which vitalizes the body, propels, and warms.[29] All texts describe its bitter taste and astringent and antiseptic properties. The *Materia Medica of Tibetan Medicine* describes haridra as "hot in potency, unctuous and promoter of the complexion of the body."[30] It is claimed not only that haridra eliminates waste products from the body, but that it also cures poisoning, itches, *kustha* (obstinate skin diseases, including leprosy), chronic rhinitis, and anorexia. As late as 1931, the *Vegetable Materia Medica of India and Ceylon*[31] attributed a host of curative properties to turmeric from *C. longa*, including: "astringent and antiseptic—topically effective for wounds, boils, ulcers, eczema, and psoriasis; when mixed with olive oil—relieves measles, chicken pox, small pox, and prevents spread of disease; used internally—stomachic, carminative, cholagogue, relief of liver congestion, febrifuge and expectorant, valuable in bronchitis, and pneumonia, and beneficial in diabetes; used externally—a treatment for bites of snakes and other animals." Although this suspiciously long list of curative properties resembles those of some bogus nostrums of the 19th century, curcumin has been extensively investigated over the past 20 years by modern scientific methods. These studies have demonstrated unequivocally its remarkable and potent antioxidant, anti-inflammatory, antiangiogenic, and antitumor properties in a variety of experimental systems.[32,33]

The chemistry of the active principles of turmeric is now well understood: it consists largely (about 80%) of curcumin, with the remainder comprising two curcuminoids lacking one (demethoxycurcumin) or two (bisdemethoxycurcumin) methoxyl groups. Curcumins block carcinogen-induced tumor formation in a variety of animal models, and appear to affect both the initiation and promotion phases in two-stage models of carcinogenesis. Curcumin is antimutagenic, scavenges free radicals, reduces carcinogen–DNA adduct formation, and decreases the expression of several oncogenes. Curcumin has been under development as an anticancer agent by the Chemoprevention Branch of the National Cancer Institute since 1988.[32]

Extensive preclinical toxicity studies have been completed, and based on knowledge of its pharmacokinetics, the planning and implementation of efficacy studies in humans are in progress. *It has taken more than 12 years of intense, systematic, planned effort to reach this stage in the development of curcumin as a potential protective/therapeutic agent.* Its development serves as an example of the extraordinary length of time and effort that may be required to produce a safe and effective treatment based on sound scientific principles from a herb that has been widely used for centuries. Preclinical efficacy, pharmacology, and toxicology must all be completed before Phase I studies in human volunteers can be undertaken. At that point, the issue of identifying surrogate markers for the protected state has to be resolved. If all of these are compatible with safety, and there are sufficient indications of efficacy, consideration can be given to intervention trials in populations that are at high risk for the development of cancer.

Sulforaphane. The isolation and identification of sulforaphane as an anticancer agent illustrates the strategy of surveying plants for a desired biological activity by means of bioassays specifically developed for this purpose.[34,35] The logic of this strategy was based on the demonstration that the elevation (induction) of phase 2 detoxification enzymes in animals reduced their susceptibility to the neoplastic effects of certain carcinogens. A simple bioassay was developed for measuring the potency of inducers of phase 2 enzymes; this involved measurement of the activities of a quinone reductase in animal cells grown in microtiter plates.[34] A systematic survey of the inducer activities of a wide variety of edible plants identified cruciferous vegetables (broccoli, Brussels sprouts, cabbage, cauliflower, kale) as particularly rich sources of this type of inducer activity.[35] The isothiocyanate sulforaphane was isolated from one variety of broccoli as the principal and extremely potent inducer of phase 2 enzymes.[35] Sulforaphane was then shown to reduce the incidence, multiplicity, size, and rate of growth of mammary tumors when administered to rats treated with the potent carcinogen, dimethylbenz(a)anthracene, thereby confirming the validity of the inducer bioassay-based isolation strategy.[36]

The enormous variability of the inducer activities of commercially available broccoli samples prompted a systematic

search for sources of higher and more consistent inducer activity. Certain cultivars of three-day-old broccoli sprouts were demonstrated to contain 20- to-50-fold higher levels of the glucosinolate of sulforaphane than an average mature broccoli.[37] Active studies are now under way to establish the safety and efficacy in humans of broccoli sprout extracts containing sulforaphane and glucoraphanin, its naturally occurring glucosinolate precursor.[38] Although many individuals consume substantial quantities of broccoli, the establishment of safety and tolerance must be completed, and effects on biomarkers for chemoprotective efficacy established, before chemoprotection trials in human populations with high cancer susceptibility can be organized.

These accounts of two compounds, curcumin and sulforaphane, which appear to be safe natural products that have been widely consumed for centuries, provide examples of the stringent scientific testing that must be undertaken to develop pharmacologic agents with proven safety and efficacy. They illustrate the types of rigorous evaluations that should be applied to alternative medicines.

CONCLUSION

Although many valuable drugs in current widespread use originate from plant sources or exist as chemically modified forms of naturally occurring phytochemicals, there is no reason to believe that a drug for every disease exists in nature. There is, however, every reason to require that all plant products used as drugs be evaluated for safety and efficacy by methods identical to those used for novel synthetic entities, according to widely (and wisely) accepted principles and procedures. These practices include evaluation of preclinical safety and efficacy; controlled phased clinical trials (placebo-controlled, randomized, double-blind, statistically validated) on research participants who have given informed consent; and a requirement that such trials be conducted in compliance with federally mandated regulations.

We also recommend that every physician, physician's assistant, nurse, or other health provider be required to interrogate every patient with respect to his or her intake of "dietary supplements." We believe that the DSHEA, which places on the FDA not the burden of approval, but only the obligation to order their withdrawal when the Secretary of the Department of Health and Human Services perceives an imminent danger, has substantially weakened the authority of the FDA with respect to ensuring the safety of dietary supplements. *In our view, the DSHEA is a disaster waiting to happen.* All previous major legislation relating to drug safety resulted from public health catastrophes (e.g., those caused by insanitary stockyards, elixir of sulfanilamide, and thalidomide). Unfortunately, attempts to strengthen current legislation will be opposed by special interests. We must always remember that Calvin Coolidge reputedly said "Idealism is America's ideal," but supposedly also added "Business is America's business."

Note added in proof. Recently Haller and Benowitz[39] reviewed 140 reports received by the FDA of adverse cardiovascular and central nervous system events in subjects taking dietary supplement preparations containing ephedra alkaloids during a 22-month period. They concluded that 31% of the events were definitely or probably related to ephedra intake, and among these there were ten deaths and 13 permanent disabilities. Commenting editorially, Fleming[40] was understandably cautious in inferring that there was proof of associative risk in this study. However, he concluded that by passing the Dietary Supplement Health and Education Act (DSHEA) Congress had created a loophole: "This act allows inadequately tested drugs to be marketed as 'dietary supplements' —an innocuous and even holistic sounding term. . . . A compound containing ephedra alkaloids should not be called a dietary supplement; it is a drug." This view is strengthened by the recent FDA order to withdraw phenylpropanolamine (an alpha-adrenergic agonist closely related to ephedrine) from over-the-counter cold remedies and weight loss aids because of an increased risk of hemorrhagic stroke in women.[41]

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ARTICLE

The Need for Educational Reform in Teaching about Alternative Therapies

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ABSTRACT

Advocacy and non-critical assessment are the approaches currently taken by most U.S. medical schools in their courses covering what is commonly called "complementary and alternative medicine" (CAM). CAM therapies are anomalous practices for which claims of efficacy are either unproved or disproved. The author's research indicates that most medical schools do not present CAM material in a form that encourages critiques and analyses of these claims. He presents the reasons for the unwarranted acceptance of CAM. These include the CAM movement's attempt to alter standards of evaluating therapies. A survey of CAM curricula in U.S. medical schools in 1995–1997 showed that of 56 course offerings related to CAM, only four were oriented to criticism. The author's course at Stanford University School of Medicine approaches CAM with the skepticism and critical thinking appropriate for unproven therapies. The author concludes by calling on all medical schools to include in their curricula methods to analyze and assess critically the content validity of CAM claims.

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I am troubled by the approaches currently taken by most U.S. medical schools in their courses on what is commonly called "complementary and alternative medicine" (CAM). Although CAM therapies are anomalous practices whose claims for efficacy are either unproved or disproved, my research indicates that most medical schools do not present CAM material in a form that encourages critiques and analyses of claims. In this article I briefly present what I believe are the reasons for the unwarranted acceptance of CAM, give highlights of my findings about CAM in the curricula of U.S. medical schools, and describe a course that I teach at the Stanford University School of Medicine that approaches CAM with skepticism and critical thinking. I conclude with thoughts about needed reforms in CAM curricula.

UNWARRANTED ACCEPTANCE OF CAM

The past 30 years have seen increased interest in CAM. But its level of acceptance is not warranted, as many CAM claims have been convincingly disproved or remain unproved. One reason for CAM's high level of acceptance is the movement's attempt to alter standards for validity. Some CAM advocates propose expanding such standards to include the acceptance of historical traditions, subjectivity, ritual, personal experience, and transcendental experience.[1] Others claim that their systems supply emotional support and cultural meaning to illness and that such support may improve course of specific diseases. Although some advocates accept common standards and participate in Cochvane Collaboration reviews for evidence, others reject accepted approaches of controlled clinical trials and other testing methods for traditional medicines and therapies as being not appropriate for certain areas of CAM.[2]

Even though some CAM concepts represent a sharp deviation from the accepted ways of evaluating medical therapies, an unidentified number of physicians and social scientists in the academic community support them. Indeed, many CAM claims have reached a high level of acceptance despite insufficient scientific support. As a result, government and large foundations generously fund the study of disproved methods and the integration of other methods.[3] Unfortunately, some governmental panels have reached erroneous conclusions, while claiming to have based those conclusions on clinical trial evidence. A case in point is the practice of acupuncture, which was approved for certain uses by a consensus conference of the National Institutes of

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Health,[4] although the predominance of evidence from the scientific literature demonstrates acupuncture's ineffectiveness except as a placebo or conditioning agent.[5] Another example is the Agency for Health Care Policy and Research's recommendation of manipulation for back pain,[6] even though the evidence for the usefulness of this therapy is largely negative. With inadequate approaches that fail to uphold criteria for validity and plausibility, so-called "evidenced-based" medicine remains fluid and loses its value to help physicians discern what is truly useful.

Other expert students of the field are speaking out with their opinions about CAM's lack of scientific validity. In a recent article published after the present article was written, Knipschild[7] reviewed briefly his conclusions after developing and reporting numerous systetmatic reviews and meta-analyses of "alternative" methods. While opining that although findings are dubious, there is room for more rigorous trials of acupuncture ("Among the better trials some are positive but many others are negative") and effectively dismissing homeopathy ("ridiculous") and whole herb therapies (he reports that the data are inconsistent), he concluded, "I still believe that, in general, alternative treatments do not work." CAM advocates coined the terms "alternative," "complementary," and "integrative" to increase CAM's acceptance. The terms obscure the fact that the methods they describe are, in fact, unproved or disproved.[8] At the same time, advocates use slogans and myths to diminish the authority of biomedicine's scientific tradition. "Doctors do not know anything about nutrition" demeans standard medicine and medical education. "Cut, burn, and poison" demonizes cancer care. The myth that "only 10–15% of medicine is proved" reduces medicine's credibility and elevates the perceived worth of CAM methods.

CAM IN THE CURRICULUM

Because of the concerns stated above and my observation that many courses that had CAM components were being taught either from an advocacy view or from a "neutral" view—in neither case considering content validity—I surveyed U.S. medical schools in 1995–1997 to learn of their approaches to CAM in their curricula. Representatives of all 125 schools surveyed responded, either to the questionnaire or by phone.

The findings of the survey were not encouraging. Of the 56 schools that had some form of relevant course offering, only nine had invited critical lecturers on occasion; their courses were otherwise generally supportive of CAM. Two course directors claimed to present information "neutrally," but did not teach critical methods or invite critical lecturers. Only four courses either presented a critical orientation or offered critical arguments in a way that significantly investigated advocacy arguments. (The complete findings of this survey are available upon request.)

Since the time of that survey, courses in medical schools concerning CAM have increased from 38 credit courses to 150 such courses in 70 schools.[9] I suspect, however, that the level of skepticism and investigation of CAM claims has not risen from the level disclosed in the 1995–1997 survey. In fact, my own informal observations in November 2000 of 15 randomly selected courses at various medical schools revealed that none had added critical analysis to the course content.

In 1996 the Office of Alternative Medicine (OAM)—now the National Center for Complementary and Alternative Medicine (NCCAM)—convened a three-day meeting on professional school CAM education in the United States. The meeting reviewed various courses and methods of teaching. All sectarian systems and methods were implicitly accepted as effective. Teaching-method evaluation was not addressed, and concern about validity was mentioned only in one address by a dean of a medical school. Courses on acupuncture and chiropractic were accepted in the same context as other courses. OAM organizers did not invite the directors of critically-oriented courses to speak. I do not believe that NCCAM's approach to professional education shows much improvement from that demonstrated at the 1996 meeting.

THE STANFORD COURSE

In the 1970s a student-sponsored lecture series at Stanford University School of Medicine featured speakers whose claims for alternative methods conflicted with rational thought and accepted knowledge. In 1979, after faculty indicated their interest in investigating the validity of CAM claims, I was encouraged to develop a course that I still teach in which students learn how to examine claims factually.

The course, Alternative Medicine—A Scientific Perspective, is modeled after two others existing at that time, one at the Loma Linda University School of Dentistry and one at San Francisco State University School of Public Health. The Stanford course operates on the general principle that science proceeds via a series of statements based on accurate observations and subsequent attempts at proof and disproof. Using this approach, claims for unproved methods are considered suspect. Students are taught to think critically about such claims and are introduced to tools for investigating them.

The course is given for two hours per week for nine weeks. The first segments explore sources of human error that contribute to misperceptions and to drawing incorrect conclusions. Guest psychologists discuss primitive modes of thought, perceptual and cognitive errors, cognitive dissonance, memory faults, and belief formation and perseverance—all associated with unproven medical belief systems. A magician demonstrates principles of misperception, misdirection, legerdemain—such as psychic surgery, and ideomotor action—such as dowsing, pendulum diagnosis, and mind reading. These and other sources of misperceived medical experiences form the bases for testimonials and unproved claims.

Other classes explore phenomena that contribute to pla-

cebo experience, including counterirritation, suggestion, expectation, consensus, conditioning and reinforcement, the natural history of illness, and regression toward the mean. Then others explore language distortion, myths, propaganda techniques, and cult-like behavior, the last sometimes presented by former cult members. Other subjects include mathematical and statistical approaches to coincidences, and probability problems, including prior probability and Bayes' theorem. The final sessions of the first half of the course concentrate on reading scientific and medical literature, principles of clinical trials, and the analysis of famous errors in science.

The last half of the course explores specific subjects, such as electromagnetic fields, vitamins and supplements, acupuncture, homeopathy, Laetrile, and other anomalous cancer therapies. Students learn methods for recognizing misinformation in medical literature. In some years, the course includes consideration of the role of dysfunctional and somatiform syndromes in CAM claims. The schedule is flexible, accommodating subjects such as books by Carlos Castaneda, quantum mechanics and consciousness, and the roles of prayer and "touch" therapies. In some years, students make a field trip to a "Whole Life Expo."

Representatives of CAM systems present talks, followed by students' evaluations using methods learned in the first half of the course. (CAM lecturers understand that they cannot report their presentations on their curriculum vitae or in advertisements.) Students are encouraged to examine a specific method or substance of interest to them. Individual students have chosen on-site visits to acupuncture clinics and other offices, where they may receive treatments or merely observe—they then report their experiences to the class. They are encouraged to relate their subjective experiences and to analyze the material objectively, juxtaposing the two descriptions.

By the end of the course, students are expected to be able to gauge the validity of CAM claims, understand those claims' subjective attraction, and appreciate the values of truly complementary methods. These include relaxation, music, massage, art, poetry, body movement, and forms of meditation. These are methods that enhance adjustment, help reduce symptoms, and add a sense of meaning to the experience of illness.

I have outlined the components of this course above in hopes that others will be encouraged to use similar critical approaches when beginning or revising courses dealing with CAM.

Need for Reform

To my knowledge, there are no formal standards for teaching about CAM in medical schools. If a survey similar to mine were done today, it would probably reveal that most CAM information taught in medical schools continues to be ideologically or advocacy-based, or is taught without concern for a therapy's or system's validity. Medical schools have allowed a double-standard system for teaching. At one extreme, the standard allows instruction about CAM as a set of viable systems of knowledge that can be integrated into practice. And even if the course teaches only *about* CAM therapies —which is more common—it provides little or no critical analysis. The other standard, applied to the usual curriculum subjects, demands both basic scientific validity and clinical evidence-based confirmation.

A consortium of medical schools recently agreed to integrate CAM into their curricula through an evidence-based approach.[10] However, evidence-based analysis of clinical trials is not sufficient to establish validity.[10] Systematic reviews do not incorporate individual reports' errors, inconsistencies, misrepresentations, or subsequent refutations. Nor do they consider plausibility or prior probability based on non-trial data or basic scientific evidence. Such evidence points to the implausibility of "therapeutic touch," homeopathic principles, and manipulative therapy, all of which require extraordinary clinical evidence prior to acceptance.

While I believe that the consortium's approach is one step in the right direction, it is not enough. It is time for all medical schools to make a concerted effort to formally include in their curricula ways to teach students to analyze and critically assess the content validity of CAM claims.

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ARTICLE

The Growing Need to Teach about Complementary and Alternative Medicine: Questions and Challenges

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ABSTRACT

With the increased popularity of complementary and alternative medicine (CAM), there is a growing interest in the topic among physicians, residents, and medical students, who feel an increased need to have proper instruction about CAM therapies. Medical schools and residency programs are starting to respond to this demand, having realized that to provide better care and foster an improved patient–doctor relationship, physicians should become informed consultants, and be able to provide educated advice about CAM to their patients and help them integrate any CAM therapies shown to be safe and effective into their health care. The authors acknowledge that opinions differ about the adequacy of research findings to certify the safety and efficacy of specific therapies, and stress that physicians' decisions about CAM use should be subject to the same exacting criteria employed by researchers to evaluate any new therapies.

The authors report on CAM curriculum developments in Germany, Canada, and the United States that illustrate various approaches to the question, "What should be taught in a CAM course?" In most cases, the approach is to teach *about* CAM therapies, although in others, therapies that the curriculum planners considered useful and safe are being integrated into the medical curriculum.

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Complementary and alternative medicine (CAM) is becoming increasingly popular in the Western world. These therapies include acupuncture, chiropractic, herbal medicine and dietary supplements, nutriceuticals, therapeutic touch, homeopathy, mind–body techniques, spirituality and faith healing, massage, and a number of others. The public is overwhelmed with the many articles and Internet sources about CAM, the vast amount of natural products and related marketing information, multiple treatment methods, and the increased number of CAM providers, courses, and schools. Patients are looking for reliable information about CAM and how to apply it to their health care. It is not uncommon to hear about patients who feel that their physicians cannot (or in some cases, do not wish to) provide that advice; one sign of this frustration is that patients sometimes do not disclose to their physicians the alternative therapies they are using (although it must be acknowledged that in some cases, there may be other, non–CAM-related reasons for such reticence).

Physicians are starting to feel the need to address this demand for CAM and thus are showing a growing interest in this topic. At least 2,750 articles in the medical literature used the term "complementary and alternative medicine" in 1999. In a survey that was done in three regions in the United States and Israel it was found that 60% of all the physicians surveyed made referrals to CAM providers.[1] Meta-analysis of 12 surveys of conventional physicians' attitudes toward CAM found that conventional physicians generally believed that CAM is moderately effective.[2] We believe that the findings of these studies—made in the mid-1990s—indicate a trend that continues today, in which the number of physicians who are reluctant to work with their patients on issues of alternative medicine (see previous paragraph) is lessening.

It is likely that medical students have an even greater enthusiasm for CAM. For example, in a recent survey of U.S. medical students at the University of Medicine and

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Dentistry of New Jersey–Robert Wood Johnson Medical School, 98% believed that CAM has beneficial effects, and 43% agreed that CAM should be incorporated into the medical school curriculum.[3] In Canada, a recent survey among first-year medical students revealed that 65% of them wanted to take a course about CAM.[4]

Medical schools and residency programs are starting to respond to this demand. In 1995, a survey of U.S. medical schools and family practice residency programs revealed that 39.2% of the medical schools were teaching CAM to their students and 28.1% of the non–university-based family practice residencies were offering CAM instruction.[5] However, a more recent survey indicates that continued growing public interest in CAM has led to a dramatic increase in the number of courses offered through medical schools and residency programs. That survey revealed that in 1997–1998, 64% of US medical schools were offering CAM instruction.[6] Much of this instruction was *about* CAM, but some of it was to teach the therapies themselves as complements to traditional therapies.

WHY DO WE NEED CAM INSTRUCTION?

As previously mentioned, patients tend to avoid disclosing their CAM use in the medical encounter. The reasons for not sharing their experiences were mentioned in a study of patients with recently diagnosed breast cancer that combined CAM and conventional medicine in their health care.[7] That study revealed that patients tended to anticipate a negative response from the physician if they were to reveal their CAM use, and that patients often sensed that the physician was not interested in CAM. Other reasons that were mentioned were the belief that physicians are unable or unwilling to contribute useful information or that patients think that their disclosures of CAM use are not relevant to the conventional treatment that they receive at the same time. The participants in this study made it clear that they value their physicians' respect and understanding regarding treatment choices even when there are times that they do not agree with those choices. They appreciated physicians who were respectful, willing to listen, and open-minded. The study concludes that both patient care and the physician–patient relationship will benefit from more comprehensive discussions of CAM use into the medical encounter. For this to occur, however, physicians must learn more about CAM so that they can become informed consultants to their patients on that topic.

With the major expansion in the use of CAM by the general population there is a growing need for physicians to provide some answers to themselves as well as to their patients about CAM and to consider possible integration of CAM into the conventional system. In order to be an informed consultant, physicians should expand their knowledge of CAM so they can take a more educated approach to the combined use of CAM and conventional therapy that their patients are already using.

In addition, the public is seeking information about the use of CAM, and a balanced approach to educate patients should come from their physicians. It seems natural that physicians should assume the role of advising patients on health issues, and CAM is one of those issues.

Practitioners and schools of CAM are not regulated or being supervised by health authorities, and there is very little protection against charlatans. On the other hand, there are practitioners of CAM that are well trained in their fields of practice and are candid and compassionate in their approach; patients can benefit from their care. Some of the remedies that are being used in CAM have the potential of interacting with conventional prescriptions with potential harm or can be toxic,[8,9] but others can bring comfort and relief in treating conditions that conventional treatment has failed to treat.[10–14] We acknowledge, however, that opinions differ about the adequacy of research findings to certify the safety and efficacy of specific therapies, and stress that physicians' decisions about CAM use should be subject to the same exacting criteria that researchers employ to evaluate any new therapies. Physicians should have a basic understanding and knowledge of CAM therapies and their effects so they can give their patients an educated opinion and balanced advice. But for physicians to gain that kind of understanding and knowledge, a consistent educational approach needs to be developed for them when they are medical students and residents, and also in their continuing medical education. Again, such an approach should emphasize scientific evidence—or the lack of it—to evaluate the safety and efficacy of CAM therapies.

WHAT SHOULD BE TAUGHT?

What, specifically, should be taught in a CAM course? Below we offer a sampling of recent informed answers to this question.

A 1998 survey of U.S. medical schools found that 123 courses in CAM were being offered in those schools. There was tremendous heterogeneity and diversity in content, format, and requirements among the different courses. Topics included acupuncture, chiropractic, massage, therapeutic touch, homeopathy, nutrition, herbal medicine, mind–body techniques, and spirituality and faith healing. Some focused on rules of evidence and critical reading of relevant medical literature. The authors of that survey suggest that teaching should focus on critical thinking and critical reading of the literature. They feel that there is a need to identify therapies and conditions in CAM, discuss them in terms of clear, con-

cise learning objectives, and include an experiential component to each of the selected topics. They mention that there is a need to promote a willingness to communicate professionally with CAM providers and teach students how to talk to patients about CAM use.[7]

Jordan J. Cohen, MD, president of the Association of American Medical Colleges, recently wrote that medical students must learn how to encourage frank and open discussion with patients about CAM use, and should have sufficient knowledge of the common CAM therapies. With that knowledge when they become physicians, they should be able to counsel their patients about possible benefits and potential harm that might be related to each therapy.[15]

Stephen E. Straus, MD, director of the National Center for Complementary and Alternative Medicine (of the U.S. National Institutes of Health) mentions that a patient-centered and less paternalistic approach should be stressed in the teaching of CAM. He states that students should receive instruction about issues such as "proven CAM methods of pain management and palliative care . . . a pharmacology of natural products, nutrition, exercise, and the role of stress management in promoting health and preventing disease." Students should become familiar with common alternative medical systems and their basic principles and at the same time emphasize the need to base treatment decisions on rigorous evidence.[16]

In Canada, many medical school faculty believe that a general conceptual overview of CAM should be provided, emphasizing the understanding of CAM as part of patients' health care belief systems.[17] In a survey to learn about the presence of CAM in Canadian medical schools it was found that acupuncture and homeopathy were the methods most often included in the course material, followed by herbal medicine, chiropractic, naturopathic medicine, biofeedback, osteopathy, massage therapy, and others.[17]

In Germany, a university project for integration of naturopathy into research and teaching was offered to students. It became a very popular course, and by the third year had 220 participants out of 700 students. The course included lectures on the basics of naturopathy and research that was related to naturopathy. Lectures concentrated on proof of effect and efficacy, indications and contraindications for individual naturopathic techniques, and the acquisition of some practical skills in some of those techniques. The demand for this therapy by patients and deficiencies in conventional care were discussed as well. Optional topics included acupuncture, manual therapy, nutrition, homeopathy, hydrotherapy, and phytotherapy.[18] (Readers should note that naturopathy is a very wide field; some aspects of it have some scientific basis, but others do not.)

Until recently at the University of Arizona College of Medicine a two-year postgraduate fellowship in CAM was offered to physicians. Fellows attended lectures on nutritional medicine and mind–body medicine, had discussions about spirituality and medicine and "healing-oriented medicine," and received information about the philosophy, theory, practice, strengths, and weaknesses of the major alternative therapies. The participants stated that their main challenge was to sort through all the evidence about all CAM healing systems and try to extract those ideas and practices that are useful, safe, and cost-effective. They tried to merge them into a new system of integrative medicine—a comprehensive system that has an evidence base and also addresses consumers' demands.[19]

In the United States, the Society of Teachers of Family Medicine Group on Alternative Medicine developed a consensus of recommended attitudes, knowledge, and skills concerning CAM for incorporation into family practice residency training. Among the suggested guidelines are the need to understand and respect (1) cultural influences on health beliefs and health choices, (2) the basic theory or philosophy of the main modalities of treatment, (3) indications and potential adverse effects of such treatment, and (4) the evidence for efficacy and cost–effectiveness of each modality. It was mentioned that a number of family practice residency programs were trying to implement those suggested guidelines, but the authors of the report of the Society's recommendations state that it remains unclear what teaching strategy would be the most effective way to integrate CAM therapies into training programs.[20]

As the information above indicates, there are many ways that the introduction of CAM into the medical school curriculum is being dealt with. But it seems that all agree that courses should review how knowledge of CAM can be integrated into the conventional system of care in a useful, safe, and cost-effective approach.

NEED FOR A CONSISTENT EDUCATIONAL APPROACH

With the increased demand for and interest in CAM there are more and more CAM instruction courses being offered in medical schools and residency programs. These courses are initial steps in the development of a consistent educational approach to CAM and are a starting point for medical educators. Our research indicates that there is agreement that a CAM curriculum should include knowledge of common CAM therapies that can be integrated into the conventional system in a useful, safe, and cost-effective way. Such a curriculum should provide a knowledge base for physicians so they can help patients understand the overwhelming amount of information (and misinformation) about CAM that they are exposed to, can give more informed advice to their patients, and, in those cases where the evidence warrants it, integrate specific CAM therapies into their strategies of care.

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